Given the Science on Malnutrition, How Does the Clinician Respond? Practical Lessons for and Application to the Dialysis Patient

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Nephrologists are only too accustomed to watching functional decline in patients who undergo long-term hemodialysis. This decline is the consequence of a complex series of biochemical and pathophysiologic processes that lead to decreased appetite, reductions in serum proteins, and loss of muscle mass and often results in fatigue, as well as reductions in stamina, exercise tolerance, and overall quality of life. This constellation of problems has been referred to by a variety of terms: protein-energy malnutrition, cachexia, muscle wasting, or simply malnutrition. This lack of precision in nomenclature surely adds to uncertainty in recognition and diagnosis. In most of cases, though, underlying causes are complicated and clearly not simply due to insufficient caloric intake. This may be a major reason that we as physicians have not been particularly successful in preventing or ameliorating these problems in our patients with ESRD. Here we review the potential causes of this functional decline at the molecular level and the current therapeutic approaches for prevention and treatment. It is our hope, of course, that extending our basic molecular knowledge of these processes will translate into better markers and more directed therapies for the catabolic dialysis patient in the not-too-distant future.

The fundamental issue underlying the malnutrition that is seen in the ESRD population is that these patients are catabolic, meaning rates of protein breakdown outstrip production of new body protein. Isotope studies in experimental animals and humans with uremia show that overall rates of protein synthesis generally are unchanged, whereas rates of protein degradation tend to increase (1,2). Because the rates of protein turnover in cells are very high (3.5 to 4.5 g protein/kg per d) (3), more than three times the average daily protein intake, even small increases in proteolysis can cause marked protein depletion. Because most body stores of protein are in skeletal muscle, protein depletion presents itself as loss of muscle mass, or muscle atrophy. Although mobilization of amino acids from muscle protein provides a life-sustaining energy source through hepatic gluconeogenesis, the ultimate effect is loss of muscle tissue. This trade-off is seen in many chronic diseases that are associated with cachexia, such as cancer, diabetes, and sepsis, and is particularly prevalent in the ESRD population (3).

Triggers of Enhanced Protein Breakdown in the Dialysis Patient

Chronic kidney disease is associated with several physiologic changes that trigger the enhanced breakdown of muscle protein. Insulin resistance/decreased insulin action (4,5) and inflammation (6) are potent activators of protein degradation, which is due, at least in part, to high circulating glucocorticoid levels (7–9). In addition, recent data have specifically implicated the newly recognized inflammatory cytokine TNF-related weak inducer of apoptosis (TWEAK) as a mediator of muscle wasting (10). Metabolic acidosis correlates with depressed levels of serum albumin (11,12) and accelerates rates of muscle protein degradation (2,13). These factors are often elaborated together and function in concert to bring about protein loss. Finally, the dialysis procedure itself promotes protein catabolism. This is likely due to many factors, including the nonphysiologic nature of the treatments, which leads to rapid fluid shifts and BP lability. In the 1990s, Bergstrom et al. (14) reported that contact of the blood of normal adults with dialysis membranes could stimulate muscle protein catabolism. More recently, Ikizler et al. (15) also showed that dialysis treatments stimulate whole-body protein degradation that persists after completion of the procedure. Ultimately, it should be remembered that hemodialysis, as typically performed, yields a GFR of only approximately 10 ml/min, barely the equivalent of stage 5 chronic kidney disease. This poor replacement of native kidney function and dramatically reduced clearance of uremic waste must promote factors, signals, and intracellular pathways that promote muscle wasting.

