Optimal Nutrition, Exercise, and Hormonal Therapy Promote Muscle Anabolism in the Elderly

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Trauma, surgery, or other stress cause a catabolic loss of muscle mass. The clinical implications of this catabolic response were first fully appreciated by Cuthbertson. Since that time, results of extensive research have enabled development of therapeutic approaches to ameliorate the potentially devastating impact of muscle protein catabolism in young, previously healthy individuals. Nonetheless, it may not be possible to entirely prevent loss of muscle mass in young, previously healthy individuals. Clinical impressions suggest that the catabolic response to stress is of even greater concern in the elderly, because of the limited muscle mass of many elderly individuals before injury and surgery. So even a small loss of muscle protein in elderly surgical patients may be sufficient to significantly affect rehabilitation and ultimately have long-term effects on muscle strength and function. Even a modest catabolic response in an elderly person who already has limited muscle strength and function could have a negative impact on quality of life and increase the risk of falls and injury. The ultimate result of loss of muscle mass and function is the inability to live independently. The potential physiologic impact of loss of muscle mass is not limited to long-term rehabilitation. In young, healthy individuals, a 5% loss in muscle mass in the acute setting (e.g., intensive care unit) can impair organ function and wound healing, and a loss of more than 20% of muscle mass can cause organ failure and death. There are no data available about the clinical impact of muscle loss in the elderly in the acute response to stress, but it is likely to be at least as devastating as in younger patients.

The central role of muscle in whole body protein metabolism

To fully understand the clinical significance of altered muscle metabolism after surgery, it is necessary to understand the role of muscle protein as a reservoir for amino acids for other organs and tissues. Maintenance of the protein content of certain tissues and organs, such as skin, brain, the heart, and liver, is essential for survival. For example, given the turnover rate of skin protein, a modest discrepancy between the rates of protein breakdown and synthesis could quickly result in sufficient loss of skin integrity to be incompatible with life. In the postabsorptive state, these essential tissues and organs rely on a steady supply of amino acids through the blood to serve as precursors for the synthesis of new proteins to balance the persistent rate of protein breakdown that occurs in all tissues. Skeletal muscle protein is the only reserve of amino acids in the body that can tolerate a significant loss in mass without jeopardizing life. In the fed state, skeletal muscle protein is the only reserve of amino acids in the body that can tolerate a significant loss in mass without jeopardizing health or survival. So whenever nutrients are not being absorbed, there is a net breakdown of muscle protein (i.e., the rate of breakdown exceeds the rate of synthesis). The resulting release of amino acids is sufficient to maintain blood amino acid concentrations. This steady supply of amino acids matches the requirements of essential tissues and organs for precursors to maintain their protein mass. So the protein mass of essential tissues and organs can be maintained despite the absence of nutritional intake.

The demands for amino acids in most organs and tissues vary significantly from the fed to postabsorptive states. For example, there is no net loss of skin protein in the fasting state, and there is no gain of skin protein in the fed state. Rather than building up surplus protein in essential tissues and organs, the primary fate of ingested amino acids is incorporation into muscle protein to replete the reserves of amino acids lost in the fasting state. So maintenance of muscle mass necessitates that gains in protein mass in the fed state balance the loss of protein in the postabsorptive state.

The stressed state imposes greater demands for amino acids. Physiologic responses necessary for recovery may
include accelerated synthesis of acute phase proteins in the liver, synthesis of proteins involved in immune function, and synthesis of proteins involved in wound healing. For example, quantitative studies of wound healing enable the calculation that a protein intake of more than 3 g protein/kg/day would be necessary to provide necessary precursors for the synthesis of proteins required for normal healing of a 50% burn injury. Coupled with the continued amino acid requirement of most tissues and accelerated requirements for tissues such as immune cells and liver, actual use of protein may exceed 4 g protein/kg/day. This represents four times or more the normal daily intake of protein for an elderly individual.

