

Protein Wasting in Patients Undergoing Maintenance Hemodialysis

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Introduction

Patients of chronic renal failure are hypercatabolic and may develop wasting and malnutrition which include negative nitrogen balance and loss of lean body mass. However, when patients with these disorders have associated with underlying or superimposed illnesses, the degree of hypercatabolism can be profound and it may contribute to their high morbidity and high mortality^{1,2)}.

Acchiardo et al studied the relationship between protein intake, morbidity and mortality over a period of 1 year in 98 nondiabetic patients who were undergoing maintenance hemodialysis. The group that had the lowest average net protein catabolic rate, which indicates the lowest protein intake, had the greatest frequency of hospitalization, the greatest number of days in the hospital and the highest mortality rate. Thus, low nutrient intake and malnutrition contributed to poor prognosis in maintenance dialysis patients³⁾. Blackburn et al observed that a study in chronic dialysis patients demonstrated a significant correlation between serum albumin and mortality. The death risk in patients with a serum albumin of less than 4.0 g/dl was two to four times higher than in patients with values above that level⁴⁾.

Mechanisms for Protein Wasting in Uremia

1. Inadequate Intake of Protein and Energy

In chronically stable maintenance dialysis

patients, protein intake is often near the prescribed level, but dietary energy intake is inadequate to maintain normal nutritional status, usually to 20 ~25% below values of normal individuals of the same age and sex. These patients suffer from a mild degree of anorexia⁵⁾.

Acute and chronic superimposed illness impair the uremic patient's ability to eat, digest, absorb or utilize nutrients. Diagnostic or therapeutic procedures may require the patient to fast. Also, the hemodialysis procedure and some medicines may cause anorexia, nausea or vomiting. Patient's depression and other psychological stresses may contribute to anorexia or poor food intake.

2. Impairment of Adaptive Responses to Low-protein Diets

Uremia could induce protein wasting by impairing the normal adaptive responses to a low-protein diet, prescribed for uremic symptoms or protect residual kidney function⁶⁾. When the dietary protein is reduced to the adequate minimum level, metabolic changes permit to achieve nitrogen equilibrium in normal subjects and the major metabolic changes include a decrease in amino acid oxidation and inhibition of protein degradation⁷⁾.

We recently assessed the adaptive responses in moderate proteinuric rats by measuring the metabolism of L-[1-¹⁴C]-leucine during its constant infusion. In response to feeding either adequate protein diet (22% protein) or low protein diet (8.5% protein), both groups adapted successfully and exhibited a decrease in leucine oxidation and a reduction in

urinary urea nitrogen excretion as a primary mechanism^{8,9}).

Goodship et al compared the adaptation of the patient with moderate chronic renal failure (serum creatinine about 5 mg/dl) with those of normal subjects of similar age, sex and weight when dietary protein was 1.0 g protein/kg/day and 0.6 g protein/kg/day. The adaptive responses to feeding either diet, both groups show a decreased in leucine oxidation and protein degradation to the same degree, but these responses were marked with the low-protein diet¹⁰. These results might not be achieved in patients with severe uremia.

Berkelhammer et al determined postabsorptive whole-body protein turnover for evaluation of muscle wasting in patient with chronic maintenance hemodialysis (MHD). In MHD, protein oxidation rate was 43% greater than that in control, whereas net protein synthesis was reduced, which may contribute to the muscle wasting¹¹).

3. Uremia Could Inhibit Protein Synthesis and/or Stimulate Protein Degradation

Protein catabolism is aggravated by renal insufficiency. This is confirmed when uremic rats exhibit decreased protein synthesis and increased protein degradation during *in vitro* muscle incubation and hind leg perfusion^{12,13}. This excessive catabolism has been variously attributed to insulin resistance, acidosis and hyperparathyroidism¹⁴⁻¹⁶).

Clark and Mitch found that protein degradation was directly correlated with the decreased responsiveness of muscle glucose metabolism to insulin. In severe uremia, inhibition of amino acid release from incubated rat muscle was less responsive to insulin. Because of the large quantity of daily protein turnover, an increase in protein degradation in muscle due to abnormal insulin responsiveness in uremia could raise nitrogen requirement sharply^{17,18}).

Also, abnormal muscle protein breakdown may be linked to defective energy metabolism¹⁹).

