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Protein catabolism in chronic uremia: is it due to malnutrition?

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Summary

The high prevalence of anthropometric measurements and laboratory values that are similar to those in patients with protein-energy malnutrition has led to the classification of a large number of dialysis patients as being malnourished. However, malnutrition in the strict sense implies that abnormalities will be reversed if more food is eaten. There is virtually no evidence, however, that simply providing more nutrients in the diet of dialysis patients will reverse the abnormalities attributed to malnutrition. This suggests that the diagnosis of malnutrition is a misdiagnosis. In this review, we discuss mechanisms that will cause the loss of protein stores, including albumin, other plasma proteins, and muscle mass in dialysis patients. We will also review the shortcomings of techniques that are used to measure the nutritional status of these patients.

Key words: malnutrition • muscle atrophy • dialysis

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Several cross-sectional studies in dialysis patients have revealed anthropometric measurements and laboratory values that are similar to those found in patients with protein-energy malnutrition (PEM), leading to the classification of a large number of these patients as being malnourished^{62, 63}.

There are two classic syndromes of protein-energy malnutrition, described mainly in children eating very poor diets: marasmus (principally a diet lacking in energy) and kwashiorkor (secondary to a protein-deficient diet or an inadequate amino-acid supply). These syndromes are diagnosed by the presence of abnormal anthropometric measurements including weight, height, and mid-arm circumference plus low concentrations of serum proteins in individuals who do not have another disease. Providing dietary supplements reverses both syndromes. Based on these definitions, abnormalities in a patient's protein mass could, in theory, be corrected by increasing protein and/or calorie intake. Similar to findings in patients with PEM, hypoalbuminemia and muscle atrophy is a common finding in dialysis patients, suggesting that supplying more food or altering the composition of the diet can overcome these changes. However, this approach of providing more nutrients in the diet has been unsuccessful in reversing these changes, suggesting that a diagnosis of malnutrition is generally a misdiagnosis for dialysis patients^{44, 62}.

The common practice of attributing low albumin levels and muscle atrophy to PEM is completely incorrect. Even with true dietary undernutrition, hypoalbuminemia is not a common finding. Patients with anorexia nervosa have loss of weight (38.9 vs 59.5 kg for matched control adults) that is accompanied by loss of both muscle and fat mass, but serum albumin concentration does not differ from control adults⁶⁴. Therefore, eating an inadequate diet can result in weight loss and even a decrease in muscle mass, but such diets do not cause hypoalbuminemia.

Due to activation of compensatory responses of decreased protein breakdown and increased protein synthesis, healthy adults and patients with uncomplicated renal insufficiency (including nephrotic subjects) can maintain neutral nitrogen balance even on low-protein (0.6 g/kg/day) diets as long as energy intake is adequate^{4, 8, 21, 42, 50, 60, 70, 71}. These, adaptive metabolic responses and nitrogen balance are preserved even with advanced renal failure, when the diet is as low as 20 g protein/day as long as a supplement of 9 essential amino acids is provided^{18, 37, 46}. However, once dialysis becomes necessary, the amounts of protein and energy required to achieve protein balance increase sharply, and it is not known

if these adaptive responses occur in dialysis patients⁴. Theoretically, the increased requirements may predispose a dialysis patient to loss of weight or muscle; however, it would not cause hypoalbuminemia due to the reasons mentioned above. This is supported by the high prevalence and persistence of nutritional abnormalities in spite of relatively adequate protein intakes by dialysis patients, suggesting that other fundamental abnormalities in muscle protein synthesis/degradation lead to the signs and symptoms often mislabeled as malnutrition⁴⁴.

Several mechanisms may result in clinical features and laboratory abnormalities resembling malnutrition in dialysis patients. First, metabolic acidemia of renal insufficiency increases net protein degradation and the oxidation of essential amino acids in muscle; these changes are attenuated by feeding sodium bicarbonate^{26, 43}. Administration of ammonium chloride causes similar metabolic abnormalities in rats with normal kidneys by increasing the activity of branched-chain ketoacid dehydrogenase and stimulation of the transcription of genes encoding components of this enzyme¹⁶. Acidosis also contributes to the low level of serum albumin in dialysis patients, as its correction by administration of oral sodium bicarbonate improves serum albumin levels^{22, 51}.

Acidosis increases the breakdown of muscle protein by activation of the ubiquitin-proteasome proteolytic system, the major system that eliminates the bulk of protein in all cells, including muscle^{5, 48}. Physiologic concentrations of glucocorticoids appear to be necessary for activating the ubiquitin-proteasome pathway⁷². These experimental observations of activation of the ubiquitin-proteasome pathway by acidosis have been confirmed in patients before dialysis as well as in end-stage renal disease (ESRD) patients treated by hemodialysis or chronic ambulatory peritoneal dialysis (CAPD)^{7, 23, 56}. Correction of acidosis in CAPD patients suppresses the ubiquitin-proteasome system and leads to a gain in body weight⁵⁶. Thus, acidosis caused by kidney failure could contribute to the abnormalities presumed to be caused by an inadequate diet (i.e. malnutrition).