From a teleologic perspective, it is not surprising that a stimulation of the net breakdown of muscle protein to provide extra amino acids is central to the metabolic response to stress. The intensity of the stimulus for muscle catabolism is of such magnitude that even with high caloric and high protein intake, muscle catabolism persists. This persistent muscle protein breakdown ensures an adequate supply of amino acids to the blood, but at the same time results in a rapid loss of muscle protein. The extent of muscle mass loss is related to the severity of the stress.

The inactivity of the bed rest component of hospitalization alone is sufficient to cause a loss of muscle mass. More importantly, bed rest primes the muscle to respond more briskly to the catabolic stimuli of stress. Recovering from severe injury, which generally couples inactivity and a catabolic response, causes a rapid rate of loss of muscle protein. In response to severe burn injury, for example, the rate of muscle protein loss in the postabsorptive state may exceed the normal rate by three- to fourfold.

**Solutions to muscle loss**

The principal factors contributing to muscle loss are insufficient nutrition, including ineffective use of nutrients; inactivity; and hormonal alterations, especially the accelerated release of the catabolic hormones cortisol, catecholamines, and glycogen; and resistance to the normal action of insulin. Accordingly, approaches to countering muscle loss include hormonal therapy, exercise, and nutrition. But even in the most optimal circumstance, it is possible only to ameliorate muscle loss after severe stress. Consequently, the reserve of muscle is inevitably drawn on, and if there are limited reserves, the results of the catabolic response, even if treated optimally, may compromise recovery to maximal function. So presumptive building up of muscle protein reserves before surgery, when feasible, is likely to result in the best outcomes. The most effective approach to increasing muscle mass should be based on altered metabolic state of muscle in the elderly individual.

**Effect of age on basal muscle protein synthesis**

From the discussion of the cyclic nature of net muscle protein balance in the fed and fasted states, it follows that the progressive loss of muscle protein with aging could be from accelerated loss in the fasting state or impaired accretion in the fed state. We have quantified the basal rates of muscle protein synthesis in young and elderly subjects. No difference was found between young and elderly (n = 26). So loss of muscle mass with aging likely occurs either because of a diminished response to the normal anabolic response to the intake of nutrients, inadequate nutritional intake, or lack of muscular activity.

**Response of elderly to nutrient intake**

Nutritional supplements have traditionally been ineffective in improving muscle mass in the elderly. One possible explanation is ineffective use of the supplement. An alternative possibility is that ingestion of a supplement in elderly may result in a diminished intake of other food of equivalent caloric value, so the supplement is really a substitute for other food normally in the diet. The supplement must be more effective at promoting net muscle protein synthesis than the normal diet to increase muscle mass. But this does not appear to be the case with many commercially available supplements. Consequently, we have performed a series of studies to determine the optimal formulation of a nutritional supplement that stimulates muscle protein synthesis more effectively than normal food or intact protein.

**The role of amino acids in controlling muscle protein synthesis**

Elevation of blood amino acid concentrations, either as a result of ingestion or infusion of exogenous amino acids or protein, stimulates muscle protein synthesis (Fig. 1). The magnitude of response is dependent on the dose given, the profile of amino acid mixture, and the nature and amount of nonprotein energy substrates ingested with protein. The dose response to amino acid intake differs between young and elderly. In younger
subjects, increasing the dose of essential amino acids (EAAs) from 7 g to 15 g resulted in a proportionate increase in muscle protein synthesis. The response to 7 g of EAAs in elderly subjects was diminished, yet the response to 15 g of EAAs was similar in elderly and young (Fig. 2). Expressed differently, increasing the dose of EAAs in elderly individuals resulted in a disproportionately greater increase in muscle protein synthesis. There are two possible explanations. A recent study found a diminished responsiveness of the factors responsible for initiation of muscle protein synthesis in elderly rats. If activation of these factors is required for amino acids to stimulate muscle protein synthesis in human subjects, and there is a diminished responsiveness in the elderly similar to that observed in elderly rats, then a greater dose of amino acids would be required to activate initiation of synthesis. Another contributing factor could be that a greater proportion of ingested amino acids is extracted by the splanchnic bed of elderly individuals. Whatever the mechanism explaining the data shown in Figure 2, the clinical implication is clear. To be effective, a large dose of supplemental amino acids is likely required to elicit robust stimulation of muscle protein synthesis in elderly individuals.

