

Nutrition and muscle protein synthesis: a descriptive review

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Background: *Doctors of Chiropractic frequently give therapeutic exercise and nutritional advice to patients. Skeletal muscle's role in health and disease is underappreciated. Creating synergy between protein consumption and exercise promotes protein synthesis and may impact patient outcomes.*

Objective: *To review the literature describing protein metabolism and exercise as it relates to the practice of chiropractic health care.*

Method: *The PubMed and Web of Science databases were searched using the key terms protein metabolism, protein synthesis, exercise, whey, soy, and resistance training in various combinations. Limits excluded the use of papers that were not based on human subjects, included infants or disease, or were published before 1988. Thirty papers were ultimately included for analysis.*

Discussion: *The amount, type and timing of protein consumption all play critical roles in promoting protein synthesis. The intracellular mechanism behind protein synthesis has many interrelated, interesting components.*

Conclusion: *An adaptation to exercise (protein synthesis) can be enhanced by controlling the type of protein, the amount of protein consumed and the timing of protein consumption. Doctors of Chiropractic may impact patient outcomes by using empirical evidence about protein consumption and exercise to maximize protein synthesis.*

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Données fondamentales : *Les praticiens en chiropratique recommandent souvent à leurs patients des exercices thérapeutiques et des conseils sur la nutrition. On sous-estime le rôle que jouent les muscles squelettiques dans la santé comme dans les maladies. Créer une synergie entre la consommation de protéines et l'exercice favorise la synthèse des protéines et peut avoir des répercussions chez le patient.*

Objectif : *Passer en revue la documentation décrivant le métabolisme de la protéine et l'exercice et la façon dont le tout est relié à la pratique des soins de santé en chiropratique.*

Méthode : *On a effectué une recherche des bases de données du PubMed et du Web of Science en utilisant les mots clés « métabolismes de la protéine », « synthèse de la protéine », « exercice », « lactosérum », « soja » et « entraînement contre résistance » ainsi que des variantes de ces derniers. On a exclu les documents ne s'appliquant pas aux êtres humains, ceux portant sur des enfants ou des personnes malades, ou qui avaient été publiés avant 1988. Trente documents ont été finalement inclus dans l'analyse.*

Discussion : *Le volume, le type et le moment de la consommation de protéines jouent tous des rôles essentiels dans la promotion de la synthèse de la protéine. Le mécanisme intracellulaire à l'origine de la synthèse de la protéine a plusieurs composantes intéressantes, qui sont interreliées.*

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Introduction

Doctors of Chiropractic commonly prescribe exercise and provide nutritional advice to patients. The National Board of Chiropractic Examiner's 2005 Job Analysis of Chiropractic Report found that 89% of chiropractors surveyed used nutritional counseling, therapy, or supplementation.¹ In addition, over 98% used corrective or therapeutic exercise within their practice of chiropractic. With regard to "Health Promotion and Wellness Care Procedures," 98.3% of chiropractors instructed patients about physical fitness/exercise promotion and 97.7% provided instruction about nutritional/dietary recommendations. Exercise prescription and/or nutritional advice, whether possessing therapeutic or wellness intent, is given with the expectation of change. Doctors and patients expect exercise to result in a positive adaptation. The desired change is fundamentally an anabolic response to synthesize protein while minimizing protein catabolism. Overtly, clinicians assess changes in strength, endurance, and/or function. The overt clinical changes are due, at least in part, to cellular changes. Whether or not the desired change occurs depends greatly on a synergistic relationship between diet and exercise. This review focuses on nutritional interventions that optimize adaptation through protein synthesis.

Method

The literature search included the use of the Web of Science and PubMed databases. Multiple combinations of the following key words were used in the search: *protein metabolism, protein synthesis, exercise, whey, soy, and re-*

Conclusion : Une adaptation à l'exercice (synthèse de la protéine) peut être améliorée en limitant le type de protéines, le volume des protéines consommées et le moment de la consommation des protéines. Les chiropraticiens peuvent avoir une incidence sur les résultats pour le patient en utilisant une preuve empirique sur la consommation des protéines et l'exercice pour maximiser la synthèse des protéines. (JACC 2009; 53(3):186–194)

MOTS CLÉS : protéine, synthèse, métabolisme, exercice, chiropratique

sistance training. This led to an initial yield of several hundred papers. When the search was limited to studies with human subjects, excluding those dealing with infants or disease (e.g. HIV) and those articles published prior to 1998 (unless their content was highly significant and seminal in establishing a line of evidence), the final yield was thirty articles on this topic.

