



THE IMPACT OF PROTEIN QUANTITY, QUALITY, DISTRIBUTION, AND FOOD MATRIX ON MUSCLE PROTEIN SYNTHESIS

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KEY POINTS

- Muscle protein synthesis rates are increased by physical activity and protein ingestion.
- The effectiveness of protein ingestion to stimulate muscle protein synthesis depends on its type, digestion rate, amino acid composition and food matrix.
- Distributing protein intake across meals and including a pre-sleep dose may optimize muscle protein synthesis rates throughout the day.
- Ingestion of plant-derived proteins can stimulate muscle protein synthesis if consumed in adequate amounts and following proper processing.
- More research is needed on how proteins behave in the context of complex meals, meal to meal interactions, over longer periods and across different populations, with women being of particular relevance.

INTRODUCTION

This Sport Science Exchange (SSE) article discusses recent advances and future directions in dietary protein research. But before discussing what's new, it's useful to first reflect on what is already known, including some of the basics in the present understanding of muscle protein metabolism. Skeletal muscle is a dynamic tissue, with muscle proteins constantly undergoing synthesis and breakdown, a process known as muscle protein turnover. Each day, 1–2% of our muscle proteins are being replaced. This constant remodeling allows skeletal muscle to adapt in response to stimuli, such as endurance or resistance-type exercise (Koopman & van Loon, 2009). This plasticity is beneficial as it allows our skeletal muscle tissue to recondition to better support its use. For example, endurance athletes and strength athletes can shape their muscle phenotype in different directions to support performance in their specific field of sports (Hawley et al., 2011). However, this plasticity also makes us vulnerable to muscle loss under adverse conditions, such as bedrest or immobilization following disease or injury (Wall et al., 2013a). This process of muscle mass loss and quality is generally referred to as deconditioning, but it is merely a reconditioning response to a less favorable change in our lifestyle. Disuse atrophy is often observed in conditions characterized by inactivity, chronic diseases (like chronic obstructive pulmonary disease, cancer or cardiovascular disease), injury or simply aging.

To maintain or improve muscle health, anabolic stimuli are essential. These come in two forms: physical activity and nutrition. From the food perspective, dietary protein is the critical factor. Protein provides amino acids, which form the building blocks of muscle proteins. Besides being building blocks, the protein derived amino acids also act as signaling molecules that directly activate anabolic pathways that stimulate muscle protein synthesis (Volpi et al., 1999; 2003). It is the essential amino acids, and more particularly the amino acid leucine, that play a key role in activating the mechanistic target of rapamycin (mTOR) pathway, leading to an increase in muscle protein synthesis (Anthony

et al., 2000; Moro et al., 2016). Of course, all amino acids, both essential and non-essential, will be required as precursors to support the post-prandial increase in muscle protein synthesis rates. Therefore, the activation of the anabolic pathways, as well as an ample supply of amino acids as precursors, will be required to optimize the muscle protein synthetic response to protein ingestion. The ingestion of a single meal-like amount of protein can enhance muscle protein synthesis rates for up to 4-6 hr (Groen et al., 2015; Moore et al., 2009a).

Several factors modulate the anabolic response to feeding, which include the amount of protein, quality of the protein, protein distribution, food processing and many more (Groen et al., 2015). In addition to protein ingestion, physical activity or muscle contraction serves as a powerful anabolic stimulus. Physical activity increases muscle protein synthesis rates, with effects lasting up to at least 24 hr following a bout of exercise (Burd et al., 2011). There is an intricate relationship between nutrition and physical activity, with physical activity augmenting the sensitivity of skeletal muscle tissue to the anabolic properties of protein ingestion (Moore et al., 2009b). Therefore, being physically active augments the capacity to utilize the ingested protein for *de novo* muscle protein synthesis (Pennings et al., 2011a), a principle that is widely applied in both sports and clinical nutrition. However, the opposite is also true, with a decline in physical activity making the muscle less sensitive to the anabolic properties of protein feeding, a condition that is now coined anabolic resistance.