The general principles described previously likely apply equally to the response to protein and amino acids. The unique aspect of amino acid supplementation is the capacity to formulate mixtures to specifically target the stimulation of muscle protein synthesis. For example, we have shown that only the EAA component of the profile of amino acids replicating beef protein is required to stimulate muscle protein synthesis in the elderly. In addition, if the mixture of EAAs is modified so that leucine is 40% of the profile, a further stimulation of muscle protein synthesis is achieved. The result of the “targeted” nutritional formulation of an amino acid supplement is an approximate fourfold amplification of the anabolic effect of whey protein on a gram-per-gram basis. When this targeted nutritional supplement was provided over a 16-week period to insulin-resistant elderly subjects, not only did lean body mass increase, but total fat mass decreased.

**Nutrition and exercise**

Common experience tells us that resistance exercise increases muscle mass, but numerous quantitative studies have shown that even a very strenuous resistance exercise workout alone fails to induce an anabolic state in muscle. Rather, exercise primes the muscle to the anabolic action of exogenous amino acids. Exogenous amino acids alone can produce an anabolic state in muscle, but earlier performance of resistance exercise amplifies the response of muscle to the same dose of amino acids (Fig. 3). So it is the interactive effects of exercise and nutrient ingestion that produce an anabolic response in muscle. These results underscore the importance of exercise in maintaining muscle mass in the elderly. Unfortunately, prolonged bed rest is a conventional aspect of the hospitalized elderly patient. The result of bed rest is the opposite of exercise—bed rest desensitizes the muscle to anabolic action of both amino acids and insulin. Consequently, every effort should be made to exercise elderly surgical patients. In particular, a program including resistance exercise plus amino acid and protein supplementation...
before surgery (if feasible) would prepare individuals for the upcoming catabolic stress.

**Hormonal therapy in elderly men**

Regardless of the amount of exercise or the adequacy of nutritional intake, muscle mass still declines with advancing age. In elderly men, the decline in muscle mass is related to a decline in serum testosterone. Consequently, we performed a study in which serum testosterone levels in elderly men were increased to normal levels for young, healthy men. This was accomplished by weekly or biweekly intramuscular injections of 200 mg testosterone enanthate. Significant gains in both muscle size and strength were achieved in the absence of any concomitant change in either activity level or diet. No adverse effects were observed including changes in liver function, prostate volume as determined by ultrasound, or urine flow rate.

In summary, the following conclusions can be drawn:

1. Muscle plays a central role in whole body protein metabolism and the response to stress.
2. Increased intake of amino acids stimulates muscle protein synthesis.
3. There is an interactive effect between exercise and amino acids on muscle protein synthesis.
4. Restoration of testosterone levels comparable to that of young adults improves muscle mass and strength in elderly men.

**Clinical implications with regard to surgery in the elderly**

There are few experimental data about the response of muscle metabolism to surgery in the elderly. But reasonable extrapolations can be made from the information presented here and the abundant data about the response of younger individuals to surgery. It is clear that elective surgery should be preceded by a combination of exercise and increased protein and amino acid intake. In this context, it is important to recognize that standardized meal replacements designed for the elderly do not contain a high proportion of protein. The recommended increase in protein intake can most readily be accomplished with ingestion of a pure protein supplement, such as whey protein.

The greatest threat from muscle mass loss as a result of surgery is that muscle function will be reduced below the level required for independent living. Increasing the reserve before surgery will provide a greater cushion. After surgery, increased protein and amino acid intake will amplify the beneficial effects of rehabilitative exercises. Finally, restoration of normal testosterone levels in elderly men to those of young healthy men could be useful approaches for improving function after surgery. Treatment with oxandrolone, a synthetic steroid analogous to testosterone, has increased muscle mass and function in severely burned children. Experiments on hormonal replacement after surgery are warranted to prove both the value and safety of the treatment.

**REFERENCES**


