Clinical Trials for the Treatment of Secondary Wasting and Cachexia

Pathophysiology of Protein-Energy Wasting in Chronic Renal Failure¹

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ABSTRACT  There is a high prevalence of protein-energy malnutrition in both nondialyzed patients with advanced chronic renal failure and in those individuals with end-stage renal disease who are receiving maintenance hemodialysis or chronic peritoneal dialysis therapy. Approximately one-third of maintenance dialysis patients have mild to moderate protein-energy malnutrition, and about 6 to 8 percent of these individuals have severe malnutrition. These statistics are of major concern because markers of protein-energy malnutrition are strong predictors of morbidity and mortality. The causes of protein-energy malnutrition in patients with chronic renal failure include: (1) decreased energy or protein intake; (2) concurrent chronic illnesses, and superimposed acute illnesses and possibly increased inflammatory cytokines; (3) the catabolic stimulus of hemodialysis; (4) losses of nutrients into dialysate, particularly amino acids, peptides, protein (with peritoneal dialysis), glucose (when hemodialysis is performed with glucose-free dialysate) and water-soluble vitamins; and (5) diagnostic or therapeutic (e.g., prednisone therapy) procedures that reduce nutrient intake or engender net protein breakdown. Other theoretically possible causes for protein-energy malnutrition include (6) chronic blood loss; (7) endocrine disorders (especially resistance to insulin and insulin-like growth factor-I, hyperglucagonemia, hyperparathyroidism and deficiency of 1,25-dihydroxycholecalciferol); (8) products of metabolism that accumulate in renal failure and may induce wasting, such as organic and inorganic acids; (9) loss of the metabolic actions of the kidney; and (10) the accumulation of toxic compounds that are taken up from the environment (e.g., aluminum).  J. Nutr. 129: 247S–251S, 1999.

KEY WORDS:  ● renal failure  ● hemodialysis  ● peritoneal dialysis  ● malnutrition  ● protein-energy malnutrition

With possibly one exception, all of the approximately 30 to 40 surveys of the nutritional status of patients undergoing maintenance hemodialysis or peritoneal dialysis indicate that there is a high incidence of protein-energy malnutrition; the prevalence rate is about 16 to 34 percent in various reports (Cianciaruso et al. 1995, Dwyer et al. 1998, Markmam 1988, Young et al. 1991). We have observed a prevalence of protein-energy malnutrition of about 40 percent in both maintenance hemodialysis and peritoneal dialysis patients. About one-third of these patients have mild or moderate protein-energy malnutrition, and about 6 to 8 percent have severe malnutrition. Patients with advanced chronic renal failure are at increased risk for depletion of a number of nutrients. These include calcium (Kopple and Coburn 1973), iron (Lawson et al. 1971), zinc (Mahajan et al. 1980, Sprenger et al. 1983), vitamin B₆, vitamin C and folic acid (Chazot and Kopple 1997), 1,25-dihydroxycholecalciferol (Brickman et al. 1974), and possibly carnitine (Bellinghieri et al. 1983). To be consistent with the subject of this workshop, this discussion will focus on protein-energy malnutrition. Protein-energy malnutrition is clearly a powerful predictor of high morbidity and mortality. In maintenance hemodialysis patients, nutritional parameters which have each been independently correlated with 12-month odds ratios for increased mortality include low visceral protein concentrations (e.g., predialysis serum albumin), reduced muscle protein mass (indicated by low predialysis serum creatinine concentrations), decreased nutrient intake (low urea nitrogen appearance rates—i.e., net urea generation, an indicator of dietary protein intake), and low predialysis serum concentrations (potassium, phosphorus, and cholesterol) (Davis et al. 1995, Lowrie and Lew 1990, Teehan et al. 1990). In chronic peritoneal dialysis patients, decreased serum albumin levels and urea nitrogen appearance rates also correlate with high morbidity and mortality (Davis et al. 1995, Teehan et al. 1990). The relationship of dietary energy intake, if any, to morbidity or mortality has not been carefully examined in maintenance dialysis patients, because it is more difficult and expensive to obtain accurate estimates of energy intake in large numbers of individuals.
The finding that parameters of protein-energy malnutrition are correlated with increased morbidity and mortality does not prove that providing better nutritional intake or improving nutritional status will reduce mortality. Indeed, it is possible that co-morbid conditions, including elevated inflammatory cytokines, may both reduce nutrient intake and cause protein-energy malnutrition and independently increase morbidity and mortality (Macdonald et al. 1993, Memoli et al. 1992). In support of this possibility are recent reports indicating that a substantial proportion of the odds ratio for serum albumin and mortality disappears if adjustments are made for co-morbid conditions (Keane and Collins 1994). Serum concentrations of several acute phase proteins are increased in chronic hemodialysis patients (Doci et al. 1990). The finding that serum C-reactive protein correlates inversely (although poorly) with serum albumin in maintenance hemodialysis patients also suggests that co-morbidity or increased generation of inflammatory cytokines contributes to the relationship between serum albumin and mortality (Bologna et al. 1995, Qureshi et al. 1995).

