



The MOSS NUTRITION REPORT

Jeffrey Moss, DDS, CNS, DACBN >> jeffmoss@mossnutrition.com >> 800-851-5444 >> www.MossNutrition.com

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SARCOPENIA UPDATE: ANABOLIC RESISTANCE PART I:

WHAT IT IS, ITS IMPACT ON CHRONIC ILLNESS, AND IDEAS ON CLINICAL MANAGEMENT

INTRODUCTION

As was mentioned in the last *Moss Nutrition Report*, the primary focus of **Entry Level Clinical Nutrition™ (ELCN)** is optimization of quality of life issues relating to patient chief complaints in chronically ill patients using methodologies that are not only efficacious but practical and time and cost effective. Interestingly, with these criteria in mind, my desire to constantly refine and improve **ELCN** inevitably leads me back to an organ system that I feel, even now, does not get the attention and respect it deserves from practitioners and patients alike – skeletal muscle. Why? More and more published literature continues to suggest that sarcopenia, or loss of muscle mass, is an incredibly important factor in determining quality of life issues as we age. Furthermore, when malnutrition is added to the equation which, as suggested in the quote below, is very prevalent in older, ailing populations, sarcopenia becomes even more important in controlling the ability to engage in the main activities that determine the degree of quality of life for most Americans. In the paper “Impact of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients: A randomized controlled trial” by Bouillanne et al (1) the authors emphasize the major role that the potent combination of sarcopenia and malnutrition play in influencing quality of life and chief complaint issues

“Aging *per se* is responsible for a gradual loss of skeletal muscle mass (40% from 20 to 80 years of age) and muscle function, termed sarcopenia. Sarcopenia is a major cause of the increased prevalence of

disability, falls, morbidity and mortality in elderly people. Malnutrition greatly accelerates sarcopenia in elderly subjects, in whom it preferentially induces a loss of lean muscle mass, unlike younger, similarly malnourished patients, in whom a loss of fat mass is preferentially induced. The prevalence of malnutrition in the elderly is between 30% and 78% on hospital admission. It is the most common cause of decreased skeletal muscle mass and strength and secondary immune dysfunction.”

Therefore, as suggested by the above quote, sarcopenia, which has been traditionally defined as purely an issue of aging, is actually, from a clinical standpoint, an issue involving a combination of factors, of which diet is at the forefront. However, when considering diet and its relationship to sarcopenia, is the problem exclusively a factor of optimal food intake and optimal digestion and absorption? Those of you who have been following my newsletters on **ELCN** over the last three years or so know that the answer to this question is a resounding “NO”. For, a large body of research under the heading of the “acute/chronic phase response” indicates that sickness, whether it is acute or chronic, introduces powerful catabolic factors that are driven by increased production of inflammatory mediators and stress hormones. These catabolic factors lead to profound changes in the way even optimal forms of nutrients that are absorbed in an optimal fashion are metabolized. Therefore, the **ELCN** model, which is based on nutritional modalities employed by critical care nutritionists, suggests that, to optimally address sarcopenia and the associated compromises in quality of life, we must not only address traditional issues of poor diet and malabsorption but factors that adversely affect systemic nutrient metabolism such as low-grade, chronic metabolic acidosis, insulin resistance, and chronic inflammation.

ANABOLIC RESISTANCE: HOW CHRONIC INFLAMMATION AND INSULIN RESISTANCE CONTRIBUTE TO SARCOPENIA

How, specifically do issues such as insulin resistance and chronic inflammation adversely affect the ability of a quality diet to optimize muscle mass and function? This question was answered in a fascinating way by the paper “Muscle wasting and resistance of muscle metabolism: The ‘anabolic threshold concept’ for adapted nutritional strategies during sarcopenia” by Dardevet et al (2).

To begin the paper, the authors answer the question as to why factors such as insulin resistance and chronic inflammation are designed, as just one of their functions, to keep dietary factors, especially amino acids and protein, from optimizing muscle mass. The reason has to do with the fact that one of the functions of muscle is to act as a storage depot for amino acids and proteins:

“The main function of skeletal muscle is to provide power and strength for locomotion and posture, but this tissue is also the major reservoir of body proteins and amino acids.”

