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Commentaries on Viewpoint: What is the relationship between acute measure of muscle protein synthesis and changes in muscle mass?

COMMENTARY RESPONSE TO VIEWPOINT: "WHAT IS THE RELATIONSHIP BETWEEN ACUTE MEASURES OF MUSCLE PROTEIN SYNTHESIS AND CHANGES IN MUSCLE MASS?"

TO THE EDITOR: Mitchell et al. (3) critique putative links between *acute* muscle protein synthesis (MPS) and ensuing hypertrophy after resistance exercise (RE) training (RT). Just two papers have addressed this longitudinally. The first reports that young but not older individuals exhibit *acute* (fasted *mixed* muscle MPS, 24 h post-RE) increases in MPS (2); yet hypertrophy gains, assessed by DXA and fiber area, were equal. Similarly, poor quantitative MPS linkages were reported 1–6 h post-RE (*myofibrillar* muscle, fed state) with ensuing hypertrophy (4), i.e., two study's suggesting bona fide dissociation. However, for (2), prior reports of age-related temporal differences in acute MPS responses to RE (1) and lack of intra/inter age group correlations (2) mitigate such resounding conclusions. Also, in (4), RE was under fed state conditions; this is significant because consumption of protein feeds *extends* (not *amplifies*) elevations in MPS post-RE (5). Therefore, MPS responses 1–6 h post-RE were chiefly predominated by feeding, i.e., the coupling of which to RE may not aptly reflect interindividual variation (5), e.g., due to isolated mechano-auto/paracrine responses to RE. Yet, *acute* MPS can/does inform on group interventions for RT-induced muscle hypertrophy, signifying it a practicable, informative end-point. But, could *quantitative* relationships still exist and what defines "*acute*" post-RE MPS? Fasted/fed? Immediately (<6 h?)/later (>24?) What muscle fraction(s)? Is there an applicable "snapshot"? Without defining *acute* this is indiscernible. The authors justifiably raise potential technical, temporal, methodological confounder(s). Because hypertrophy is a heterogeneous and temporally dynamic process we hypothesize that (coupled to not isolating/fractionating/holistically capturing "*acute*" MPS) interindividual trajectories and *plateauing* hypertrophy in the face of fixed study end-points are the major barriers to defining quantitative links between *acute* MPS and RT-induced hypertrophy.

REFERENCES

1. **Drummond MJ, Dreyer HC, Pennings B, Fry CS, Dhanani S, Dillon EL, Sheffield-Moore M, Volpi E, Rasmussen BB.** Skeletal muscle protein anabolic response to resistance exercise and essential amino acids is delayed with aging. *J Appl Physiol* 104: 1452–1461, 2008.
2. **Mayhew DL, Kim JS, Cross JM, Ferrando AA, Bamman MM.** Translational signaling responses preceding resistance training-mediated myofiber hypertrophy in young and old humans. *J Appl Physiol* 107: 1655–1662, 2009.
3. **Mitchell CJ, Churchward-Venne TA, Cameron-Smith D, Phillips SM.** Viewpoint: What is the relationship between the acute muscle protein synthetic response and changes in muscle mass? *J Appl Physiol*; doi: 10.1152/japplphysiol.00609.2014.
4. **Mitchell CJ, Churchward-Venne TA, Parise G, Bellamy L, Baker SK, Smith K, Atherton PJ, Phillips SM.** Acute post-exercise myofibrillar protein synthesis is not correlated with resistance training-induced muscle hypertrophy in young men. *PLoS One* 9: e89431, 2014.
5. **Moore DR, Tang JE, Burd NA, Rerecich T, Tarnopolsky MA, Phillips SM.** Differential stimulation of myofibrillar and sarcoplasmic protein synthesis with protein ingestion at rest and after resistance exercise. *J Physiol* 587: 897–904, 2009.

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COMMENT VIEWPOINT: "WHAT IS THE RELATIONSHIP BETWEEN ACUTE MEASURES OF MUSCLE PROTEIN SYNTHESIS AND CHANGES IN MUSCLE MASS?"