FROM PROTEIN INGESTION TO AMINO ACID INCORPORATION

Regulation of post-prandial protein metabolism on a whole-body level is complex (Groen et al., 2015). The increase in muscle protein synthesis following protein ingestion is regulated at multiple levels, beginning with the ingestion of protein and its subsequent digestion and the absorption of the protein-derived amino acids. The greater part of those protein-derived amino acids will be released into the circulation. Whether

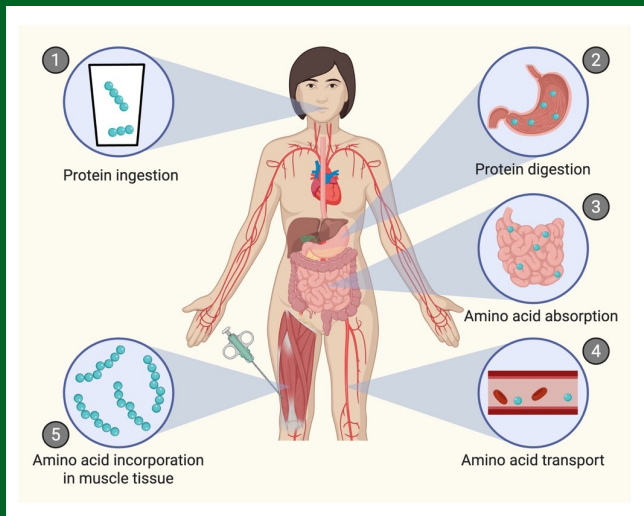


Figure 1: Post-Prandial Protein Handling

Protein digestion and amino acid absorption and the subsequent increase in muscle protein synthesis rate is regulated on various levels, from protein digestion and amino acid absorption, followed by the release of protein derived amino acids in the circulation, the increased perfusion of muscle tissue, the uptake of amino acids in muscle, the subsequent anabolic signalling response and finally, the incorporation of amino acids into skeletal muscle protein.

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these amino acids will reach the muscle will depend on the hormonal response to the ingested meal. The post-prandial release of insulin will stimulate the perfusion of the insulin sensitive tissues, including skeletal muscle. The circulating amino acids will subsequently be delivered to muscle tissue, where they will activate the signalling pathways involved in muscle protein synthesis. The stimulation of the anabolic signalling cascade, combined with an adequate supply of essential as well as non-essential amino acids, will then support the post-prandial rise in muscle protein synthesis rates. This coordinated response highlights the critical role of nutrition and metabolic regulation in maintaining and improving skeletal muscle health. These processes can be studied using stable isotope-labeled amino acids. By administering labeled amino acids and tracking their incorporation into muscle tissue protein, muscle protein synthesis rates can be directly measured. However, this only provides insight into the process of muscle protein synthesis.

To study protein digestion and amino acid absorption, intrinsically labeled proteins can be applied (Trommelen et al., 2021; van Loon et al., 2009). These proteins can be produced, for instance, by administering labeled amino acids to cows, chickens or even insects. Combining the ingestion of these proteins with the intravenous administration of stable isotope tracers (with a different label) allows tracking of the entire journey of the ingested protein: from protein digestion and amino acid absorption, to amino acid appearance in the circulation, and ultimately, their incorporation into muscle proteins. Ingestion of a meal-like bolus (20-25 g) of a high-quality protein can strongly increase muscle protein synthesis rates by up to 40% for 4-6 hr. Using intrinsically labeled milk protein, it can show that following the ingestion of 20 g of (milk) protein, about 55% of protein derived amino acids are released in the circulation

within a 5 hr post-prandial period, with 20% of those amino acids being used for *de novo* muscle protein synthesis. In other words, ingested protein is rapidly digested and absorbed, providing building blocks to support the post-prandial increase in muscle protein synthesis, revealing that '*you are what you just ate*' (Groen et al., 2015). So far various factors have been identified that modulate the postprandial rise in muscle protein synthesis rates. These factors include the source of protein, the amount of protein, the timing of protein intake, the matrix in which the protein is embedded and many more (Gorissen et al., 2015; 2020).