Therefore, when needed in stressful situations, factors such as insulin resistance and inflammation will redirect protein and amino acids away from muscle and towards formation of factors such as the pro-inflammatory acute phase protein, C-reactive protein (as I have discussed in previous newsletters). This key point is elaborated upon in the following quote:

“Although each muscle wasting situation is characterized by its specific mechanism(s) and pathways leading to muscle loss, an increase of catabolic factors such as glucocorticoids, cytokines, and oxidative stress, often occurs and it is now well established that these factors have potential deleterious effects on the amino acids or insulin signaling pathways involved in the stimulation of muscle anabolism after food intake.”

What is the net result of this redirecting of protein and amino acids away from muscle and towards other entities that have been deemed a higher priority? The authors state:

“These signaling alterations lead to an ‘anabolic resistance’ of muscle even if the anabolic factor requirements (amino acids e.g.) are theoretically covered, that is, with a normal nutrient availability fitting the recommended dietary protein allowances in healthy subjects.”

Because of this “anabolic resistance,” the threshold amount of factors needed to stimulate increases in muscle mass and strength are increased:

“This anabolic resistance may be in part explained by an increase of the muscle ‘anabolic threshold’ required to promote maximal anabolism and protein retention. Because the muscle ‘anabolic threshold’ is higher, the anabolic stimuli (including aminoacidemia) cannot reach anabolic threshold anymore and by consequence, muscle anabolism is reduced with the usual nutrient intake.”

As I hope you can see – if our priority is to optimize the many quality of life issues our patients present, which are related to muscle mass and function, the clinical manifestations of this reality of chronic illness are profound and immediate. As the numbers of elderly, ailing, overweight baby-boomer Americans continue to mushroom, the aging but still often used platitude touted by various government and industry organizations who maintain an anti-supplement stance stating that most Americans, being healthy, only need 0.8 grams protein per kilogram body weight, which can easily obtained from dietary sources, must now, except in rare instances of the true, optimally healthy American, be filed away along with the typewriter and the rotary telephone. In contrast, several papers that I have reviewed in previous newsletters make it clear that elderly and /or ailing populations generally require 1.2 grams protein per kilograms per day or more to optimize muscle mass and function, for reasons emphasized by Dardevet et al (2) and their discussion about “anabolic threshold.” While this amount of quality protein can theoretically be obtained through diet alone, from a practical standpoint, most Americans are unwilling to spend the amount of time with shopping, food preparation and actual dining to make long term ingestion of this amount of protein a reality. What is the best, most cost and time effective way to use supplementation to meet these more rigorous

protein needs? This question will be answered in part II of this series.

Dardevet et al (2) continue their discussion by giving a basic overview of how to address elevated anabolic resistance nutritionally:

“A possible nutritional therapy is then to increase the intake of anabolic factors (especially amino acids) to reach the new ‘anabolic threshold.’ There are several ways to increase amino acid availability to skeletal muscle: increase protein intake, to supplement the diet with one or several free amino acids or to select the protein source on its amino acid composition and physicochemical properties when digested in the digestive tract.”

Next the authors discuss the underlying biochemistry and physiology that underlie anabolic resistance.

“Sarcopenia, as other catabolic states, has been found to result from a decreased response and/or sensitivity of protein synthesis and degradation to physiologic concentrations of amino acids. This is related to a defect of the leucine signal to stimulate the mTOR signaling pathway activity.”

Can this defect in leucine signaling be addressed by just supplementing with leucine? Not really, as noted by the authors:

“Choosing free leucine as a supplement over a normal protein diet creates a desynchronization between leucine signal and the rise in all amino acids. Indeed the free leucine is absorbed immediately whereas the other amino acids are released later after gastric emptying and proteolytic digestion in the gut. This nonsynchronization between the stimulation of muscle leucine-associated protein metabolism pathways and the delayed availability of amino acids as substrates can explain that protein anabolism was only stimulated for a very short period of time during the postprandial period and then could not translate into a significant muscle protein accretion.”

With the above in mind, it could be suggested that a solution would be to give leucine in conjunction with a quality protein such as whey protein. While this hypothesis may have validity from an academic standpoint, it was not very successful when considering overall improvements in muscle mass in animal studies:

“Studies with a synchronized leucine signal and amino acid availability have been performed by using leucine rich proteins that are rapidly digested (whey proteins). With such proteins, leucine availability is increased simultaneously with the other amino acids to reach the increased muscle anabolic threshold. However, as observed for free leucine supplementation, when such dietary proteins were given on the long term in elderly rodents, muscle anabolism was acutely improved but muscle mass remained unchanged.”