On the other hand, two retrospective studies indicate that nutritional therapy of malnourished maintenance patients reduces mortality (Capelli et al. 1994, Chertow et al. 1994). Chertow and coworkers (1994) compared the odds ratio for mortality in 1,679 malnourished maintenance hemodialysis patients who received intradialytic parenteral nutrition, (i.e., intravenous feeding given only during hemodialysis treatments about thrice-weekly) to a matched group of 22,517 hemodialysis patients who did not receive parenteral nutrition. The data indicate that when the serum albumin was 3.3 g/dl or lower, and particularly when the serum creatinine was also 8.0 mg/dl or less, treatment with intradialytic parenteral nutrition was associated with a significantly lower odds ratio of mortality.

Capelli and coworkers (1994) examined the mortality rate in a nonrandomized study of 81 malnourished maintenance hemodialysis patients. Thirty-one of the patients did not receive intradialytic parenteral nutrition and served as controls, whereas 51 patients received intradialytic parenteral nutrition for a mean of nine months. The patients receiving intradialytic parenteral nutrition had a significantly greater survival rate.

The foregoing research findings therefore suggest that both comorbid disorders and inadequate nutrient intake contribute to the increased morbidity and mortality rates of maintenance dialysis patients. Prospective, randomized clinical trials will be necessary to determine the relative contributions of poor nutrition vs. comorbid or inflammatory states to the adverse outcomes and the extent to which nutritional therapy may improve prognosis.

Indeed, the process may well be more complex. For instance, associated illnesses may both increase morbidity and mortality and cause malnutrition by ways in which the malnutrition makes little or no contribution to the elevated mortality. Metastatic small cell carcinoma of the lung may be such an example. Alternatively, a comorbit illness might cause an increase in morbidity and mortality in part by engendering protein or energy wasting, even though nutrient intake remains adequate. An example might be a disseminated infection, such as AIDS, where the wasting may not be completely reversible by nutritional support and may ultimately contribute to morbidity and mortality. On the other hand, malnutrition caused by low nutrient intake or impaired intestinal absorption of nutrients engendered by associated illnesses, such as radiation enteritis, might increase morbidity or mortality. Finally, inadequate nutrient intake due to anorexia, e.g., caused by chronic uremia, may increase morbidity and mortality. These issues may be relevant when one considers research strategies or therapeutic approaches for patients with chronic renal failure. For example, the potential therapeutic value of anti-inflammatory agents, anticytokines, growth factors or nutritional support, theoretically, could depend upon the causes of the malnutrition and its contribution to the morbidity and mortality rates of the patients.

There are many potential causes of protein-energy malnutrition in maintenance dialysis patients. These include the following:

1. Inadequate nutrient intake is probably the most important single cause of malnutrition (Ciancareuso et al. 1995, Dwyer et al. 1998), and anorexia is the most important cause of reduced nutrient intake. Anorexia may be caused by uremic toxins (Bergström et al. 1994), underlying illnesses such as diabetes mellitus, which in its advanced stages alters gastric motility and emptying, and emotional disorders—particularly emotional depression which occurs commonly in patients with advanced chronic renal failure. Chronic illnesses, such as lupus erythematosus, emphysema or congestive heart failure, and acute superimposed illnesses (e.g., vascular access site infection in hemodialysis patients, peritonitis in peritoneal dialysis patients, or septicemia) may also impair the patient's ability to eat. Seemingly mundane problems such as loss of dentures or inability to buy food not uncommonly decrease the intake of essential nutrients in maintenance dialysis patients. The high incidence of poverty in patients with end-stage renal disease commonly contributes to these latter causes for suboptimal nutrient intake.