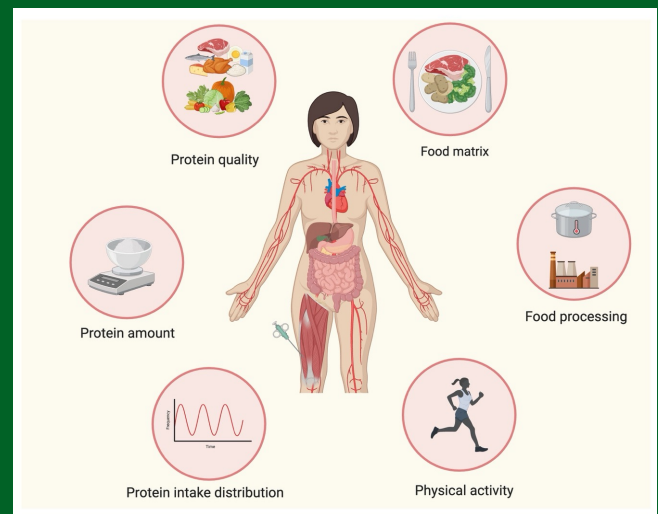


Figure 2: Factors That Affect Post-Prandial Protein Handling

Protein digestion and amino acid absorption and the subsequent increase in muscle protein synthesis rates can be modulated by various factors including the quality and amount of the ingested protein, the distribution of protein intake throughout the day, the matrix in which the protein is consumed, the level of processing or food preparation prior to consumption, and the level of habitual physical activity and exercise training. Created in <https://BioRender.com>

PROTEIN QUALITY AND AMOUNT

One of the factors that determines the post-prandial stimulation of muscle protein synthesis is the source of protein ingested. Ingesting a protein that is rapidly digestible allows a greater proportion of the ingested protein-derived amino acids to be released more rapidly into circulation, thereby stimulating muscle protein synthesis (Koopman et al., 2009; Pennings et al., 2011b; Tang et al., 2009). Besides protein digestion and amino acid absorption kinetics, the amino acid composition of the protein can also modulate the capacity of a protein (source) to stimulate muscle protein synthesis (Gorissen et al., 2015). Ingestion of a protein with a higher essential amino acid content, and a higher leucine content in particular, generally results in a greater increase in muscle protein synthesis rates. In support, prior work has shown that co-ingesting free leucine with protein can further enhance muscle protein synthesis rates (Holwerda et al., 2019; Katsanos et al., 2006; van Loon, 2012; Wall et al., 2013b). In short, rapid digestion and absorption, and a high leucine content are two key characteristics that define the anabolic properties of a protein (source). This is why athletes

generally prefer to supplement with whey protein, as whey protein is both rapidly digestible and has a high leucine content. It should be noted that differences in post-prandial muscle protein synthesis rates following ingestion of most animal derived protein isolates and concentrates are very small, and from a practical perspective less relevant in the context of a daily pattern of food intake.

Of course, the capacity to increase post-prandial muscle protein synthesis is also determined by the amount of protein ingested. Prior work has demonstrated that ingesting 20 g of a high-quality protein (such as whey or egg protein) maximizes post-prandial muscle protein synthesis rates, both at rest and during recovery from exercise, for up to 4-6 hr after protein ingestion (Moore, Robinson, et al., 2009a; Witard et al., 2014). Consuming more than 20 g protein does not seem to further increase muscle protein synthesis rates during this relatively short period in healthy adults. For this reason, athletes are generally recommended to consume 20-25 g of a high-quality protein (source) during recovery from a workout session.

PROTEIN INTAKE DISTRIBUTION

In addition to the source and amount of protein consumed, the timing of protein intake throughout the day has been proposed as another critical factor to consider. Some evidence suggests that a more balanced distribution of protein ingestion across 3 main meals leads to greater protein retention and improved muscle protein synthesis (Areta et al., 2013; Arnal et al., 1999). For this reason, it has been suggested that consuming 20-25 g of protein with each main meal will maximize muscle protein synthesis rates throughout a day. In addition, it was hypothesised that protein ingestion prior to sleep (as a fourth meal moment) may represent an effective strategy to further stimulate muscle protein synthesis. A series of studies demonstrated that protein consumed in the evening is effectively digested and absorbed during overnight sleep, increasing muscle protein synthesis rates throughout the night (Snijders et al., 2019). This approach, which has long been utilized by resistance-type athletes, is now also being applied in healthcare settings for patients who are at a high(er) risk of muscle loss. As muscle protein synthesis rates are not further increased following the ingestion of more than 20-25 g of a high-quality protein throughout a 4-6 hr period, it has made athletes worry about missing a post-workout shake and question whether there is a strict “*anabolic window*” that they need to cater to. This is of particular interest considering that it has been speculated that ingesting more protein will simply result in the excess protein being directed towards oxidation. While timing does matter, the body's protein handling is much more flexible than often assumed. A recent study demonstrated that the ingestion of a larger protein dose (e.g., 100 g protein) resulted in more prolonged protein digestion and amino acid absorption, over as much as 12 hr, with a sustained stimulation of muscle protein synthesis (Trommelen et al., 2023). In short, excess protein isn't simply oxidized, it is conveniently used over a more prolonged timeframe. So, athletes should worry less about skipping a meal or missing a post-workout snack. Nonetheless, the general advice to pursue a protein distribution that is more balanced