Why wasn't the combination of leucine and whey protein effective in increasing muscle mass? The answer lies with duration. The authors suggest that levels needed after absorption to overcome anabolic resistance did not last long enough to have a significant effect on muscle mass:

“According to these data, it can be concluded that besides counteracting the muscle anabolic resistance, the duration during which the anabolic resistance is muzzled also plays a critical role in leading to a significant muscle protein accretion. A prolonged stimulation could not be achieved with fast proteins at normal dietary level (even enriched with leucine) since the concentration of amino acids as substrates declines rapidly after their intake.”

What is the solution? Dardevet et al (2) suggest a form of “pulse feeding” where the majority of the ideal daily requirement is ingested at one meal:

“However, by strongly increasing protein intake, such ideal situations could be nevertheless achieved. The ‘protein pulse feeding’ initially developed by Arnal et al. have shown that, by concentrating 80% of the total daily protein intake in one meal, protein retention was improved in elderly women subjected to such a nutritional strategy. Similarly, when very large

amounts of amino acids (wherein leucine formed the highest percentage of the mixture), positive results have been observed.”

Of course, I would expect that you would be rightfully questioning the practicality of this approach as well as its safety in terms of renal function. As noted by the authors, you would not be alone with this concern:

“The above nutritional strategies discussed raised the problem that the organism has to cope with large amounts of nitrogen to eliminate. This point can be critical with already frail sarcopenic subjects or patients for whom the renal function will be oversolicited whereas it may already be altered.”

Because just raising protein/amino acid intake to a high enough level to overcome anabolic resistance may not only be impractical but possibly risky, another option might be to, in addition to raising protein/amino acid intake in a more practical, safe fashion, employ an ELCN-type of approach where the factors that lead to the anabolic resistance in the first place are also addressed. This is exactly what Dardevet et al (2) suggest:

“In order to minimize this deleterious side effect of high protein intake, a strategy to reverse the increase in the ‘anabolic threshold’ would restore the anabolic stimulation during the postprandial period with lower intake of dietary proteins or amino acid supplementation. This requires the knowledge of the factors involved and responsible in the ‘anabolic threshold’ elevation. The causes can be multiple and specific for each catabolic state. However, most of these muscle loss situations have in common an increase of the inflammatory status. Regarding aging, levels of inflammatory markers, such as interleukin-6 (IL6) and C reactive protein (CRP), increase slightly, and these higher levels are correlated with disability and mortality in humans. Even if the increase is moderate, higher levels of cytokines and CRP increase the risk of muscle strength loss and are correlated with lower muscle mass in healthy older persons. We have recently shown that the development of a low grade

inflammation challenged negatively the anabolic effects of food intake on muscle protein metabolisms and that the pharmacologic prevention of this inflammatory state was able to preserve muscle mass in old rodents. A resensitization of muscle protein synthesis to amino acids could also be achieved with other nutrients such as antioxidants.”

The authors conclude by emphasizing that the usual diet cannot increase muscle mass in inflamed and/or elderly patients because of an increased “anabolic threshold” in the muscle of these patients. To overcome this challenge, a two-fold approach is recommended that involves both increasing protein/amino acid intake with emphasis on leucine and addressing factors such as inflammation that caused the increase in “anabolic threshold”:

“Two strategies can be used (alone or in combination) to deal with this decreased ‘efficient’ postprandial period: (1) by increasing the anabolic signals and particular amino acid availability; however, it is necessary to synchronize the anabolic stimuli with the substrates in order to optimize the incorporation of amino acids into muscle proteins; (2) by increasing the efficiency of the postprandial period with strategies aiming at partially restoring (i.e., decreasing) the muscle ‘anabolic threshold’.”

In part II of this series I will review research that goes into detail about how protein and leucine supplementation in amounts that are practical from a clinical standpoint can effectively increase muscle mass.

MORE RESEARCH ON ANABOLIC RESISTANCE

The next paper I would like to discuss is “Skeletal muscle protein metabolism in the elderly: Interventions to counteract the ‘anabolic resistance’ of aging” by Breen and Phillips (3). In this paper the authors provide both additional detail about the biochemical and metabolic nature of anabolic resistance and options concerning correction of this abnormality. Breen and Phillips (3) begin by emphasizing the contribution that sarcopenia makes to this incidence of the most common chronic maladies seen in this country today:

“...aging is accompanied by numerous increasingly prevalent clinical conditions such as rheumatoid- and osteoarthritis, vascular disease, Type II diabetes, and osteoporosis that require extensive health care resources, which can lessen the quality of life, and reduce independence.

