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Human Kinetics
COMMENTARY

The Anabolic Response to Protein Ingestion During Recovery From Exercise Has No Upper Limit in Magnitude and Duration In Vivo in Humans: A Commentary

Oliver C. Witard[1] **and Samuel Mettler**[2]
[1]Centre for Human & Applied Physiological Sciences, King's College London, London, United Kingdom;
[2]Department of Health, Bern University of Applied Sciences, Bern, Switzerland

A comprehensive recent study by Trommelen et al. demonstrated that muscle tissue exhibits a greater capacity to incorporate exogenous exogenous protein-derived amino acids into bound muscle protein than was previously appreciated, at least when measured in "anabolically sensitive," recreationally active (but not resistance-trained), young men following resistance exercise. Moreover, this study demonstrated that the duration of the postprandial period is modulated by the dose of ingested protein contained within a meal, that is, the postexercise muscle protein synthesis response to protein ingestion was more prolonged in 100PRO than 25PRO. Both observations represent important scientific advances in the field of protein metabolism. However, we respectfully caution that the practical implications of these findings may have been misinterpreted, at least in terms of dismissing the concept of protein meal distribution as an important factor in optimizing muscle tissue anabolism and/or metabolic health. Moreover, based on emerging evidence, this idea that the anabolic response to protein ingestion has no upper limit does not appear to translate to resistance-trained young women.

Keywords: protein meal distribution, sex differences, muscle protein synthesis, resistance exercise

An elegant recent study published by Trommelen et al. (2023) in *Cell Reports Medicine* provides unique insights into the postprandial protein handling of a "meal-like" (25 g) or "feast-like" (100 g) dose of protein ingested following an intense (60 min, 4× 10 sets/reps @65%–80% one repetition maximum) bout of whole-body (leg press, leg extension, latissimus dorsi pulldown, and chest press) resistance exercise in recreationally active young men. The principal finding was a greater myofibrillar fractional synthetic rate following the postexercise ingestion of 100 g (100PRO) versus 25 g (25PRO) of intrinsically labeled milk protein, measured over the early 0–4 hr (~20%), later 4–12 hr (~40%), and overall (0–12 hr) postprandial period. Consistent with this observation, muscle myofibrillar protein-bound enrichments were greater in the 100PRO group than the 25PRO group over the cumulative 12-hr postprandial period.

On a mechanistic level, these comprehensive in vivo data highlight that muscle tissue exhibits a greater capacity to incorporate exogenous protein-derived amino acids into bound muscle protein than was previously appreciated, at least when measured in "anabolically sensitive," recreationally active (but not resistance-trained), young men following resistance exercise. Moreover, this study demonstrated that the duration of the postprandial period is modulated by the dose of ingested protein contained within a meal, that is, the postexercise muscle protein synthesis (MPS) response to protein ingestion was more prolonged in 100PRO than 25PRO. Both observations represent important scientific advances in the field of protein metabolism, and so it is critical that the practical implications of these findings are carefully considered relative to various different contexts. Specifically, to consider what these findings mean: (a) for the importance of daily protein distribution for muscle anabolism and metabolic health, and (b) for the upper limit (or lack thereof) in resistance-trained young women.

Protein Meal Distribution

Trommelen et al. (2023) challenge the generally accepted viewpoint that protein meal distribution represents an important nutritional variable in modulating the anabolic response to ingested protein when combined with resistance exercise (Areta et al., 2013; Loenneke et al., 2016; Moore et al., 2012). This assertion stems from the dose-dependent (100PRO > 25PRO) increase in magnitude and duration of hyperaminoacidemia, and the subsequent MPS response to ingested protein following exercise that was observed in the absence of a notable increase in amino acid oxidation rates. Hence, the authors reasoned that the prolonged MPS response to this single "feast-like" protein dose circumvents the metabolic effect of consuming a subsequent protein-rich meal in close temporal proximity in order to recapitulate the muscle anabolic response. While these data present a theoretical argument for greater flexibility when devising protein feeding patterns aimed at enhancing muscle anabolism, we contend that it may be premature to dismiss the practical relevance of protein meal distribution altogether, at least in the context of athletic populations. There are three key points that, in our opinion, warrant further consideration in light of the existing evidence base and this new dataset that has emerged since this publication.