Discussion

The primary objective of this review is to describe protein metabolism and exercise as it relates to the practice of chiropractic health care. The spine does not consist solely of bone. Skeletal muscle plays a pivotal role in providing the spine with support, movement, proprioception and endurance. When patients engage in exercise, whether it is aerobic or resistance, muscle breaks down and rebuilds protein in response to the stimulus. New empirical evidence exists that can optimize the relationship between stimulus and response. As stated previously, most Doctors of Chiropractic incorporate exercise and nutrition in practice. Recognizing and applying empirical evidence on how the type, timing and amount of protein intake influences adaptation can help doctors and patients achieve optimal results.

Importance of Skeletal Muscle

The function of skeletal muscle can be underestimated by assigning it the mere role of "moving the body." Skeletal muscle is the primary reservoir of amino acids for other tissues. In fact, skeletal muscle amino acid reserves are the only storage depot capable of large losses without

compromising the ability to sustain life.² When blood glucose falls, amino acids are the liver's primary gluconeogenic substrate. The digestive tract's rapid turnover of cells requires a continual supply of amino acids. Nitrogen contained within amino acids is a vital component of DNA and other molecules necessary for cell maintenance and replication. Tissue demands for amino acids become critical in times of stress, such as sepsis, cancer, or traumatic injury. Muscle export of amino acids can result in large protein losses or sarcopenia. Recovery from future disease or trauma may be greatly hindered by sarcopenia.³ This is of special concern for geriatric individuals that may fail to recover from disease largely as a result of sarcopenia. They become too frail and cease to thrive. Elderly individuals have a much more difficult time adding muscle;⁴ therefore, caution should be taken to preserve lean mass throughout life. Arts found the biceps brachii and quadriceps femoris muscles' mean thickness of healthy 90-year-old men to be similar to that of 5-year-old children.⁵ This is of concern when one considers the added weight an adult must carry during activities of daily living. Wolf's review³ has a more complete discussion of skeletal muscle's underappreciated role in health and disease. Doctors of Chiropractic should appreciate the value maintaining lean mass throughout life and understand the role of exercise and nutrition in protein synthesis.

This paper describes the impact of nutrition and exercise on protein synthesis. Resistance exercise is a powerful signal that can be augmented by the amount, timing and type of protein consumed. The mechanism behind protein synthesis is complex and fascinating. A more complete understanding of this topic may allow the chiropractic physician to develop more effective strategies for increasing or preserving skeletal muscle throughout life.

Resistance Exercise, Nutrition and Protein Synthesis

Skeletal muscle is continually breaking down and synthesizing protein. If muscle is going to maintain its mass, the net level of protein balance must equal zero. If muscle is going to gain mass, protein synthesis must exceed protein breakdown. While it may be common to view resistance training as a powerful stimulus for protein synthesis, it is also important to recognize that it is a signal for protein

breakdown. Phillips et al.⁶ has shown that resistance exercise results in increased muscle net protein balance for 24–48 hours. Both protein anabolism and catabolism increase after exercise, but the increase in anabolism is relatively larger, causing the net muscle protein balance to be positive. In his experiment, Phillips et al.⁶ used 8 sets of 8 concentric and eccentric muscle actions at 80% of each subject's single repetition maximum effort. The participants in the study were allowed to consume meals prior to and after the exercise. This is important, as later research showed a lack of protein synthesis after exercise when nutrition was absent.⁷ Esmarck et al.⁸ resistance trained 2 groups for 12 weeks and showed that a control group receiving no nutrition for 2 hours post-exercise decreased lean body mass while those consuming 10gm of protein immediately after exercise increased lean mass.

Both protein anabolism and catabolism are evident after resistance training. Yet, if nutrition is absent after exercise, protein synthesis can be reduced or absent. The amount of protein consumption is an important consideration for maximizing the rate and duration of protein synthesis. Borsheim et al.⁹ showed that 6 gm of mixed amino acids elevated protein synthesis after exercise. In the same experiment, 6gm of essential amino acids doubled protein synthesis, leading the researchers to conclude that non-essential amino acids were not required to promote protein synthesis. The role of non-essential amino acids in protein synthesis remains controversial. Cuthbertson et al.¹⁰ showed an oral dose of 10 gm of essential amino acids maximally stimulated protein synthesis and hypothesized that this would occur by eating the equivalent of 6 oz of meat, fish, eggs or milk in a single meal. Phillips et al.¹¹ stated that 25 gm of a quality source of protein (milk products, meat and eggs) contain approximately 10 gm of essential amino acids and should maximally stimulate protein synthesis after exercise.

