Exercise-Induced Muscle Damage and Hypertrophy: A Closer Look Reveals the Jury is Still Out

*Brad J. Schoenfeld[1]

Bret Contreras[2]

1. Department of Health Sciences, CUNY Lehman College, Bronx, NY.
2. Sport Performance Research Institute, AUT University, Auckland, New Zealand

*Corresponding author email: brad@workout911.com, telephone: 718-960-1999, fax: 718-960-1999

We read with interest the paper by Damas et al (Damas et al. 2017) titled, "The development of skeletal muscle hypertrophy through resistance training: the role of muscle damage and muscle protein synthesis," which, in part, endeavored to review the role of exercise-induced muscle damage on muscle hypertrophy. This is a multifaceted topic and the authors are to be commended for attempting to delve into its complexities. That said, we feel there are a number of issues in interpretation of research and extrapolation that preclude drawing the inferences expressed in the paper that muscle damage neither explains nor potentiates increases in muscle hypertrophy. The intent of our letter is not to suggest that a causal role exists between hypertrophy and microinjury. Rather, we hope to provide balance to the evidence presented and offer the opinion that the jury is still very much out as to providing answers on the topic.

Firstly, the authors cite a study by Damas et al (Damas et al. 2016) as evidence that muscle damage is not involved in the hypertrophic response. However, this study was not designed to investigate a cause-effect relationship, or even correlation, between muscle damage and growth. While the study eloquently demonstrated that an initial bout of damage was explanatory as to why muscle protein synthesis is not associated with exercise-induced hypertrophy over time, it in no way can be used to draw inferences as to the long-term effects of damage on muscular adaptations. To properly study the topic would require carrying out a longitudinal resistance training (RT) study whereby one group experienced a predetermined level of damage and then comparing with another group that experienced minimal damage. Unfortunately, such a design is problematic as attempting to isolate damage in this fashion would invariably involve altering other RT variables that would confound the ability to draw causality. With respect to the Damas et al (Damas et al. 2016) study, it is impossible to determine whether some level of muscle damage experienced by subjects contributed to the observed hypertrophic changes in the study. Moreover, it is not clear whether more (or less) damage may have influenced hypertrophy over time. The only thing that can be concluded in this regard is that an initial exercise bout in untrained individuals appears to be directed toward structural repair as opposed to hypertrophy; the effects of repeated exposure to varying levels of damage beyond the initial bout cannot be extrapolated from the study design.

Second, the authors go on to cite the recent meta-analysis from our group (Schoenfeld et al. 2017) as evidence that there are no hypertrophic differences between the performance of concentric and eccentric actions and thus, given the well-established link between eccentric

actions and micro-injury, indirectly inferring that muscle damage does not play a role in muscle growth. The authors' conclusion was based on *a priori* alpha analysis, whereby the reported p-value ($p = 0.07$) did not reach "statistical significance." However, null hypothesis testing at a predetermined alpha level has been widely criticized as a flawed statistical method that should not be used to draw practical inferences (Bernards et al. 2017; Gelman and Stern. 2012; Hopkins et al. 2009). A closer inspection of our data using the reported magnitude-based statistics show that eccentric actions may indeed promote a superior hypertrophic response. As noted in our paper, the effect size difference (0.25) showed a modest but potentially meaningful magnitude of effect favoring eccentric exercise, and the 95% confidence intervals (-0.03, 0.52) clearly favored the eccentric condition. Moreover, based on the guidelines for statistics in exercise science proposed by Hopkins et al (Hopkins et al. 2009), results were likely/probably not due to chance alone. Thus, our data actually lend support to a hypertrophic benefit for eccentric actions. It also should be noted that eccentric actions have been shown to produce differential intracellular anabolic signaling responses compared to other muscle actions (Eliasson et al. 2006; Franchi et al. 2014), and the regional hypertrophic changes demonstrated between concentric and eccentric actions in several longitudinal studies have been hypothesized to be resultant to damage along the length of myofibers (Franchi et al. 2014; Hedayatpour and Falla. 2012). It remains speculative as to whether microinjury contributes to these differential effects between muscle actions, but the possibility that it may play a role cannot be dismissed based on current evidence. Lastly, the authors make the claim that satellite cells (SC) derived from damaging exercise are not involved in hypertrophic adaptations but rather function solely to mediate tissue regeneration. In support of this view, the authors cite a study by Hyldahl et al (Hyldahl et al. 2015) who found no evidence of myonuclear addition for up to 27 days following an initial bout of lengthening contractions. However, as the authors note in their review, myonuclear addition is not realized until an increase in muscle size exceeds ~26%; the theoretical threshold above which additional myonuclei are necessary to support continued growth. A lack of increase in the incorporation of myonuclei therefore would be expected in the Hyldahl et al (Hyldahl et al. 2015) study as minimal hypertrophy would necessarily occur from an acute bout of RT. Accordingly, under these circumstances there would be no impetus for SC-mediated myonuclear addition. Whether SC accretion from exercise-induced damage potentiates hypertrophic increases over time with repeated exercise damaging exercise bouts would require a longitudinal

study comparing the effects of two distinct levels of muscle damage. It also is interesting to speculate that an increase in SC via damage may be particularly important for low responders to RT as well as older individuals, as evidence shows that their ability to expand the SC pool is suppressed, which may in turn explain the observed blunted hypertrophic response (Petrella et al. 2006; Petrella et al. 2008).Whether SC derived from micro-injury could enhance hypertrophy in these populations requires future study.