A second factor that could lead to malnutrition-like changes in dialysis patients is the evidence that kidney failure induces signs associated with chronic inflammation, although the source of inflammation in dialysis patients has not been identified. In addition, all the evidence is derived from cross-sectional analyses of dialysis patients showing elevation of an acute phase reactant protein (e.g. C-reactive protein or CRP). Therefore, this information does not yield insights into the cause of the inflammation, its persis-

tence over time, or its effect on protein mass. Although a cross-sectional analysis can prompt additional studies, conclusions based solely on this analysis about mechanisms should be made very cautiously⁴⁵. Several cross-sectional studies have shown a strong correlation between malnutrition, inflammation, and atherosclerosis in dialysis patients, leading some authors to call it the malnutrition, inflammation, and atherosclerosis syndrome; this combination is associated with a high mortality rate, but the reasons for the high mortality have not been identified^{29, 53, 63, 66, 67, 73}. Activation of the ubiquitin-proteasome proteolytic system is the common pathway leading to loss of muscle mass in models of inflammatory conditions, as has been repeatedly demonstrated in models of sepsis and similar conditions⁴⁸. Strong evidence that inflammation causes a loss of muscle mass come from elegant studies by Kaysen et al.^{30, 31}, who provided systematic examination of the contribution of inflammation (acute-phase reactant proteins) and dietary protein to changes in serum albumin in well-characterized hemodialysis patients. Investigators found that high circulating levels of longer-lived, acute-phase proteins, such as ceruloplasmin, measured in one month predicted a decrease in serum albumin in the following month. In sharp contrast, a high value of CRP in one month did not predict a future decrease in serum albumin. Recently, the same investigators have found that dietary protein and its variability played only a minor role in determining future changes in serum albumin³².

A third factor that may lead to signs of malnutrition and laboratory abnormalities in dialysis patients is elevated levels of pro-inflammatory cytokines^{36, 55}. The mechanism by which an excess of cytokines could increase proteolysis to cause loss of muscle mass has not been well characterized. Administration of tumor necrosis factor α to rodents can stimulate protein degradation in muscle, but it is unlikely that this response is the consequence of a single cytokine^{19, 20}. There is evidence that the initial step in the process of muscle protein breakdown also involves activation of apoptotic pathways, specifically caspase-3, and it is established that cytokines can activate apoptotic pathways¹⁵. The mechanism is complicated, however, because there is a role for glucocorticoids, and how this activates the ubiquitin-proteasome system is unknown^{14, 41, 48, 49, 59, 68, 69}.

A fourth factor responsible for muscle atrophy in uremic patients is the decreased responsiveness of peripheral tissues to the major anabolic hormone insulin. This leads to decreased protein synthesis and increased protein degradation, and in experimental models acute diabetes mellitus causes rapid loss of

body weight and muscle mass due to activation of the ubiquitin-proteasome proteolytic system⁵⁸. Although administration of insulin rapidly reverses these responses independently of the acidosis of acute diabetes⁴⁷, the responses are dependent on glucocorticoids^{12, 59, 72}. Decreased insulin as a factor in the muscle atrophy is supported by the studies showing increased protein catabolism when patients are dialyzed against a glucose-free bath²⁵.

A fifth factor that contributes to muscle atrophy and malnutrition-like features in dialysis patients is the catabolism associated with the dialysis procedure itself. Borah et al.⁸ found that hemodialysis patients are in negative nitrogen balance on the day of dialysis, even when their intake of protein is adequate. Follow-up studies in the 1990's by Bergstrom and collaborators reported that contact of the blood of normal adults with dialysis membranes could stimulate protein catabolism in leg muscles²⁴. Lim et al.³⁹ validated these observations of increased protein catabolism using stable isotope tracer studies. Recently, Ikizler et al.²⁸ not only found that dialysis stimulated whole body and muscle protein degradation, but their most intriguing finding was that this catabolic response persisted even after completion of the dialysis⁶¹. Infusion of a mixture of amino acids, dextrose, and lipids during dialysis led to partial suppression of whole body or muscle protein breakdown⁶¹. However, the suppression was only short-lived and the increase in protein degradation reappeared when the parenteral nutrition infusion was stopped. Despite the fact that plasma insulin levels increased 6-fold and muscle protein synthesis 4-fold, there was significant muscle protein breakdown. Thus, dialysis stimulates muscle protein breakdown, but the mechanism causing this increase are unknown.

Finally, accumulated waste products and metabolic abnormalities caused by the loss of kidney function also contribute to ESRD-associated abnormalities in weight, muscle mass, serum proteins, etc. However, the cause-effect association between the accumulation of nitrogen-containing waste products and the generation of a specific syndrome has not been proven despite intriguing reports about links between unidentified "middle molecules" and a depressed appetite³. Figure 1 summarizes the mechanisms that cause loss of protein stores in patients on dialysis.