Contributing to the risk of these diseases or as a direct predictor of disability itself, is the slow and inevitable age-related decline in skeletal muscle mass, referred to as sarcopenia.”

Next, the authors emphasize a continuing theme of my discussions on ELCN that chronic illness is not a function of a single issue, whether it is sarcopenia or any other entity. Rather, chronic illness is a culmination of several factors coming together:

“Age-related sarcopenia begins in our 4-5th decade and proceeds at ~0.6% annually thereafter. Such a rate of sarcopenic muscle mass loss would not likely have overly dire consequences; however, during periods of muscle disuse/unloading that occur with increasing frequency in the elderly, for example, due to illness or hospitalization, the rate of sarcopenic muscle is exacerbated. Following such periods of disuse, even something as benign as a reduction in daily step counts, can accelerate sarcopenic muscle loss, from which it is more difficult for the elderly to require.”

The next quote from this paper that I would like to feature goes into more detail about how inflammation can impair muscle protein synthesis (MPS):

“In humans, Toth et al. have shown a strong relationship exists between MPS and circulating concentrations of several markers of immune activation. At the mechanistic level, cytokines, in particular TNF- α , may impair MPS by blunting the phosphorylation of proteins in the mammalian target of rapamycin (mTOR) intracellular signaling pathway; shown to be critical for the regulation of mRNA translation and MPS for muscle hypertrophy.”

In addition, physical inactivity can have much the same effect as inflammation on muscle protein synthesis:

“In addition to age-related phenomenon, there is no doubt that physical inactivity per se has a detrimental effect of rates of MPS. In young adults, a reduction in physical activity through cast-induced immobilization of the legs blunts basal and amino-acid stimulated rates of MPS. Thus, it is apparent that disuse induces anabolic resistance in skeletal muscle. Recent work also indicates that even short-term abrupt sedentarism, leading to a reduced relative loading of skeletal muscles, results in loss of muscle mass in the legs.”

Addition information on leucine and anabolic resistance

The previous paper discussed by Dardevet et al (2) introduced the idea that the amino acid leucine plays an important role in reducing anabolic resistance. Breen and Phillips (3) provide much more detail on this crucial relationship:

“The mechanism facilitating the impaired dose-response of MPS to amino acids in the elderly compared with the young is still elusive. However, we and others have hypothesized the existence of a leucine ‘threshold’ that must be surpassed after protein ingestion to stimulate MPS above rest. This threshold is not absolute and is graded with lower leucine stimulated responses in young persons, whereas the elderly become less sensitive and the threshold becomes higher. The leucine threshold hypothesis is based on a number of recent observations, the most striking of which is that leucine ingestion/infusion results in a phosphorylation of proteins critical for the mTOR pathway. We postulate that young muscles are more sensitive to the anabolic actions of leucine as ~1 g of orally ingested leucine seems to be sufficient to stimulate MPS above rest. In contrast, our recent observations indicate that the elderly are less sensitive to the anabolic actions of leucine as ~2 g of leucine found in 20 g of whey protein was required to increase MPS rates above rest.”

Next, additional research is discussed concerning the amount of leucine necessary to help counteract anabolic resistance:

“Consistent with the thesis that leucinemia is important in ‘driving’ MPS, the work of Katsanos and colleagues demonstrated that 6.7 g of essential amino acids (EAA) (equivalent to ~15 g whey), increased MPS above rest in the elderly, but only after the leucine content of EAA’s was increased from 26 to 41% (1.7 to 2.8 g). In line with our hypothesis that younger muscles are more anabolically sensitive, the 26% low leucine treatment in this study was sufficient to increase MPS in the young. Thus, when considering protein feeding strategies that will acutely increase MPS in the elderly, a protein source with high leucine content and rapid digestion kinetics, in order to promote a transient leucinemia ‘spike’ would be an effective option.”

However, it must be kept in mind that leucine must be ingested along with other amino acids to be effective in stimulating MPS. Breen and Phillips (3) point out:

“A recent study by Verhoeven and colleagues was the first, to our knowledge, to investigate the long-term effects of free leucine supplementation (7.5g per day) in the elderly. The authors showed no effect of leucine supplementation on muscle mass or strength compared with a non-supplemented placebo group. One possibility is that free-leucine simply ‘turns on’ mRNA translational processes, but other essential amino acids are required to facilitate the anabolic actions of leucine and promote hypertrophy. Another suggestion is that leucine supplementation may need to be provided over a much longer period (i.e. > 8 months) than has previously been studied.”