First, the study by Trommelen et al. (2023) fundamentally was not designed to investigate the impact of protein meal distribution on the muscle anabolic response to ingested protein. In this regard, the inclusion of a study arm comprising of 4× 25 g protein boluses ingested at 3-hr intervals represents a prerequisite for a valid comparison. Hence, no information could be garnered regarding the second-, third-, or fourth-meal response to ingested protein that,

Mettler https://orcid.org/0000-0002-5329-7296
Witard (oliver.witard@kcl.ac.uk) is corresponding author, https://orcid.org/0000-0002-5875-8397

theoretically, may not be equivalent in magnitude to the first meal ingested after an overnight fast. Nonetheless, based on the calculation that 17% of the ingested milk protein was incorporated into muscle protein in 25PRO compared with a 13% fraction in 100PRO, one could argue that an aggregated 4× 25 g protein meal distribution would have resulted in a greater 12-hr cumulative MPS than in response to the single 100 g protein dose. This interpretation would support, rather than refute, the view that protein meal distribution represents an important nutritional variable in modulating the anabolic response to ingested protein.

Over a decade ago, the study design of Areta et al. (2013) distributed 80 g of protein as either 8× 10 g boluses spaced 1.5 hr apart (PULSE), 4× 20 g boluses spaced 3 hr apart (INTERMEDIATE), or 2× 40 g boluses spaced 6 hr apart (BOLUS) in resistance-trained young men. Aligned with Trommelen et al. (2023), the temporal response of MPS was measured over a 12-hr postprandial period, albeit following an acute bout of leg-only, rather than whole-body resistance exercise. Areta et al. (2013) reported a greater cumulative 12-hr MPS response in INTERMEDIATE than BOLUS or PULSE that was primarily driven during the intermediate (4–6 hr) and later (6–12 hr) postprandial phases, rather than the early (1–4 hr) postprandial period. Unfortunately, this study did not include a 1× 80 g bolus arm; hence, a similar feast-like comparison to Trommelen et al. (2023) was not possible. Nonetheless, utilizing a study design specifically purposed to investigate the effect of protein meal pattern, the findings of Areta et al. (2013) appear to contradict the conclusions presented by Trommelen et al. (2023) that protein meal distribution elicits a negligible effect on the muscle anabolic response.

As acknowledged by Trommelen et al. (2023), the calculation that 13% (=13 g) of the ingested 100 g milk protein was incorporated into muscle protein over the 12-hr postprandial period exceeds previous estimates (i.e., ~2.2 g) in a typical three-square meal cycle (Stokes et al., 2018). Hypothetically, if we introduce a second meal and assume that 26 g of amino acids are incorporated into myofibrillar protein over 24 hr, these math would extrapolate to a ~47 kg gain in muscle mass over the course of a year (see Box 1 for a hypothetical calculation), which is clearly unrealistic. A physiological explanation for this disconnect relates to the training status of the studied participants. Trommelen et al. (2023) recruited recreationally active, but not resistance-trained, young men, and previous work suggests that no relationship exists between the acute response of myofibrillar MPS to an initial resistance exercise bout and chronic changes in muscle mass following a period of resistance training (Damas et al., 2016). Instead, it has been proposed that the increased response of MPS to a novel resistance exercise stimulus and protein ingestion is likely related more to the repair and remodeling of existing older, damaged muscle proteins, rather than to driving a functional muscle hypertrophic response (Damas et al., 2016; Witard et al., 2022).