Several laboratory parameters, anthropometric measurements, lean body-mass measurements by dual-energy X-ray absorptiometry or bioelectrical impedance analysis, as well as more sophisticated techniques such as total body nitrogen (TBN) have been used to measure somatic proteins and nutritional sta-

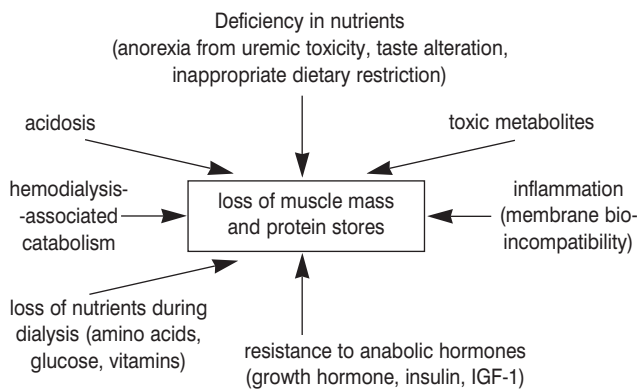


Figure 1. Causes of muscle loss in dialysis patients.

tus in patients with ESRD^{1, 44}. Serum albumin is the most frequently used marker of abnormalities in protein stores, and hypoalbuminemia is a strong predictor of death in dialysis patients^{38, 40}. However, hypoalbuminemia is more frequently seen in patients with inflammation than in patients with a true dietary deficiency of proteins. Plasma volume expansion, albumin redistribution, and exogenous losses (in peritoneal dialysis) are other causes of hypoalbuminemia^{33, 65}. Although serum pre-albumin and transferrin levels could uncover malnutrition early, similarly to serum albumin they are also frequently affected by inflammatory response. In addition, changes in urinary excretion and iron metabolism also affect these plasma proteins^{10, 27, 53}. TBN is considered the “gold standard” of the nutritional state in patients with ESRD^{1, 57}. There are advantages and disadvantages of these techniques in defining abnormalities in dialysis patients, as they are affected by kidney failure^{2, 9, 35}.

Subjective global assessment (SGA) as a tool for evaluating protein stores in dialysis patients is becoming popular among nephrologists due to its simplicity⁶. SGA refers to an overall clinical evaluation, including body weight and weight change, dietary intake, gastrointestinal symptoms, and functional status^{6, 13}. Although Enia et al.¹⁷ showed that SGA obtained in a cross-sectional study of 59 hemodialysis patients correlated significantly with anthropometric and biochemical measurements and bioelectrical impedance in detecting loss of protein stores, the reproducibility of the SGA and other measurements was not evaluated in this study. In addition, Cooper et al.¹¹, using TBN as the gold standard, determined the sensitivity and specificity of SGA scores in diagnosing abnormal protein stores. They found considerable observer variability in SGA scores and the measurement was of limited value in identifying loss of protein stores in dialysis patients (only 20–50% of patients with significant nutritional

compromise were identified). In particular, the SGA failed to discriminate between mild-to-moderate and severe degrees of malnutrition in dialysis patients. On the positive side, however, patients determined by SGA assessment to be well nourished generally had adequate TBN measurements (negative predictive values, 70–83%). Although the National Kidney Foundation-Dialysis Outcomes Quality Initiative has endorsed the use of SGA in evaluating protein-energy nutritional status, the above shortcomings must be kept in mind⁵².

As different causes of muscle atrophy in dialysis patients are becoming more recognized, the need to develop a classification for malnutrition-like features in these patients depending on the root cause(s) has become apparent. Keefe and Daigle³⁴ attempted to classify malnutrition, defined as albumin <3.5 g/dl, based on cause in their dialysis patients. Depending on the equilibrated normalized protein catabolic rate (enPCR), they identified two groups of patients: those consuming adequate protein and calories, yet presenting with hypoalbuminemia, and those suffering from a protein/calorie deficiency. Different treatment options were used for the two groups of patients, depending upon the cause. If protein/calorie intake is poor (enPCR <0.9), patients were counseled to increase protein/calorie intake and nutritional supplementation was provided. On the other hand, if enPCR was >0.9–≥ 1.4, a complete search for occult infection and inflammation was made and anti-inflammatory medications (anti-oxidants) were used³⁴. Although the outcomes of the interventions were not reported in detail, such approaches aimed at identifying patients who have true malnutrition from inadequate protein and nutrient intake and who would benefit from increasing dietary intake of nutrients are urgently required to improve outcomes in these patients.

In summary, despite the availability of several techniques to assess muscle mass, none address the important issue of why muscle protein breakdown occurs. Techniques that can identify true malnutrition caused by a deficiency of nutrients so that the patient can benefit from nutritional supplementation are urgently required. We would suggest that before assigning abnormalities in proteins stores of dialysis patients to malnutrition, careful evaluation of other causes should be made. Given the complexity of the pathophysiologic basis of protein breakdown in dialysis patients, the presumption that malnutrition or a deficiency of nutrients causes the loss of muscle mass and protein stores in dialysis patients is unwarranted, and we suggest a more accurate description be used: “uremic muscle atrophy”.

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