TO THE EDITOR: Mitchell et al. (4) state that acute measurements of muscle protein synthesis may not necessarily reflect the magnitude of hypertrophy during long-term training studies, which we agree with. Two points deserve further comment: *1*) magnitude of muscle protein synthesis does not necessarily equate with hypertrophy, but rather remodeling, and *2*) limitations of acute measurements are a primary reason some in the field advocate for long-term measurements of synthesis. Regarding the first point, as the authors mention, synthesis is more commonly measured than breakdown and is likely the driving factor behind phenotypic change. However, it is still important to consider that breakdown can change the outcomes. If a high rate of synthesis is accompanied by equal or slightly lower rates of degradation, one would have hypertrophy, whereas the other may not. Importantly though, both are indicative of remodeling. This concept is clear when one studies endurance exercise where there is a high degree of protein remodeling, and phenotypic change, without hypertrophy (5). Regarding our second point, we have advocated for the use of deuterium oxide to measure long-term changes in protein synthesis (1, 3) because of the limitations of acute protein synthesis measurements (4). We have even emphasized this point in a previous "Viewpoint" (2). Although acute measurements of protein synthesis have value, the overall outcome of a long-term treatment or intervention should be assessed by long-term measurement techniques to understand the integrated responses over time. We hope that others, like Mitchell et al., continue to recognize this important point.

REFERENCES

1. **Miller BF, Drake JC, Naylor B, Price JC, Hamilton KL.** The measurement of protein synthesis for assessing proteostasis in studies of slowed aging. *Ageing Res Rev* 18: 106–111, 2014.
2. **Miller BF, Hamilton KL, Cuthbertson DJ, Smith K, Williams J, Mittendorfer B, Greenhaff P, Atherton P.** Commentaries on Viewpoint: The curious case of anabolic resistance: old wives' tales or new fables? *J Appl Physiol* 112: 1236, 2012.
3. **Miller BF, Hamilton KL.** A perspective on the determination of mitochondrial biogenesis. *Am J Physiol Endocrinol Metab* 302: E496–E499, 2012.

4. **Mitchell CJ, Churchward-Venne TA, Cameron-Smith D, Phillips SM.** Viewpoint: What is the relationship between the acute muscle protein synthetic response and changes in muscle mass? *J Appl Physiol*; doi: 10.1152/japplphysiol.00609.2014.
5. **Scalzo RL, Peltonen GL, Binns SE, Shankaran M, Giordano GR, Hartley DA, Klochak AL, Lonac MC, Paris HLR, Szallar SE, Wood LM, Peelor FF, Holmes WE, Hellerstein MK, Bell C, Hamilton KL, Miller BF.** Greater muscle protein synthesis and mitochondrial biogenesis in males compared with females during sprint interval training. *FASEB J* 28: 2705–2714, 2014.

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THE POSTEXERCISE INCREASE IN MUSCLE PROTEIN SYNTHESIS RATE IS INDICATIVE OF SKELETAL MUSCLE RECONDITIONING RATHER THAN MUSCLE HYPERTROPHY PER SE

TO THE EDITOR: We regard the acute muscle protein synthetic response to exercise as an indicator of skeletal muscle reconditioning rather than predictive for muscle hypertrophy. For example, a single bout of endurance-type exercise also acutely increases muscle protein fractional synthetic rate (FSR) (1–3). The increase in the muscle protein synthetic response to endurance type exercise is generally not accompanied by substantial gains in muscle mass and, as such, is far from predictive for muscle hypertrophy in healthy, lean individuals. Instead, the postexercise increase in muscle protein synthesis is rather representative of muscle reconditioning, comprising muscle repair and remodeling. Consequently, the postexercise increase in muscle protein FSR should not be regarded as a marker for exercise training induced hypertrophy but rather as an indicator of skeletal muscle reconditioning, which comes in many different forms and measures. The muscle protein synthetic response to a single bout of resistance type exercise training may provide some insight in the extent of muscle hypertrophy observed during more prolonged resistance type exercise training but does not provide a quantitative estimation of hypertrophy in the individual (4).