Molecular Mechanisms of Enhanced Protein Breakdown

Studies of animals have established that accelerated muscle protein breakdown induced by uremia involves similar cellular mechanisms as muscle wasting in a variety of other catabolic conditions (3). Muscles from uremic animals and from humans with similar conditions show a conserved pattern of changes (both increases and decreases) in the expression of approximately 100 atrophy-related genes (also termed atrogens) (16–20). Many of these regulated genes comprise parts of the ubiqui-
The ubiquitin-proteasome pathway (UPP), a pathway that has taken center stage in the past two decades in the study of cellular protein breakdown. The UPP consists of concerted actions of enzymes that link chains of the small protein ubiquitin onto other proteins to mark them for degradation (21,22) (Figure 1). This tagging process leads to their recognition by the 26S proteasome, a very large protease complex that degrades ubiquitinated proteins to small peptides (23). Three enzymatic components (E1, E2s, and E3s) are required to link chains of ubiquitin onto proteins that are destined for degradation. The key enzymes in the process are the E3s (Ub-protein ligases), because they recognize specific protein substrates and catalyze the transfer of ubiquitin to them. Upregulation of specific E3s has become a recently discovered signature of wasting muscle (next paragraph). The discovery of ubiquitin and the biochemistry of its conjugation to substrate proteins culminated in the awarding of the Nobel Prize in Chemistry in 2004 (http://nobelprize.org/nobel_prizes/chemistry/laureates/2004/).

Because the UPP serves many essential functions in cell regulation and homeostasis throughout the body, its activation in disease states must be highly selective to avoid the unwanted removal of proteins that are essential for cell function. This specificity is accomplished in muscle atrophy states through the regulated production of certain E3s that target specific muscle proteins for destruction. In muscle, at least two E3s, atrogin-1 (also known as MAFbx) and MuRF-1, serve this role; their expression increases dramatically in catabolic states such as uremia. Atrogin-1 and MuRF-1 play a critical function in mediating loss of muscle protein; animals that lack these genes are at least partly resistant to atrophy (24,25). However, the process of muscle loss is more complex than simply an activation of the UPP, because myofibrillar proteins (e.g., actin, myosin, troponins), which comprise approximately two thirds of the protein in muscle, are digested only very slowly by the UPP when they are present as complexes or in intact myofibrils (26). Recent findings suggested that myofibrillar proteins may first be cleaved by cytosolic proteases such as caspasases and then further degraded by the UPP. Catabolic states such as renal failure are characterized by high circulating levels of TNF-α or insulin resistance, conditions that also activate the caspase cascade (27–29). In support of this concept, caspase-3 can cleave actomyosin in vitro to produce substrates that are rapidly degraded by the UPP as well as a 14-kD C-terminal fragment of actin that accumulates in the insoluble fraction of the cell (30). A similar 14-kD actin fragment has been found in atrophying muscle of dialysis patients (31).

Activation of the UPP and a common transcriptional program in various types of muscle wasting also suggest that common intracellular signaling pathways are involved (16) (Figure 2). Recent studies established that in insulin-deficient (e.g., diabetes) and insulin-resistant (e.g., uremia) states and during metabolic acidosis, the general rise in proteolysis is mediated by decreased signaling through the phosphatidylinositol 3 kinase/PI3K/AKT pathway (32,33), which is normally activated by insulin or IGF-1. This occurs through both a reduction in IGF-1 levels and defects in postreceptor signaling (34). The reduction in signaling by the IGF-1/phosphatidylinositol 3 kinase/AKT pathway leads to two intracellular effects that promote atrophy: It reduces protein synthesis by suppressing protein translation, and it activates the forkhead family of the transcription factors that catalyze the transcription of certain atrogenes, such as atrogin-1 and MuRF-1, leading to increased muscle proteolysis (33,35,36). There is also emerging evidence that an unrelated transcription factor, NF-jB, leads to increased expression of MuRF-1 and muscle atrophy (37,38). In the various conditions that cause muscle atrophy, both transcription factors seem to contribute to muscle wasting, but their relative importance remains to be resolved.

**Figure 1.** Ubiquitin-proteasome pathway.

**Figure 2.** Intracellular signaling in growing and atrophying muscle.
Therapy: Can We Reverse the Forces that Promote Muscle Protein Loss in Dialysis Patients?

The extensive list of reasons for loss of muscle mass in patients with ESRD provides a useful context in which to evaluate the interventions that are available to physicians to treat these patients and bolster their nutritional status (Table 1). Because generally the currently available treatments do not modify the underlying biochemical, metabolic derangements in these patients, it is perhaps understandable that modifying weight loss and muscle wasting in the dialysis population is difficult. Despite this, the potential impact of improving nutritional status in the dialysis population is marked. In one analysis of disease hospitalization, death, and treatment costs, it was estimated that increasing albumin levels from <3.5 g/dl could save as many as 1400 lives, 20,000 hospital days, and much as $36 million in Medicare costs (39).