Second, and as highlighted above, Trommelen et al. (2023) reported a negligible increase in amino acid oxidation rates in both 25PRO and 100PRO groups. This observation supports the notion that MPS, rather than oxidation, served as the primary fate of protein-derived amino acids, irrespective of ingested protein dose. While previous studies have reported a marked increase in amino acid oxidation rates after ingesting a 40-g dose of protein (Moore et al., 2009; Witard et al., 2014), when expressed relative to protein intake, Trommelen et al. (2023) calculated that <15% of the ingested protein-derived amino acids were oxidized over the 4-hr postprandial period. Nonetheless, we contend that low amino acid oxidation rates do not necessarily imply that amino acids are directed to MPS/muscle hypertrophy. Dependent on meal distribution, dietary protein-derived amino acids may reside in other tissues (e.g., the splanchnic tissues) or may be diverted for the synthesis of noncontractile muscle protein fractions such as mitochondrial, sarcoplasmic, or connective tissue proteins. Moreover, another metabolic fate of amino acids is urea production following the removal of nitrogen via transamination or deamination that was not measured in the present study and has been shown to increase with the ingestion of a 40 g protein dose (Witard et al., 2014).

Third, in making the case that protein meal distribution has limited utility with regard to optimizing metabolic health, we argue that the dataset presented by Trommelen et al. (2023) is a thorough and focused analysis but understandably does not address all aspects of metabolic health. Of course, metabolic health is a multifactorial concept that includes, but is not limited to, muscle anabolism (Wolfe, 2006). Taking appetite as an alternative component of metabolic health with clear implications for weight management and reducing Type 2 diabetes risk, the regular feeding of satiating protein-rich meals across the day remains an intuitive strategy to regulate subsequent energy intake and warrants experimental investigation in clinically compromised populations.

Box 1

- 26 g × 365 days = 9,490 g of muscle protein/year
- Assuming skeletal muscle constitutes 20% protein (Dickerson & Widdowson, 1960)
- 9,490 g of muscle protein × 5 = +47,450 g muscle/year
- = +47 kg muscle mass/year

Translation to Females

The preponderance of protein dose–MPS response (postexercise) studies published to date, including Trommelen et al. (2023), has been conducted exclusively in male volunteers (Churchward-Venne et al., 2020; Moore et al., 2009; Witard et al., 2014). A timely new study (Mallinson et al., 2023) published simultaneously with Trommelen et al. (2023) investigated the dose–response (15, 30, or 60 g) of MPS to ingested whey protein following two bouts of intense (3× 8 sets/reps of leg press, latissimus dorsi pulldown, and chest press @75% one repetition maximum) whole-body resistance exercise in resistance-trained young women. Consistent with Trommelen et al. (2023), MPS was measured over both acute (0–4 hr) and prolonged (0–8 hr, 0–24 hr) postprandial periods. Although the response of MPS increased in a dose-dependent manner up to 30 g of ingested protein, there was no additional stimulation of MPS with the 60 g protein dose (15 g < 30 g = 60 g). Hence, in contrast to the dataset presented by Trommelen et al. (2023) in males, an upper limit to the muscle anabolic response was evident in this female cohort. These discrepant findings (Mallinson et al., 2023; Trommelen et al., 2023) are difficult to reconcile given that (a) a comparable (whole-body) bout of resistance exercise was conducted in both studies; (b) both studies conducted measurements of MPS over a prolonged incorporation period; (c) a similar protein source (dairy) was administered; and (d) limited evidence exists for sex differences in the response to MPS to ingested protein, at least in young adults (West et al., 2012). Although speculative, one possible explanation relates to differences in training status between studies, that is, resistance trained in Mallinson et al. (2023) versus physically active but not resistance trained in Trommelen et al. (2023). Nonetheless, these data challenge the concept

that the anabolic response to protein ingestion during recovery from exercise has no upper limit in magnitude and duration in vivo in humans, at least in resistance-trained women.

Conclusion

As a closing remark, we congratulate Trommelen et al. (2023) for conducting this robust (quadruple tracer approach), comprehensive (mixed, myofibrillar, and connective tissue MPS rates measured during early and later phases of a 12-hr postprandial period), and labor-intensive ($n = 36$) study that adds valuable new mechanistic insights into protein dosing strategies for muscle anabolism. Our intention is not to diminish the quality of the data presented. Instead, we hope to stimulate (pun intended!) scientific discussion within the readership of *International Journal of Sport Nutrition and Exercise Metabolism* in order to further progress this exciting, and fast-evolving, field.

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