May et al have found that metabolic acidosis stimulated protein breakdown in rat muscle, and the acidosis-induced proteolysis required glucocorticoid. Leucine one of the branched-chain amino acids (BCAA) stimulates muscle protein synthesis while its ketoacid, α -ketoisocaproate (α -KIC) inhibits protein breakdown. Metabolic acidosis increases catabolism of leucine in muscle by stimulating the activity of branched-chain ketoacid dehydrogenase. Abnormal protein turnover might involve excessive breakdown of leucine, or its ketoacid, α -ketoisocaproate²⁰. These mechanisms presumably explain the improvement in nitrogen balance and decrease in urea production that occurs when metabolic acidosis is corrected in chronically uremic patients²¹).

4. Abnormality of Amino Acid, Protein Metabolism in Uremia

Patients undergoing dialysis have significantly lower valine, serine, tyrosine, histidine, and arginine levels, and significantly higher levels of taurine, aspartic acid, glycine, and alanine, as well as citrulline, proline, and cystine²²). Plasma concentrations of several nonessential amino acids are elevated while those of essential amino acids, especially the branched-chain amino acids, are reduced²³). The ratios of valine to glycine and tyrosine to phenylalanine are depressed in these patients²⁴).

The valine concentration highly correlates with other indices of malnutrition such as low arm muscle circumference, body fat, prealbumin and retinol-binding protein. Indeed, abnormal intracellular muscle amino acid distribution seen in uremics is restored to normal by maintenance hemodialysis, provided that a protein diet of more than 1g/kg/day is consumed²⁵) (Table 1).

Dialysis Induced Catabolism

The dialytic procedure per se seems to be a strong stimuli for protein catabolism. Hemodialysis may

Table 1. Potential Factors Changing the Components of Muscle Protein Turnover

Factors that cause an increase	Factors that cause a decrease
Protein synthesis	
Insulin	Starvation
Amino acid supply	Glucocorticoid
Leucine	Diabetes
Exercise	
Protein degradation	
Starvation	Insulin
Inactivity	KIC
Acidosis	

contribute to protein catabolism as 5 to 8 g of amino acids are lost in the dialysate²⁶. Nitrogen balance measurements in dialyzed patients have shown that there is always a negative nitrogen balance on dialysis days, irrespective of the protein intake. When protein intake is low, however, about 0.5 g/kg/day, cumulative nitrogen balance (dialysis and non-dialysis days) remains negative, whereas cumulative nitrogen balance is positive with a protein intake of 1.4 g/kg/day. The negative nitrogen balance observed on dialysis days is associated with a high rate of urea production, which suggests that hemodialysis may be a catabolic event²⁷.

1. Loss of Amino Acid and Glucose During Dialysis

Fasting patients loss averaging 7 g of free amino acids, 2~3 g of peptides or bound amino acids, 20~30 g of glucose and a small quantity of water-soluble vitamins during hemodialysis. If patients do not eat during hemodialysis, these nutrient losses are replaced from endogenous compartment and lipolysis, also gluconeogenesis and protein wasting are accelerated²⁸.

Wathen et al demonstrated that intradialytic ketogenesis was significantly reduced and gluconeogenesis was inhibited by adding glucose to

the dialysate in dialysis patient²⁹. Kopple et al also showed in a study of fasting hemodialysis patients, glucose (25 mmol/liter) reduced amino acid losses by 50%. Glucose enhances cellular amino acid uptake, thereby decreasing plasma levels³⁰.

However, Goth et al found that the replacement of dialyzer amino acid losses by continuous amino acid infusion did not lower intradialytic protein catabolism, but appeared to increase it. Addition of glucose to the dialysate was reported to lower but not eliminate intradialytic protein catabolism³¹. Farrell et al showed that glucose was ineffective in reducing dialysis-induced catabolism. Average intradialytic urea generation was increased by 28% with glucose-free dialysis, 25% with 26 mmol/liter of glucose dialysis than predialytic urea generation³². To explain for this controversy, there could be a connection between this observation and the fact that several catabolic hormones are known to have raised levels during dialysis, while levels of certain anabolic hormones are reported to decrease.

2. Several Catabolic Hormone

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With respect to amino acid/protein metabolism, insulin is known to promote branched chain amino acid transport and to regulate protein synthesis by muscle. If insulin antagonism were to involve amino acid metabolism, the resulting intracellular amino acid deficiency may contribute to the muscle wasting which is commonly encountered in uremic patients.