Within the dialysis population, the renal nutritionist works hard to ensure that caloric goals of 1.2 g/kg per d protein and 30 to 35 kcal/kg per d total calories are met, and numerous small studies demonstrate the effectiveness of this effort (40,41); however, dialysis patients with more significant nutritional issues are clearly commonplace and certainly difficult to treat. The most basic intervention aimed at treating catabolic dialysis patients is increasing caloric, specifically protein, intake with oral nutritional supplements. As discussed already, a fundamental flaw in this approach is an underlying assumption that the major problem in such patients is simply inadequate intake, which is typically not the case. Furthermore, patient compliance with these interventions is usually poor. In one study (42), >11% of patients took less than three quarters of the amount prescribed and an additional 20% refused to take the supplements altogether. Despite this, intensive use of oral supplements has been shown to increase serum albumin modestly (41) and improve subjective global assessment and quality-of-life measures (43). Unfortunately, given the variability in study design and supplement composition, as well as the small size of many analyses (44), no clear patient outcome data are available on the use of oral supplements. As a result, few consensus data are available to guide clinicians in protein and/or caloric prescriptions for patients with ESRD. This is especially true in pediatrics, where catabolism and malnutrition may limit child development.

Attempts have been made to increase more aggressively protein stores in dialysis patients by administering intradialytic parenteral nutrition (IDPN), and early studies suggest benefit in patient outcomes (45,46). The rationale for this approach is that one can administer large amounts of calories and protein quickly and efficiently (albeit in smaller amounts than can be attained with daily total parenteral nutrition), and the infusions can be given during the dialysis sessions, which themselves are catabolic. In fact, the administration of oral supplements during the dialysis session may also have utility in counteracting the catabolic nature of the dialysis sessions (42,47). The IDPN approach has been studied carefully in a cohort of seven dialysis patients by measuring rates of protein synthesis and degradation using isotope dilution techniques (48). Although it was found that IDPN increased rates of protein synthesis and reduced protein degradation rates by 50%, these effects were not sustained beyond 2 h after dialysis. More recently, a larger randomized, controlled trial that compared IDPN and oral supplements with oral supplements alone was performed (49). Although modest increases in albumin were reported in both groups, there were no difference in survival, although both groups seemed to obtain a survival benefit compared with historic control subjects (50). At present, IDPN remains an expensive option, possibly useful, but without marked validation in controlled trials.

Promoting Anabolism: Exercise, Androgens, and Growth Hormone

Exercise is another area that has received significant attention as a countermeasure against loss of muscle mass and malnutrition in the dialysis population (51). Physical activity in the dialysis population is low as a result of many factors, including lack of clear guidelines and fear of injury, but activity has nutritional as well as important cardiovascular benefits. Current recommendations are for at least 30 min of moderate activity (e.g., walking) at least three times per week (52), although more intensive regimens may have additional utility (51). It has been well established that exercise is a potent anabolic factor that is capable of both increasing muscle protein synthesis and suppressing protein breakdown (53–55). Trials have studied the use of both aerobic activity (e.g., bicycle pedaling) and resistance training (e.g., ankle weights) during dialysis sessions. Two studies underline the potential impact of even small amounts of resistance exercise during dialysis sessions. Johansen et al. (56) showed that short periods of weight training during dialysis could increase not only quadriceps size but also quality-of-life measures; and Cheema et al. (57), as part of the Progressive Exercise for Anabolism in Kidney Disease (PEAK trial) demonstrated a decrease in C-reactive protein and a small increase in quadriceps cross-sectional area among dialysis patients who were given a 24-wk protocol of resistance.