Timing of Protein Consumption

The timing of protein consumption is critical for increasing protein synthesis. Immediate post-exercise consumption of protein stimulates protein synthesis while waiting as little as 2 hours after the exercise blunts the response.⁸ Rasmussen et al.⁷ found elevated protein synthesis in those consuming 6 gm of essential amino acids post-exercise in comparison to a control group. Protein was consumed either 1 or 3 hours after the exercise. In contrast

to Esmark et al.,⁸ there was no difference in protein synthesis rates in the 1- or 3-hour post-exercise groups. Tipton et al.¹² found a larger anabolic response when a carbohydrate and protein drink was consumed prior to exercise than if it were consumed immediately after exercise. In this experiment, 6gm of essential amino acids were consumed by both groups either before or after resistance training. They theorized that larger blood flow and amino acid delivery to the muscle during exercise was the reason for the observed increased protein synthesis.

Type of Protein

The type of protein consumed may also be an important factor in stimulating protein synthesis. Both soy and whey protein supplementation have been shown to increase lean mass and strength in comparison to a placebo.¹³ Candow et al.¹³ showed this with 6 weeks of resistance training in young adult humans. Anthony et al.¹⁴ found both whey and soy protein supplements promoted skeletal muscle protein synthesis more than a carbohydrate-only supplement. They noted greater intracellular signaling (phosphorylation of S6K1 and mTOR) in the group receiving whey protein compared to the soy group. Intracellular signaling will be discussed in more detail below. Anthony et al.¹⁴ used aerobic conditioning and rats in their experiment; however, this may not parallel resistance training in a human population. Wilkinson et al.¹⁵ also demonstrated both soy and milk protein's ability to increase net protein balance in humans after resistance training. They found greater fractional synthesis rate of protein and greater net muscle protein balance after milk ingestion in comparison to soy. The subjects in their experiment consumed 18.2 grams of protein shortly after exercise. Morifuji et al.¹⁶ showed whey protein supplementation in comparison to casein caused a decrease in the activity of hepatic lipogenic enzymes and increased lipogenic enzyme activity in muscle. Whey protein may give skeletal muscle an advantage in allowing it to store more energy (fat) needed for protein synthesis. It may also decrease hepatic production of fat and be helpful in combating obesity.

Tipton et al.¹⁷ published a thought-provoking study comparing the ability of casein and whey protein to stimulate skeletal muscle anabolism in response to resistance exercise. Both casein and whey are milk proteins, but whey remains soluble in the stomach and is more rapidly emptied into the small intestine. Casein exits the stomach

more slowly. They found whey protein elevated plasma and intracellular leucine levels greater than casein or the control group. Whey protein increased intracellular leucine concentration by 110% 1 hour after consumption. The whey group also had higher serum insulin concentrations after consumption. The casein group had 35% greater phenylalanine uptake in comparison to the whey group. Phenylalanine uptake positively correlates to protein synthesis. This was not a long-term study that looked at muscle accretion. The authors concluded that both casein and whey stimulate an anabolic response in muscle after exercise, but it is equivocal whether one offers an advantage over the other.