REFERENCES

1. **Beelen M, Zorenc A, Pennings B, Senden JM, Kuipers H, van Loon LJ.** Impact of protein coingestion on muscle protein synthesis during continuous endurance type exercise. *Am J Physiol Endocrinol Metab* 300: E945–E954, 2011.
2. **Carraro F, Stuart CA, Hartl WH, Rosenblatt J, Wolfe RR.** Effect of exercise and recovery on muscle protein synthesis in human subjects. *Am J Physiol Endocrinol Metab* 259: E470–E476, 1990.
3. **Harber MP, Konopka AR, Jemiolo B, Trappe SW, Trappe TA, Reidy PT.** Muscle protein synthesis and gene expression during recovery from aerobic exercise in the fasted and fed states. *Am J Physiol Regul Integr Comp Physiol* 299: R1254–R1262, 2010.
4. **Mitchell CJ, Churchward-Venne TA, Cameron-Smith D, Phillips SM.** Viewpoint: What is the relationship between the acute muscle protein synthetic response and changes in muscle mass? *J Appl Physiol*; doi: 10.1152/japplphysiol.00609.2014.

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COMMENT ON VIEWPOINT: WHAT IS THE RELATIONSHIP BETWEEN ACUTE MEASURES OF MUSCLE PROTEIN SYNTHESIS AND CHANGES IN MUSCLE MASS?

TO THE EDITOR: Mitchell and colleagues (2) present a nicely balanced viewpoint regarding the discordance between acute measurements of muscle protein synthesis (MPS) and long-term muscle mass gains in response to exercise training and nutrition. Individual genetic and other physiological characteristics, as well as methodological limitations of the endpoint measures, are correctly identified as contributing factors to the hypertrophic variability inherent in these types of training studies (1). However, the practicalities of controlling long-term training studies themselves are not addressed.

Consideration is warranted for the difficulties in controlling extended-duration intervention studies to generate appropriately valid and reliable results. Changes and variability in diet, timing of exercise in relation to meal ingestion, sleep patterns, daily stress, and compliance with the training regimen will contribute to the considerable intrinsic variability of measured changes in muscle mass (3). Small differences between interventions may easily be missed when these confounding factors are coupled with the variations outlined in the Viewpoint. Acute measurements are much easier to control and differences between interventions often can be easily detected. Therefore, any disconnect between acute metabolic studies and long-term changes in muscle mass do not necessarily reflect the worth of the metabolic studies.

There is no question that acute measurements of MPS alone should not be used to predict the training response of any given individual. However, with appropriate appreciation for their limitations, these methods can play a valuable role in acquiring information to help determine appropriate training and nutrition interventions for various populations.

REFERENCES

1. **Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, Phillips SM.** Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. *Am J Clin Nutr* 86: 373–381, 2007.
2. **Mitchell CJ, Churchward-Venne TA, Cameron-Smith D, Phillips SM.** Viewpoint: What is the relationship between the acute muscle protein synthetic response and changes in muscle mass? *J Appl Physiol*; doi: 10.1152/japplphysiol.00609.2014.
3. **Tipton KD.** Efficacy and consequences of very-high-protein diets for athletes and exercisers. *Proc Nutr Soc* 70: 205–214, 2011.

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COMMENTARY RESPONSE TO VIEWPOINT: "WHAT IS THE RELATIONSHIP BETWEEN ACUTE MEASURES OF MUSCLE PROTEIN SYNTHESIS AND CHANGES IN MUSCLE MASS?"

TO THE EDITOR: The authors raise several insightful points while describing the discordance they observe between acute measures of postexercise muscle protein synthesis (MPS) and the subsequent resistance exercise (RE) training-induced muscle hypertrophy (1, 2). Although the authors suggest that intersubject variability in the MPS response to RE is a likely major contributory factor, the impact of recruiting individuals naive to the mode of RE employed cannot be overstated. Moderate (60–75% of 1-repetition maximum) noneccentric RE in unaccustomed individuals has been shown to result in myofibrillar damage, increased inflammatory signaling (5), and induction of the unfolded protein response (4), events that are thought to modulate MPS drive. Moreover, we have observed that 24 h after a single-bout of unaccustomed concentric RE, the transcriptional "program" elicited in muscle appears dependent on whether damage has purportedly occurred and varies between individuals (3). Specifically, we observed a discord in the transcriptional regulation of gene pathways associated with MPS signaling, which could in part explain the variability observed by the authors. In contrast, the transcriptional response to a repeat session of RE performed days later was consistent across volunteers and was not punctuated by increased markers of muscle damage (3). Collectively, these observations suggest that, when attempting to translate acute, exercise-induced changes in MPS to longer term gains in muscle mass, using subjects who have already undergone a period of familiarization to laboratory RE protocols may offer a more promising approach.