Alfred et al reported that catabolic hormones such as cortisol, thyroxine, and glucagon rose during dialysis, whereas anabolic hormones such as growth hormone tended to decrease. There is considerable dialysis-induced catabolism which is unresponsive to glucose be added to the dialysis³³.

In the renal failure, there is resistance to the

actions of insulin, and glucagon are increased in uremic sera, this hormone antagonizes many of the actions of insulin and stimulates gluconeogenesis³⁴.

Serum growth hormone concentrations are usually elevated, and serum somatomedin, which mediated the actions of growth hormone, tend to be normal or increased. However, the biological activity of somatomedin is reduced in uremic patients. Since somatomedin are anabolic hormones, it is possible that impaired somatomedin activity may also promote wasting in chronic renal failure³⁵.

PTH promotes protein wasting. It may do this indirectly by raising serum calcium and by causing anorexia, nausea, vomiting or disability through bone disease. PTH also directly promotes gluconeogenesis. Injection of PTH extract into human increases urinary nitrogen excretion and promotes negative nitrogen balance. Parathyroidectomy in patients with primary hyperparathyroidism may lead to improved nitrogen balance³⁶.

Recombinant human growth hormone (rhGH) improves nitrogen balance and protein-anabolic effect³⁷.

3. Uremic Toxins and Altered Metabolism Disorders

Delaporte et al reported that a dialysate of plasma obtained from non-dialyzed patient impaired protein synthesis in a cell-free system from mouse Krebs II ascites cells³⁸.

MaCaleb et al have partially purified and characterized a factor from uremic sera which inhibits glucose metabolism in normal rat adipocytes. This factor is a middle molecule (molecular weight between 1,000 and 2,000 daltons), contains a protein component and its specific for uremia. This middle molecule accumulates and inhibits the generation of second messenger for insulin, which leads to an impairment in muscle glucose metabolism³⁹.

The kidney has many metabolic and endocrine activities which maintain body nutrient mass. 25-

hydroxycholecalciferol has been reported to stimulate muscle protein synthesis *in vitro*⁴⁰. Lack of 1, 25-dihydroxycholecalciferol, carnitine deficiency, and aluminum toxicity can cause weakness of the proximal muscles of the lower extremities in chronic uremic patients and this debility might promote wasting⁴¹.

4. Metabolic Acidosis

A major stimulus for protein wasting in uremia is metabolic acidosis. Metabolic acidosis overrides the metabolic adaptive response to a low protein diet. The associated impairment of nitrogen utilization in uremia not only diminished the efficacy but also accelerated the loss of lean body mass⁴². Metabolic acidosis stimulates branched chain ketoacid oxidation and suppresses the protein sparing effect of leucine and α -ketoisocaproic acid (α -KIC), and accelerates the catabolism in chronic renal failure. In addition, metabolic acidosis stimulates both glucocorticoid production and muscle protein degradation which is blocked simply by feeding sodium bicarbonate in chronic uremia rats¹⁶.

5. Blood-Membrane Interaction During Hemodialysis

Blood-membrane interaction may also favor protein catabolism. During regular hemodialysis treatment circulating blood monocytes adhering to the dialysis membranes, activate and lead to production of interleukin-1 (IL-1). Endotoxin or its fragments are able to activate monocyte to release IL-1 Monocyte. In addition, sodium acetate stimulates mononuclear cells IL-1 production. Complement activation via the alternative pathway occurs during hemodialysis and C5a stimulate IL-1 production. The production of IL-1 is responsible for the following dialysis-related the increased catabolism and protein breakdown^{43,44,45}.

Baracos et al have identified that IL-1 causes fever and enhances protein degradation in rat muscle, and

IL-1 stimulates muscle synthesis of prostaglandin E2 which promotes muscle protein degradation by stimulating lysosomal proteolysis. Inhibitor of prostaglandin E2 synthesis and inhibitor of lysosomal thiol protease block the stimulatory effects of leukocyte pyrogen on muscle protein degradation⁴⁶⁾.

6. Trauma and Surgery

Kidney transplantation, gastrointestinal bleeding, the surgical procedures, and persistent abscess of the abdominal wall probably contribute to wasting and malnutrition. Protein and other nutrients are also lost from blood drawing, draining wounds and fistulae.