throughout the day, with 20-25 g protein provided per main meal combined with a protein rich snack in the evening, seems the more practical and sound advice for any athlete aiming to support muscle conditioning during intense exercise training.

PLANT-BASED PROTEINS

There has been a strong trend for a transition towards consuming a (more) plant-based diet. Consequently, many questions have been raised regarding potential differences in the anabolic properties of plant- versus animal-derived proteins or protein sources. We have previously addressed this in more extensive reviews (Pinckaers et al., 2021; van Vliet et al., 2015). There are relatively few studies that have assessed the anabolic properties of plant-derived proteins. Some, but certainly not all, of these studies report a smaller post-prandial stimulation of muscle protein synthesis following ingestion of plant-derived versus animal-derived proteins (Gorissen et al., 2016; Tang et al., 2009). The proposed lesser anabolic properties of plant-based proteins may be attributed to differences in protein digestion and amino acid absorption kinetics and/or differences in the amino acid composition of these proteins (Gorissen et al., 2018). Most plant-derived proteins have a low(er) essential amino acid content, a low(er) leucine content and are often deficient in one or more specific amino acids. The proposed lower anabolic properties of plant-derived proteins may be compensated for by consuming a greater amount of the plant-derived protein (source), by using a blend of different plant-based proteins to provide a more balanced amino acid profile, and/or by fortification of the plant-derived protein or protein source with the specific deficient amino acid(s) (Pinckaers et al., 2021). In agreement, a range of recent studies were unable to observe differences in muscle protein synthesis rates following the ingestion of ample amounts (30 g) of plant- versus animal-derived protein isolates and concentrates, both at rest as well as during recovery from exercise in healthy adults (Pinckaers et al., 2023). However, it should be noted that ingestion of the same amount of protein in the form of plant-based whole-foods may result in a lesser anabolic response due to a lower digestibility, a more delayed protein digestion and amino acid absorption rate and, as such, a lower overall bioavailability of protein-derived amino acids when consumed in a plant-based whole-foods product or meal matrix (Pinckaers et al., 2024).

FOOD MATRIX

Protein digestion and amino acid absorption are not only influenced by the type and amount of the protein isolate or concentrate, but also by the matrix in which the protein is being consumed. The food matrix encompasses the structural and compositional properties of a food product or a mixed meal. These properties are defined by the presence of other macro- and micronutrients, fibers, (other) anti-nutritional factors, as well as the form of the food(s) and how they have been processed or prepared. Processing, whether industrial or home-based, can strongly impact the bioavailability of the protein-derived amino acids (Weaver, 2021). For example, minced meat is digested more rapidly than a

steak (Pennings et al., 2013), and amino acids derived from raw eggs are absorbed less efficiently than cooked eggs (Fuchs et al., 2022). Whereas cooking can improve more rapid protein digestion and amino acid absorption, heating dairy can also have less favourable impact. Recently, it was shown that heating milk protein can lead to glycation, reducing the capacity to absorb the available lysine (van Lieshout et al., 2025). These findings underline that the context in which we consume protein, liquid vs solid, raw vs cooked, isolated vs whole food, protein source vs mixed meal, etc., all impact post-prandial protein handling and, as such, modulate the metabolic fate of the ingested protein-derived amino acids. So far, most research on post-prandial protein handling has assessed protein digestion, amino acid absorption and/or muscle protein synthesis rates after ingestion of protein isolates or concentrates following an overnight fast. However, this is certainly not reflective of daily living conditions in which we typically consume various complex meals throughout the day(s). Furthermore, the way we consume meals, including factors such as chewing and swallowing and even the position in which we eat, all affect the protein digestion and amino acid absorption kinetics (Holwerda et al., 2016; Remond et al., 2007). This real world complexity is difficult to replicate in a laboratory setting and, therefore, more work is needed to start understanding how proteins behave in the context of complex meals, with inclusion of meal to meal (and protein supplement) interactions.