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training. Unfortunately, in the latter study, a control group without exercise was not used (instead, comparison was with a 12-wk exercise protocol), so statistical differences between groups was minimal. A pilot study that evaluated exercise in pediatric patients with ESRD and also points toward benefits of exercise was recently published (58). At the least, it seems that improved efforts at increasing exercise among the dialysis population are cost-effective and likely to be worthwhile from both a cardiovascular and an anabolic perspective. Pharmacologic interventions to promote anabolism and muscle growth have also been used in the dialysis population. Megestrol acetate (Megace), an oral progesterone derivative, can stimulate appetite at large dosages and may increase nutritional parameters (59,60), although there are no evidence-based recommendations for its use in dialysis patients. It can be associated with numerous adverse effects, including thrombembolism, adrenal insufficiency, and gonadal failure (61,62), but adverse effects may be minimized with appropriate tapering (61). Anabolic steroids, such as intramuscular nandrolone decanoate, showed encouraging results in two recent randomized, controlled studies (56,63) without leading to significant adverse effects. The main drawback of these agents seems to be the potential for virilizing effects, especially in women (although few were seen in the published studies) and the difficulty in administration (weekly intramuscular injections). Despite these problems, anabolic steroids show promise in the management of muscle wasting and cachexia in dialysis patients. Finally, in recent years, there has been growing interest in the use of growth hormone (GH) to increase muscle mass and treat nutritional problems in the dialysis population (64). Conceptually, as a secretagogue for IGF-1, GH administration should counteract many of the hormonal imbalances in dialysis patients that lead to malnutrition and loss of muscle mass (e.g., insulin resistance, decreased IGF-1). Indeed, a large randomized, controlled trial (the OPPORTUNITY study) was developed to test the effect of daily human GH injections in dialysis patients (65); however, the trial was terminated because of recruitment problems. Conceptually, given the general suppression of IGF-1 signaling in patients with ESRD, insulin sensitizers may ultimately have a role in promoting anabolism and suppressing catabolism. As yet, there have been no careful studies of the effects of thiglitazones or other insulin sensitizers on muscle mass and nutritional status in the dialysis population.

Providing More Physiological Dialysis

As described, the dialysis process itself contributes to the general catabolic state of patients with ESRD. It is obvious that thrice-weekly intensive hemodialysis sessions inadequately replace native kidney function and produce numerous unwanted effects. In terms of minimizing hypercatabolism and muscle protein loss, there is general agreement that more physiologic renal replacement therapy is beneficial. Patients who undergo peritoneal dialysis generally report a better quality of life, although nutritionally actually have higher protein losses through the peritoneal dialysate, which can worsen their negative nitrogen balance. Efforts have been made to counter this by adding amino acids to the dialysate, but this is not widely available or of clear utility. Daily (quotidian) and slow nocturnal hemodialysis modalities have gained wider acceptance following the lead of clinicians in Ontario, Canada, and Lyon, France. Patients who used these dialysis methods showed marked improvements in most physiologic parameters (BP, volume management, and potassium and phosphorus control) compared with conventional modalities. Small studies also suggested improvement in serum albumin, prealbumin, and muscle mass (66–69).

Future Perspectives: New Markers and Therapies

Protein-energy malnutrition and muscle wasting are important, underrecognized, and complex problems in the ESRD and dialysis population. Clearly, we need better ways to measure, define, and stratify these patients in clinical practice and more effective ways to treat them. The basic science underlying these clinical problems is rapidly progressing and may soon lead to better diagnostic markers. For instance, the presence of muscle-specific ubiquitin protein ligases such as atrogin-1 and MuRF-1 or the muscle-specific actin fragment in patients may allow us to define better the presence of muscle wasting. Unfortunately, these molecular markers have been verified only in muscle biopsy samples. It is not known whether levels of these molecules circulate in the serum of patients with cachexia as well. Although the ideal treatment for muscle wasting in the dialysis population remains elusive, we as nephrologists need to do a better job of promoting and exploring current therapies. Therapeutically, physicians need to promote, as much as possible, exercise programs and physical activity to their patients (70). Pharmacologic therapy with anabolic steroids and, potentially, GH showed promise in early studies. Other, more specific anabolic agents, such as specific androgen receptor modulators, are in early clinical trials and may afford an oral alternative to injectable steroids, with fewer adverse effects (71). Further in the future, it seems likely that agents that are capable of specifically inhibiting inflammation (72), the proteasome (e.g., bortezomib, Velcade), or muscle-specific ubiquitin-protein ligases may ultimately be most useful to prevent or reverse the biochemical changes that lead to these complications.

Disclosures

None.

References

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