REFERENCES

1. **Mitchell CJ, Churchward-Venne TA, Cameron-Smith D, Phillips SM.** Viewpoint: What is the relationship between acute of muscle protein synthesis response and changes in muscle mass?. *J Appl Physiol*; doi: 10.1152/japplphysiol.00609.2014.
2. **Mitchell CJ, Churchward-Venne TA, Parise G, Bellamy L, Baker SK, Smith K, Atherton PJ, Phillips SM.** Acute post-exercise myofibrillar protein synthesis is not correlated with resistance training-induced muscle hypertrophy in young men. *PLoS One* 9: e89431, 2014.
3. **Murton AJ, Billeter R, Stephens FB, Des Etages SG, Graber F, Hill RJ, Marimuthu K, Greenhaff PL.** Transient transcriptional events in human skeletal muscle at the outset of concentric resistance exercise training. *J Appl Physiol* 116: 113–125, 2014.
4. **Ogborn DI, McKay BR, Crane JD, Parise G, Tarnopolsky MA.** The unfolded protein response is triggered following a single, unaccustomed resistance-exercise bout. *Am J Physiol Regul Integr Comp Physiol* 307: R664–R669, 2014.
5. **Thalacker-Mercer AE, Dell'Italia LJ, Cui X, Cross JM, Bamman MM.** Differential genomic responses in old vs. young humans despite similar levels of modest muscle damage after resistance loading. *Physiol Genomics* 40: 141–149, 2010.

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NEED FOR MEASURES OF SATELLITE CELL ACTIVATION ALONG WITH MUSCLE PROTEIN SYNTHESIS?

TO THE EDITOR: The Viewpoint by Mitchell and colleagues (4) provides a timely reminder that acute responses to exercise-nutrient interventions are not always the perfect proxy for chronic training-induced adaptations and/or changes in functional outcomes. Skeletal muscle displays remarkable plasticity with the capacity to alter the type and amount of protein in response to habitual level of contractile activity, the prevailing substrate availability, and environmental conditions (3). Such "adaptation plasticity" is common to all vertebrates but a large variation in the degree of adaptability between humans is evident, explaining the large inter-individual responses after exercise-nutrient interventions (2). The author's state that an individual's "inherited genetic predisposition, epigenetic influence, and transcriptional plasticity" are potential sources for "hypertrophic variability" after resistance training (RT). Added to that list is the possibility that satellite cell activation may underlie part of the variability in the muscle hypertrophic response. Previous work shows the acute satellite cell response to a single bout of resistance exercise is associated with the subsequent accretion of lean mass (LM) after 16 wk RT (1). Although this suggests postexercise measures of satellite cell activity could be a valid surrogate of an individual's ability to accrue LM after RT, acute measures of MPS still provide important mechanistic insight to the "anabolic" events in response to exercise-nutrient interventions. Ultimately it is clear that chronic training studies with comprehensive time-course responses of selected cellular and functional outcomes are required to provide mechanistic insight as to why training-nutrient interventions result in variable responses between individuals.

REFERENCES

1. **Bellamy LM, Joanisse S, Grubb A, Mitchell CJ, McKay BR, Phillips SM, Baker S, Parise G.** The acute satellite cell response and skeletal muscle hypertrophy following resistance training. *PLoS One* 9: e109739, 2014.
2. **Bouchard C, Rankinen T, Timmons JA.** Genomics and genetics in the biology of adaptation to exercise. *Compr Physiol* 1: 1603–1648, 2011.
3. **Hawley JA, Hargreaves M, Joyner MJ, Zierath JR.** Integrative biology of exercise. *Cell* 159: 738–749, 2014.
4. **Mitchell CJ, Churchward-Venne TA, Cameron-Smith D, Phillips SM.** Viewpoint: What is the relationship between the acute muscle protein synthetic response and changes in muscle mass? *J Appl Physiol;* doi: 10.1152/japplphysiol.00609.2014.