DIET AND MUSCLE CONDITIONING

Though differences in anabolic response to the ingestion of a single bolus of a protein source or composite meal may exist, they do not necessarily predict the impact they have on the skeletal muscle adaptive response to more prolonged (exercise) interventions. It has been well established that protein supplementation during prolonged resistance-type exercise training generally results in greater gains in muscle mass and strength, albeit the surplus benefits are very small when compared to the impact of exercise training per se (Cermak et al., 2012; Morgan et al., 2021; Morton et al., 2018). Whether the gains in muscle mass and strength during resistance-type exercise training would be affected differently when consuming an equivalent amount(s) of different protein(s) or protein source(s) remains equivocal. Based upon the described differences in protein digestibility, protein digestion and amino acid absorption kinetics, and postprandial muscle protein synthesis rates following ingestion of protein or protein sources, it could be hypothesised that when transitioning towards a more plant-based diet, more (plant-based) protein should be consumed to allow a similar stimulation of muscle protein synthesis. However, most athletes already consume ample amounts of protein due to their high(er) overall energy intake. A nation-wide survey of well-trained athletes reported a protein intake of ~1.5 g protein/kg body mass/day (Gillen et al., 2017). This represents a daily protein intake well above the Recommended Daily Allowance proposed by the World Health Organization (0.8 g protein/kg/day; WHO, 2007), and will be more than sufficient to allow maximal gains in muscle mass and strength during prolonged resistance-type exercise training (Phillips & van Loon, 2011; Phillips et al., 2022). As active adults generally consume ample amounts of protein in their diet

(when maintaining energy balance), a diet providing low(er) quality protein(s) would be unlikely to compromise muscle conditioning during exercise training. Small differences in protein quality will, therefore, not have much impact on skeletal muscle conditioning when ample protein is consumed. It is evident that the impact of protein intake or protein supplementation on muscle mass and strength gains will depend more on the population, the type of training, the training status of the volunteers, the amount of protein supplemented and habitual protein intake. Regarding the population, surprisingly few data have been obtained on post-prandial protein handling at rest and during recovery from exercise in women (Elliott-Sale et al., 2021). There are not enough data available to provide insight on the impact of the type, amount, quality, and/or distribution of protein intake on muscle protein synthesis rates in women. To accurately advise female athletes, more work will be required to assess aspects of post-prandial protein handling at rest and during recovery from exercise in females.

PRACTICAL GUIDELINES

- Ingest 20-25 g protein via one or more high-quality protein sources with each main meal
- Consume 20-25 g protein after a workout session, which could be consumed as part of a main meal or as a convenient, protein-rich snack
- During intense training periods it may be beneficial to consume a protein rich-snack in the evening to support recovery during overnight sleep.
- In active adults, daily protein intake is generally sufficient (1.2-1.5 g/kg body mass/d) to optimize muscle conditioning during prolonged exercise training.
- It is advised to assess habitual daily protein intake before considering whether additional protein supplementation may be beneficial.

SUMMARY

Skeletal muscle protein synthesis is stimulated by physical activity and nutrition. Protein ingestion stimulates muscle protein synthesis and further augments the post-exercise increase in muscle protein synthesis rates, thereby supporting skeletal muscle conditioning. Advances in dietary protein research highlight the importance of protein type, amount, matrix and timing in protein digestion and amino acid absorption kinetics and the subsequent post-prandial stimulation of muscle protein synthesis. The bioavailability of plant-based protein sources may be compromised when compared with animal-based protein sources, resulting in a lesser anabolic response. However, ingestion of plant-derived proteins can effectively increase muscle protein synthesis rates when properly processed and provided in adequate amounts. Food matrix and its processing can alter protein bioavailability and biofunctionality. Future work should address all aspects of post-prandial protein handling in the context of complex meals and meal-to-meal interactions. The latter should be assessed

in both males and females as potential sex based differences remain underexplored and require more targeted research.

The views expressed are those of the authors and do not necessarily reflect the position or policy of PepsiCo, Inc.

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