To summarize, the paper by Damas et al (Damas et al. 2017) addresses an important topic for understanding the mechanisms of muscle growth and raises some pertinent considerations as to what role, if any, muscle damage plays in the process. However, in the quest to provide answers to mechanistic questions we must avoid the temptation to prematurely infer conclusions that cannot be supported by the available literature. The question at hand is not whether muscle damage is the primary driver of hypertrophy; clearly it is not as compelling evidence indicates mechanical stress is predominant in this regard. The relevant question is whether muscle damage may enhance the hypertrophic response to regimented RT over time. And to this question, we contend that the current body of evidence is not sufficient to draw conclusions with any degree of confidence. There would seem to be a sound rationale for a potential beneficial effect as previously detailed in the literature (Schoenfeld. 2012). Moreover, Lilja et al (Lilja et al. 2017) recently demonstrated that high doses of anti-inflammatory drugs suppressed hypertrophic adaptations in young, healthy individuals, conceivably by inhibiting the cyclooxygenase (COX) pathway. It is intriguing that the inflammatory response elicited by muscle damage has been implicated in COX induction, and thus raises the possibility that repeated micro-injury from RT may augment its hypertrophic effects. How all this theory plays out in practice remains to be determined and highlights the need for more rigorous research. Until such research is carried out and in the absence of sufficient quality evidence on the topic, scientific protocol dictates the importance of remaining prudent, inquisitive and cautiously skeptical.

The authors report no conflicts of interest.

References

Bernards JR, Sato K, Haff GG, Bazyler CD (2017) Current Research and Statistical Practices in Sport Science and a Need for Change. Sports 5:87

Damas F, Libardi CA, Ugrinowitsch C (2017) The development of skeletal muscle hypertrophy through resistance training: the role of muscle damage and muscle protein synthesis. Eur J Appl Physiol . doi:10.1007/s00421-017-3792-9 [doi]

Damas F, Phillips SM, Libardi CA et al (2016) Resistance training-induced changes in integrated myofibrillar protein synthesis are related to hypertrophy only after attenuation of muscle damage. J Physiol 594:5209-5222. doi:10.1113/JP272472 [doi]

Eliasson J, Elfegoun T, Nilsson J, Kohnke R, Ekblom B, Blomstrand E (2006) Maximal lengthening contractions increase p70 S6 kinase phosphorylation in human skeletal muscle in the absence of nutritional supply. Am J Physiol Endocrinol Metab 291:1197-1205

Franchi MV, Atherton PJ, Reeves ND et al (2014) Architectural, functional and molecular responses to concentric and eccentric loading in human skeletal muscle. Acta Physiol (Oxf) 210:642-654. doi:10.1111/apha.12225 [doi]

Gelman A, Stern H (2012) The Difference Between “Significant” and “Not Significant” is not Itself Statistically Significant. The American Statistician 60:328-331

Hedayatpour N, Falla D (2012) Non-uniform muscle adaptations to eccentric exercise and the implications for training and sport. J Electromyogr Kinesiol 22:329-333. doi:10.1016/j.jelekin.2011.11.010 [doi]

Hopkins WG, Marshall SW, Batterham AM, Hanin J (2009) Progressive statistics for studies in sports medicine and exercise science. Med Sci Sports Exerc 41:3-13. doi:10.1249/MSS.0b013e31818cb278 [doi]

Hyldahl RD, Nelson B, Xin L et al (2015) Extracellular matrix remodeling and its contribution to protective adaptation following lengthening contractions in human muscle. FASEB J 29:2894-2904. doi:10.1096/fj.14-266668 [doi]

Lilja M, Mandic M, Apro W et al (2017) High doses of anti-inflammatory drugs compromise muscle strength and hypertrophic adaptations to resistance training in young adults. Acta Physiol (Oxf) . doi:10.1111/apha.12948 [doi]

Petrella JK, Kim JS, Cross JM, Kosek DJ, Bamman MM (2006) Efficacy of myonuclear addition may explain differential myofiber growth among resistance-trained young and older men and women. Am J Physiol Endocrinol Metab 291:E937-46. doi:10.1152/ajpendo.00190.2006

Petrella JK, Kim J, Mayhew DL, Cross JM, Bamman MM (2008) Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: a cluster analysis. J Appl Physiol 104:1736-1742

Schoenfeld BJ, Ogborn DI, Vigotsky AD, Franchi MV, Krieger JW (2017) Hypertrophic Effects of Concentric vs. Eccentric Muscle Actions: A Systematic Review and Meta-analysis. J Strength Cond Res 31:2599-2608. doi:10.1519/JSC.0000000000001983 [doi]

Schoenfeld BJ (2012) Does exercise-induced muscle damage play a role in skeletal muscle hypertrophy? J Strength Cond Res 26:1441-1453. doi:10.1519/JSC.0b013e31824f207e