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ARE NOT INTRACELLULAR HEAT AND NEURAL ELECTRICITY STRESSES THE CAUSE OF EXERCISE-INDUCED PROTEIN SYNTHESIS?

TO THE EDITOR: Dr. Mitchell and colleagues (5) support their thesis for a possible lack of correlation between acute and chronic muscle protein synthesis (MPS) partly with their Refs. 14, 15, and 16. The conclusion for such a lack is drawn in all of these three references. However, while in Refs. 15 and 16 the quadriceps hypertrophy after 10 or 16 wk of resistance training (RT) was between 5 and 9.5% the same in Ref. 14 after 16 wk RT was 37–40%. In our view, the difference was because in Ref. 14 the load was progressively increased during the RT, while in Refs. 15 and 16 it was not. Qualitatively, it is the same difference as between MPS response after acute and chronic RT.

Myocytes are extremely vulnerable to overheating, because they can increase energy production more than 100-fold in less than a second. They do not have intracellular convective heat transfer because almost 80% of their water is entrapped in the myofibrils. The anaerobic nature of RT increases with the increase of loading because more energy is released during contraction, when muscle capillaries are compressed, preventing blood flow and cooling. Elevated myocyte temperature prevents protein synthesis, causes protein denaturation, and stimulates heat shock protein synthesis, which during postexercise repair in excess damaged protein (3, 4). This reasoning is supported by the similar effect produced by the blood flow restriction (2). Stimulation of protein synthesis by electric field (1) hints that excessive muscle neural electricity, triggered by unaccustomed loading, should have supportive MPS effect.

REFERENCES

1. **Bourguignon GJ, Bourguignon LY.** Electric stimulation of protein and DNA synthesis in human fibroblasts. *FASEB J* 1: 398–402, 1987.
2. **Gundermann DM, Fry CS, Dickinson JM, Walker DK, Timmerman KL, Drummond MJ, Volpi E, Rasmussen BB.** Reactive hyperemia is not responsible for stimulating muscle protein synthesis following blood flow restriction exercise. *J Appl Physiol* 112:1520–1528, 2012.
3. **Matts RL, Horst R.** The relationship between protein synthesis and heat shock proteins levels in rabbit raticulocyte lysates. *J Biol Chem* 267: 18168–18174, 1992.
4. **McNaughton L, Lovell R, Madden. Heat shock proteins in exercise: A review.** *J Exer Sci Physioter* 2: 13–26, 2006.
5. **Mitchell CJ, Churchward-Venne TA, Cameron-Smith D, Phillips SM.** Viewpoint: What is the relationship between acute of muscle protein synthesis response and changes in muscle mass? *J Appl Physiol*; doi: 10.1152/japplphysiol.00609.2014.

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TO THE EDITOR: Mitchell and colleagues have identified an important problem: can a single measurement of protein synthesis be extrapolated to provide changes in muscle mass(1)? Muscle mass is often used as a surrogate for muscle protein content, but although muscle weight reflects muscle mass, muscle weight includes muscle proteins, adipose tissue (especially, in aged or type II diabetes), and up to 70% water (3). For example loss of muscle mass in exercise reflects loss of water with or without loss of muscle protein. As suggested by Mitchell, although an increase in protein synthesis suggests increased muscle protein mass, no conclusion is possible without measurement of protein degradation. Infusion of L-(1–13C) leucine or L-(ring-2H5) phenylalanine has been used to measure whole body or skeletal muscle protein metabolism in humans (2). In animal models, rates of protein synthesis and degradation are often assayed *ex vivo* by measuring the rate of tyrosine incorporation into protein (protein synthesis) plus the release of tyrosine from muscle proteins (protein degradation) (4). This approach, however, does not allow both synthesis and degradation information to be gathered from the same animal. The rate of protein degradation is virtually always greater than the rate of protein synthesis regardless of whether undergoing muscle hypertrophy or atrophy. If the goal of measuring protein synthesis is to provide an index of changes in muscle protein mass, we suggest that investigators assess the distribution of the areas of myofibers in a cross section of muscle as described for assessing the effects of XIAP on muscle hypertrophy (5).