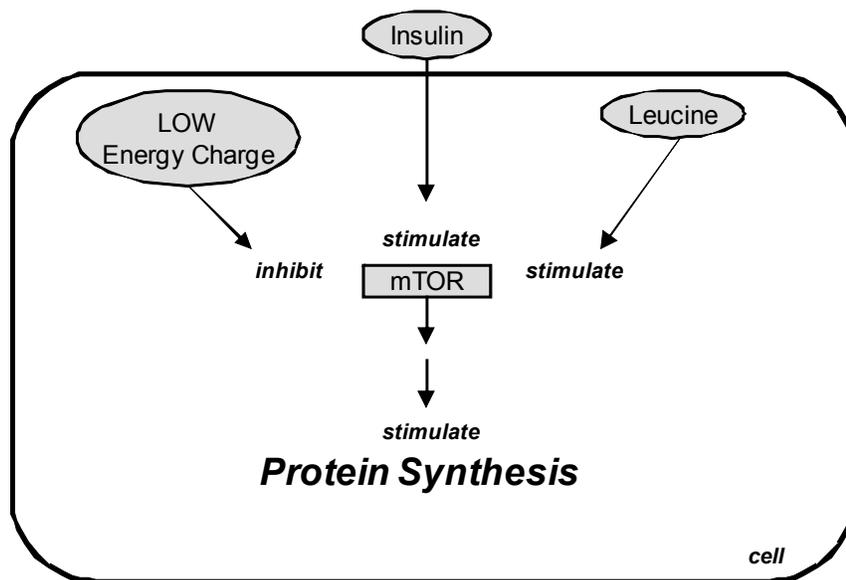
Typical measurement of protein synthesis usually involves skeletal muscle's import and export of the amino acid, phenylalanine.¹⁸ Skeletal muscle has the ability to oxidize six amino acids (leucine, isoleucine, valine, aspartate, asparagine, and glutamate). Import of these amino acids does not directly correlate to their addition in protein structure. Phenylalanine is an essential amino acid that muscle cannot oxidize. Its uptake and incorporation into muscle is assumed to be an accurate indicator of muscle protein synthesis.¹⁸

Intracellular Signaling

The results from Tipton et al.¹⁷ open a complex discussion regarding intracellular signaling and protein synthesis. Leucine, found in higher amounts in whey protein, is not just a building block in protein synthesis, but an important intracellular signal directing skeletal muscle to translate protein. A complete review of intracellular signaling is beyond the scope of this review; however, Proud¹⁹ provides a more in-depth review of the mechanisms involved in cellular protein synthesis. The following is a brief look at potential signals for increasing protein synthesis in skeletal muscle. Three key components of signaling include: the energy status of the muscle cell, insulin, and the amino acid leucine (figure 1).

Changes in the rate of protein synthesis begin prior to changes in mRNA content.²⁰ This implies a posttranscriptional mechanism plays a predominant role in activating protein synthesis. The variables affecting transcription are many, but the cell's energy charge, insulin, and leucine seem to be very important. During exercise, the cell's energy charge or abundance of ATP (adenosine triphosphate) is reduced. The mammalian target of rapamycin (mTOR)

Figure 1 Key Components of Intracellular Signaling



is seen as a “master regulator” of translation within the cell.¹⁹ There are 2 types of mTOR subunits: mTORC1 and mTORC2. When ATP levels are depressed, AMP activated protein kinase (AMPK) is activated. AMPK phosphorylates an intermediary molecule (TSC2) which turns off mTORC1 signaling. Bolster et al.²¹ have shown a negative correlation between AMPK activation and phosphorylation of mTOR and other key signaling molecules (S6K1, and 4E-BP1).

Lowering cellular ATP levels reduces protein synthesis within the cell. This seems to make sense as protein synthesis demands a great deal of energy. Adding 1 amino acid during the translation process requires the breakdown of 4 ATP molecules.¹⁹ Protein synthesis may require approximately 485 kilocalories per day in a muscular, young male and approximately 120 kilocalories per day in an active, elderly woman.³ After a good night’s sleep without consuming food, protein synthesis is decreased by 15–30 percent.²² Feeding cells after exercise allows them to maintain a high energy charge and promote ongoing protein synthesis.

Resistance exercise changes the energy status of skeletal muscle. Koopman et al.²³ documented changes in muscle glycogen and lipid levels after resistance training.

A single bout of resistance exercise reduces muscle glycogen levels in both type I and II fibers. In the experiment, 8 sets of 10 repetitions of leg presses followed by 8 sets of 10 repetitions of leg extensions lowered glycogen content by 23, 40, and 44% in type I, IIa and IIx fibers respectively. Intramuscular triglyceride (IMTG) levels were reduced by 27% in type I fibers, but remained constant in type IIa and IIx fibers. Type I fibers’ IMTG levels returned to baseline after 2 hours of post-exercise rest. Type II fibers are responsible for most of the hypertrophy seen after resistance training.^{24,25} They also suffer a greater energy drain during resistance exercise. Nutrition and intracellular energy availability substantially impact muscle protein metabolism.