Recent evidence obtained from nonrandomized studies suggests that increasing the dose of dialysis will improve serum albumin, presumably by increasing appetite and nutrient intake (Izikler et al. 1995). However, in all of these studies, a substantial subset of patients still ingested low-protein diets. This should not be surprising because there is a high prevalence of comorbidity in these patients which might be expected to impair their appetite regardless of their dialysis dose. Moreover, even with what are currently considered to be high doses of dialysis, patients still have substantially elevated plasma levels of large numbers of metabolic products. At present, it is not known at what level of dialysis treatment the nutrient intake will no longer increase as the dose of dialysis continues to rise.

2. Patients with chronic renal failure frequently sustain superimposed acute illnesses that induce a hypercatabolic state and may also, as indicated above, reduce food intake (Grodstein et al. 1980).

3. As indicated above, several studies in maintenance dialysis patients indicate that part of the predictive value of serum albumin can be accounted for by co-morbid conditions (Keane and Collins 1994), that serum albumin concentrations do not always correlate with dietary protein intake (Teehan et al. 1990), and that serum albumin levels correlate inversely with certain acute phase proteins including C reactive protein (Bologna et al. 1995; Qureshi et al. 1995). These observations have engendered the hypothesis that the direct correlation between serum albumin and mortality reflects the presence of co-morbid conditions in patients with low serum albumin concentrations; the low serum albumin is caused by increased tissue levels or actions of inflammatory and catabolic cytokines due to the
4. The dialysis procedure also may accentuate malnutrition by removing nutrients. During a hemodialysis treatment in maintenance hemodialysis patients, amino acid losses vary on average from about 6 to 12 g, depending upon the permeability and clearance characteristics of the dialyzer membrane, the blood and dialysate flow rates, duration of dialysis and whether the patient is or is not fasting (Ikizler et al. 1994, Wolfson et al. 1982). Peptide losses average 2 to 3 g per hemodialysis treatment with low permeability dialyzer membranes and are probably slightly greater with high flux (large pore size), high-clearance hemodialyzers. About 15 to 25 g of glucose are lost if glucose-free dialysate is used; however, hemodialyzed containing d-glucose monohydrate (dextrose) 100 to 200 mg/dl is usually employed, and glucose gain or loss during hemodialysis is small if the patient is euglycemic (e.g., 8.8 ± 0.5 (SEM) g of total protein, including 5.7 ± 0.4 g of albumin, are lost each day into peritoneal dialysate and the glucose absorption from the peritoneal dialysate is severe. Protein losses fall rapidly with antibiotic therapy, but may remain elevated for many weeks to months after the peritoneal infection has been eradicated. There are losses of water-soluble vitamins and other bioactive compounds with both hemodialysis and peritoneal dialysis (Blumenkrantz et al. 1981). During acute peritonitis, which is not an uncommon complication of chronic peritoneal dialysis, protein losses increase. We observed the total quantity of protein removed by peritoneal dialysis to rise to 15.1 ± 3.6 g per day with mild peritonitis (Blumenkrantz et al. 1981), and losses may be much greater if peritonitis is severe. Protein losses fall rapidly with antibiotic therapy, but may remain elevated for many days to weeks after the peritoneal infection has been eradicated. Also, the metabolism or actions of some vitamins are altered in patients with chronic renal failure (Chazot and Kopple 1997). These factors may lead to deficiencies of some water-soluble vitamins, most commonly vitamin B<sub>6</sub>, vitamin C and folic acid, if vitamin supplements are not taken.

5. Other medical therapies also may promote wasting. For example, many patients with renal disease receive treatment with medicines (e.g., glucocorticoids), surgery, irradiation, or other diagnostic or therapeutic procedures that impair nutrient intake or stimulate net protein breakdown.

6. Patients with chronic renal failure may lose substantial amounts of blood from gastrointestinal bleeding, frequent blood sampling for laboratory measurements and the sequestration of blood in the hemodialyzer (Linton et al. 1977). The gastrointestinal blood losses may be occult and only detectable by chemical testing of feces for hemoglobin. Since blood is rich in protein, these blood losses may contribute to protein malnutrition. For example, an individual with a hemoglobin concentration of 12.0 g/dl would lose about 16.5 g of protein in each 100 ml of blood removed.