As I suggested before, in part II of this series I will discuss other papers that present specific recommendations about optimal dosing of protein/essential amino acid combinations that are fortified with additional leucine.

To conclude their paper, Breen and Phillips (3) discuss other treatment modalities that can be implemented to increase MPS in the elderly.

Resistance exercise and anabolic resistance

Of course, we are all aware that resistance exercise can, in a very predictable manner, increase muscle mass. However, given that much, or even most, of the research on resistance exercise and muscle mass has been performed on young subjects and/or athletes, the question needs to be asked whether the results of these studies can be extrapolated to the sarcopenia seen in older patients. According to Breen and Phillips (3), the answer to this question is a qualified yes:

“Resistance exercise acutely increases muscle protein synthesis and, when practiced frequently over time, promotes muscle hypertrophy in older adults, although the anabolic response is generally blunted compared with younger adults. It has been suggested these divergent responses to resistance exercise may be due to the fact that the elderly generally lift a much lower volume of weights than the young. However, we suggest that resistance to the anabolic nature of hypertrophic exercise may be critical in mediating the muscle adaptive remodeling in the elderly.”

This quote, of course, further emphasizes the contention I have made in discussing the ELCN approach that, unlike younger healthy individuals who can very often derive benefit from single modality interventions; ailing older individuals will require a multiphasic approach to realize optimal benefit. Therefore, our typical chronically ill patients will gain the most benefit from resistance exercise when we combine it with other modalities that include the dietary change discussed above plus that which follows – polyunsaturated fatty acids.

Polyunsaturated fatty acids and anabolic resistance

Given the significant catabolic impact of chronic inflammation on lean muscle mass, it is not surprising that several studies would suggest that omega-3 fatty acid ingestion might counteract anabolic resistance. Breen and Phillips (3) point out:

“Fish-oil-derived omega-3 fatty acids (n-3 polyunsaturated fatty acids) might be a potentially useful therapeutic agent for the treatment and prevention of sarcopenia. Initial studies in animals showed that supplementation with omega-3 fatty acids increased the phosphorylation of anabolic signaling proteins, whole body protein synthesis and attenuated the loss of muscle mass in burned animals. In elderly humans, Smith et al. showed that 8-weeks of omega-3 fatty acid supplementation augmented hyperinsulinemic-hyperaminoacidemic induced increases in muscle protein synthesis and mTOR signaling, suggesting that omega-3 fatty acids attenuate age-related anabolic resistance.”

What is the mechanism of this effect? As suggested above, it most likely lies with the anti-inflammatory properties of omega-3 fatty acids:

“Whilst the exact mechanisms by which omega-3 fatty acids act on translational signaling and muscle protein synthesis in the elderly are not entirely clear, the anti-inflammatory properties of omega-3 fatty acids may be a critical factor, particularly in the frail elderly who display elevated levels of inflammation.”

However, other research suggests that the anti-inflammatory effects of omega-3 fatty acids are just the beginning:

“On the other hand, recent evidence suggests that fatty acids may have intrinsic

muscle protein anabolic properties, as long-chain n-3 polyunsaturated fatty acid supplementation augments hyperinsulinemic-hyperaminoacidemic stimulated muscle protein synthesis in healthy young subjects, in whom inflammation would be expected to be relatively low. Taken together, these data suggest that fatty acid supplementation alone is insufficient to promote an anabolic response (as basal muscle protein synthesis is not increased). Instead, additional stimuli, such as amino acids, may be required to permit the anabolic effect of fatty acids.”

Again, as stated in the above quote, the need for a multiphasic approach towards sarcopenia and, indeed, all chronic illness must be emphasized. Even though the media, certain popular authors and lectures, and major supplement companies continue to suggest both to the public and the allopathic and alternative health care communities that single intervention “panaceas” are the surest path to optimization of health, quality research papers such as the one I have just reviewed by Breen and Phillips (3) suggest otherwise. Therefore, I will continue to emphasize the broad-based approach of **Entry Level Clinical Nutrition™** as the most predictable path to resolution of chief complaints and quality of life improvements in chronically ill patients.

In part II of this series on anabolic resistance and its correction, I will be examining in detail some of the most current research on the use of protein and amino acid supplementation to optimize muscle mass and function.

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