During acute catabolic stress, serum levels of epinephrine, glucagon, and cortisone often rise, and there may be resistant to the actions of insulin. These altered serum hormone concentrations or activities promote degradation of amino acids, gluconeogenesis, and urea formation.

Bacteremia and endotoxemia may cause hypotension, lactic acidosis, enhanced gluconeogenesis, and increased peripheral glucose uptake. Patients with severe gram-negative septicemia may also have suppressed gluconeogenesis and glucose production (Table 2).

Table 2. Causes of Protein Wasting in Uremic Patients

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1. Altered nutrition :
Inadequate food intake, dialysis lossess, abnormal metabolism of nutrients
 2. Uremic toxins :
Alteration of enzyme activities ; impaired membrane transport, altered protein binding
 3. Superimposed illness :
Decreased food intake, increased catabolism, enhanced gluconeogenesis
 4. Endocrinopathies :
PTH, glucagon, insulin, growth hormone, vitamine D₃
 5. Altered renal metabolism and degradation of peptides, proteins, insulin, vitamin D, and other hormones.
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Prevention of Protein Wasting

1. Maintenance of Good Nutritional Intake

1) 1.2 g (>1.0 to 1.4) of protein/kg of desired body weight, half of protein should be of high biological value. It is important that patients with advanced chronic renal failure undergoing conservative therapy not be subjected to inappropriately low protein diets that may deplete their protein stores⁴⁷⁾. Patient on very low protein diets should be carefully assessed at frequent intervals to evaluate their nutritional status, anthropometry, biochemical measurement since malnutrition prior to initiation of dialysis is associated with a higher morbidity and mortality rate after initiation of dialysis⁴⁸⁾.

2) 35~45 Cal/kg of desired body weight

Adequate energy intake is important to avoid further deterioration of nitrogen balance. On the other hand, excessive carbohydrate feeding should be avoided⁴⁹⁾. Supplementation with intravenous or oral essential amino acids should not be necessary in the stable hemodialysis patients⁵⁰⁾. To improve protein balance in the hemodialysis patients, glucose-containing dialysate solution (100 mg/dl) and intake of high biological protein are highly recommended.

3) Phosphorus intake should be reduced to no more than 0.9~1.1 g/day. The patient will require phosphorus and aluminum binders, though reduced phosphorus intake.

4) The daily calcium should be supplied 1.0~1.4 g/day.

5) Magnesium 0.2 g/day, up to 70 mEq/day of potassium.

6) A daily vitamin supplement: 10 mg of pyridoxine HCl, 70~100 mg of ascorbic acid, 1.0 mg of folic acid and recommended daily allowance for healthy adults for the other water-soluble vitamins. The dietary intakes of calcium and several vitamins by these patients are also often insufficient to maintain good nutrition, unless the patients take nutritional

supplements.

2. Control of Hyperparathyroidism

Hyperparathyroidism can cause severe debility and promote protein wasting⁵¹). PTH increases the rate of protein degradation in isolated muscle. Serum phosphorus should be decreased to normal values with a combination of dietary phosphorus restriction and phosphate binders.

3. Prevent Catabolic Illness

Catabolic illness cause rapid deterioration in nutritional status, such as congestive heart failure, fluid overload.

4. Exercise

Exercise can augment the magnitude of the response to insulin. Davis et al found that exercise training of chronically uremic rats increases the sensitivity of muscle to insulin, thereby improving glucose uptake, glycolysis and suppression of protein breakdown^{15,52}). An exercise regimen often improves abilities of social adaptation, and other metabolic and clinical benefits, reduces debility and raises hematocrit, but it needs to be excluded coronary artery disease and to be determine exercise tolerance.

5. Counseling by Social Worker, Psychologist, or Psychiatrist

Counseling may help to improve the patients's willingness to cooperate and comply with the treatment protocols.

6. Periodic Monitor the Patient's Nutritional Status

The nutritional parameters, which should be char-
ted on a flow sheet, include nutritional intake, urea nitrogen appearance edema-free body weight, relative body weight, triceps and subscapular skinfolds thickness, percent body fat, mid-arm circumference,

serum albumin, transferrin, predialysis serum calcium, phosphorus, potassium, and urea and hemato-
crit.

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