7. It is possible, but not established, that the many endocrine disorders in renal failure may promote protein or energy malnutrition. There is resistance to the actions of the anabolic hormones, insulin and insulin-like growth factor-I (DeFronzo et al. 1978, Fouque et al. 1995). There are increased plasma concentrations of...
two other hormones, glucagon and parathyroid hormone, which may promote amino acid catabolism and gluconeogenesis (Moxley et al. 1974, Sherwin et al. 1976). Indeed, secondary hyperparathyroidism can be severe in patients with chronic renal failure (Llach et al. 1986). Altered vitamin D metabolism also may promote malnutrition. 1,25-dihydroxycholecalciferol deficiency, as well as hyperparathyroidism, has pervasive effects on calcium metabolism; vitamin D deficiency may cause a proximal myopathy; and 25-hydroxycholecalciferol stimulates skeletal muscle protein synthesis in vitro (Birge and Haddad 1975). Hence, it is possible, but not proven, that deficiency of 1,25-dihydroxycholecalciferol also causes protein wasting.

8. Toxic metabolic products that accumulate in renal failure may engender malnutrition. There are probably hundreds of metabolic products that accumulate in plasma or tissues in renal failure; many of these compounds have already been identified (Bergström 1997). Some of these compounds are bioactive (Bergström 1997) and may have catabolic or anti-anabolic actions. One of the classes of compounds that accumulates is acids. In animals with or without renal failure, acidemia enhances the decarboxylation of branched-chain amino acids and causes protein catabolism. In humans, acidemia suppresses albumin synthesis, promotes negative nitrogen balance and also induces protein degradation (Ballmer et al. 1995, Reaich et al. 1992).

9. It is also possible that the loss of metabolic actions in the failing kidneys may promote protein-energy malnutrition. The kidney is one of the most metabolically active organs in the body. It synthesizes or degrades many biologically active compounds such as amino acids, peptide hormones and other peptides, glucose and fatty acids. It is not known whether the loss of these metabolic processes may engender malnutrition.

10. Finally, it is possible, but not proven, that exogenously derived toxins that are retained in renal failure may promote malnutrition. These substances may be ingested or enter the body as contaminants from dialsate. One such candidate might be aluminum which accumulates in renal failure and can cause microcytic anemia, bone disease, encephalopathy and debility (Coburn and Alfrey 1995). Many of the foregoing causes of protein-calorie malnutrition are operative before patients develop end-stage renal disease and commence maintenance dialysis therapy. Recent studies indicate that dietary protein and energy intake diminish spontaneously long before end-stage renal disease develops (Kopple et al. 1989 and 1997). In one study, spontaneous reductions in dietary protein and energy intake were observed when the glomerular filtration rate was 30-35 ml/min/1.73 m² or even higher (a normal glomerular filtration rate is approximately 100-120 ml/min/1.73 m²). Patients typically are urged to commence maintenance dialysis therapy when the glomerular filtration rate falls below 5 to 10 ml/min/1.73m². This reduction in intake was associated with biochemical and anthropometric evidence of worsening protein- calorie nutritional status. The changes in dietary intake and nutritional status at these levels of renal function, in general, were rather mild and did not become more pronounced until the glomerular filtration rate subsequently falls. However, the prevalence and severity of protein-energy malnutrition in patients who are beginning chronic dialysis treatment appears to be similar to the prevalence in patients who are well established on maintenance dialysis treatment. Moreover, both in children undergoing chronic peritoneal dialysis and in adult maintenance hemodialysis patients, we have found that their nutritional status at the onset of dialysis treatment is a strong predictor of their nutritional status one or two years later.

In my personal experience, nondialyzed patients with chronic renal failure appear to be at greatest risk for developing protein-energy malnutrition between the time that the GFR decreases below 8 to 10 ml/min, and especially when the GFR is below 5 ml/min, and the time when the patient is well established on maintenance dialysis therapy. Hence, this is a stage in the patient’s illness when it may be particularly critical to monitor the patient’s nutritional and metabolic status closely and to aggressively institute dialysis therapy and other procedures, if necessary, to prevent protein-energy malnutrition.

LITERATURE CITED


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PROTEIN-ENERGY WASTING