Carbohydrate consumption and insulin secretion play an indirect role in skeletal muscle protein synthesis. Insulin activates the phosphoinositol-3-kinase (PI3K) pathway that causes skeletal muscle’s glucose transport protein (GLUT4) to translocate to the sarcolemma and, therefore, permits glucose to enter the cell.²⁶ In short, insulin replenishes glucose for the cell. Within the PI3K pathway, a protein (Akt) is activated that stimulates mTOR. Akt also phosphorylates and inactivates glycogen synthase kinase (GSK-3) which allows the activation of

eukaryotic initiation factor 2B (eIF2B). Both mTOR and eIF2B stimulate protein synthesis. Yet, elevated insulin levels do not increase protein synthesis in the absence of high amino acid concentrations.²⁷ Biolo et al.²⁷ hypothesized that prior experiments failed to show elevated protein synthesis in response to insulin because insulin cleared blood amino acids into other cell types creating hypoaminoacidemia during the trials. In the presence of hyperaminoacidemia, insulin appears to promote protein synthesis by aiding the amino acids' entry into cells and through tangential signaling resulting from the PI3K pathway.

Leucine is likely the most influential amino acid concerning skeletal muscle protein synthesis. Amino acids, especially leucine, stimulate the secretion of insulin from the pancreatic β cells.²⁸ The liver lacks branched-chain-aminotransferases and therefore lacks the ability to significantly oxidize branched-chain amino acids, including leucine. Consumption of branched-chain amino acids leads to elevated blood leucine levels reaching peripheral tissues, including skeletal muscle. Leucine directly stimulates mTOR as well as indirectly stimulating mTOR through its promotion of the insulin cascade.²² The Tipton et al.¹⁷ finding that whey protein greatly increases plasma and intramuscular leucine may explain the potential anabolic effect of whey consumption. Whey protein consumption elevates leucine; leucine directly and indirectly stimulates protein synthesis through mTOR.

To achieve the best response to exercise, Doctors of Chiropractic should recognize the timing of protein consumption, the type of protein consumed and the amount of protein consumed all play a significant role in promoting adaptation through protein synthesis.

Excessive Protein Consumption

Concerns of excessive protein consumption are valid. Deamination of amino acids results in the production of ammonia. Ammonia is toxic, particularly to the central nervous system. The major route for the excretion of ammonia is the creation and excretion of urea. It is possible to consume protein in excess of the body's ability to deal with it. Rudman et al.²⁹ found the maximal rate of urea excretion to be $55 \text{ mg urea N} \cdot \text{h}^{-1} \cdot \text{kg}^{-0.75}$. In their review of dietary protein intake in humans, Bilsborough and Mann³⁰ state that an 80kg individual could deaminate up to 301 grams of protein per day. At the levels previ-

ously cited^{7,9,11} as eliciting maximal rates of protein synthesis, amounts greater than 300gm per day would be absolutely unnecessary. Yet, Phillips¹¹ et al. review of excess protein consumption does not find damning outcomes for consumption of up to 3 gm of protein per kilogram of body mass. More dietary protein has been related to increased peak bone mass, but has not been related to progressive decline in kidney function. Continued research concerning excess protein consumption is warranted, but only flawed reasoning would conclude a need of over 300 gm of daily protein.

Conclusion

Empirical evidence is highlighting the important role protein consumption plays in stimulating protein synthesis after resistance exercise. Multiple sources of protein promote protein synthesis after exercise, but only those with essential amino acids elevate synthesis. Milk proteins are apparently more effective than soy proteins.¹⁵ Whey protein may promote important cellular signaling changes through its ability to elevate plasma and intracellular leucine.¹⁷ Whey protein also promotes intramuscular accumulation of triglycerides while inhibiting hepatic accumulation of fat.¹⁶ Carbohydrate consumption may be important in facilitating intracellular signaling through insulin and by elevating and maintaining the cell's energy status. Yet, it is important to recognize that significant protein synthesis is unlikely with a carbohydrate-only supplement. Consuming protein prior to and after the exercise seems to be warranted.¹⁸ Ten grams of essential amino acids or twenty-five grams of a complete protein are sufficient to maximally stimulate protein synthesis.¹¹ Type, timing and amount of protein are all factors in maximizing muscle mass.

There is still much to discover that will help in promoting health and wellness. We are beginning to develop a greater appreciation for skeletal muscle's role in healthcare. Recognition of the need to create synergy between the exercise and diet is critical. Many chiropractic physicians give nutritional advice and exercise to patients. Recognizing and applying the synergistic relationship between exercise and diet may help achieve better adaptations to exercise. For Doctors of Chiropractic, the adaptation may be seen in objective measures of patient strength, endurance, or functional ability.

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