REFERENCES

1. **Mitchell CJ, Churchward-Venne TA, Cameron-Smith D, Phillips SM.** What is the relationship between the acute muscle protein synthetic response and changes in muscle mass? *J Appl Physiol*; doi: 10.1152/japplphysiol.00609.2014.
2. **Pupim LB, Flakoll PJ, Majchrzak KM, Aftab Guy DL, Stenvinkel P, Ikizler TA.** Increased muscle protein breakdown in chronic hemodialysis patients with type 2 diabetes mellitus. *Kidney Int* 68: 1857–1865, 2005.
3. **Wang X, Hu Z, Hu J, Du J, Mitch WE.** Insulin resistance accelerates muscle protein degradation: Activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling. *Endocrinology* 147: 4160–4168, 2006.
4. **Wang XH, Du J, Klein JD, Bailey JL, Mitch WE.** Exercise ameliorates chronic kidney disease-induced defects in muscle protein metabolism and progenitor cell function. *Kidney Int* 76: 751–759, 2009.
5. **Wang XH, Hu J, Du J, Klein JD.** X-chromosome linked inhibitor of apoptosis protein inhibits muscle proteolysis in insulin-deficient mice. *Gene Ther* 14: 711–720, 2007.

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SIGNIFICANCE OF LONG-TERM STUDIES IN RESISTANCE TRAINING AND MUSCLE HYPERTROPHY

TO THE EDITOR: Muscle being a postmitotic tissue is endowed with an efficient means of cell replacement to avoid muscle cell death and maintain skeletal mass. This is carried out through the dynamic balance between muscle protein synthesis and degradation (1). Muscle hypertrophy occurs when protein synthesis exceeds protein breakdown. Although the Viewpoint authors (2) agree with the importance of acute measurements in understanding mechanisms of divergent exercises and nutritional manipulations, they advocate the need for long-term studies to understand the holistic adaptations due to altered phenotype.

Muscle hypertrophy is a multifactorial process involving mechanical tension, muscle damage, and metabolic stress. In addition, many have observed numerous other factors, such as genetic predisposition, epigenetic influence, and transcriptional plasticity, age, gender, habitual physical activity, and training status, to influence the hypertrophic response to a training protocol affecting both the rate and the total gain in lean muscle mass. Hormones and cytokines, namely growth hormone, testosterone, interleukin-5, interleukin-6, etc., are also shown to play complex roles in hypertrophic process (3). Additionally, some of these hormones

have effects on immune system, bone remodeling, and extracellular fluid volume. A 20-wk-long RT revealed greater adaptability within endocrine system only in younger men (4). A discrepancy in immune responses to short-term and moderate exercise training is reported recently (5). Exercise-induced free norepinephrine concentration was reported to have effect on circulating hematopoietic stem and progenitor cell number and functionality (3). In the light of such varied complexities, it is appropriate to pursue long-term effects of exercise training on muscle hypertrophy.

REFERENCES

1. **Toigo M, Boutellier U.** New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. *Eur J Appl Physiol* 97: 643–663, 2006.
2. **Mitchell CJ, Churchward-Venne TA, Cameron-Smith D, Phillips SM.** Viewpoint: What is the relationship between acute measures of muscle protein synthesis and changes in muscle mass? *J Appl Physiol*; doi: 10.1152/japplphysiol.00609.2014.
3. **Schoenfeld BJ.** The mechanisms of muscle hypertrophy and their application to resistance training. *J Strength Conditioning Res* 24: 2857–2872, 2010.
4. **Walker S, Santolamazza F, Kraemer W, Häkkinen K.** Effects of prolonged hypertrophic resistance training on acute endocrine responses in young and older men. *J Aging Phys Act,* May 2. 2014.
5. **Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, Fleshner M, Green C, Pedersen BK, Hoffman-Goetz L, Rogers CJ, Northoff H, Abbasi A, Simon P.** Position statement. Part one: Immune function and exercise. *Exerc Immunol Rev* 17: 6–63, 2011.

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