

# Anabolic Processes in Human Skeletal Muscle: Restoring the Identities of Growth Hormone and Testosterone

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**Abstract:** Testosterone supplementation acts via numerous mechanisms as a highly potent anabolic agent to skeletal muscle. Although growth hormone (GH) strongly affects collagen synthesis and lipolysis, as well as increasing lean body mass, it is not anabolic toward the contractile (ie, myofibrillar) muscle tissue in healthy individuals. However, there is a persistent belief (both in scientific literature and among recreational weightlifters) that exercise-induced release of GH and testosterone underpins muscular hypertrophy with resistance training. This is a premature assumption because although pharmacological GH supplementation can increase muscle strength or size in individuals with clinical GH deficiency, there is no evidence that transient exercise-induced changes in GH have the same effects in individuals with normal GH levels. Exercise paradigms are designed based on the assumption (not necessarily evidenced-based mechanisms) that GH and testosterone facilitate anabolic processes that lead to skeletal muscle protein accretion and hypertrophy. Our recent work disputes this assumption. Instead, our data indicate that exercise-induced hormonal elevations do not enhance intracellular markers of anabolic signaling or the acute postexercise elevation of myofibrillar protein synthesis. Furthermore, data from our training study demonstrate that exercise-induced increases in GH and testosterone availability are not necessary for and do not enhance strength and hypertrophy adaptations. Instead, our data lead us to conclude that local mechanisms that are intrinsic to the skeletal muscle tissue performing the resistive contractions (ie, weightlifting) are predominant in stimulating anabolism. The purpose of this article is 1) to provide a brief overview of the mechanisms of action of testosterone and GH; 2) to discuss the inability of physiological exercise-induced elevations in these hormones to have a measurable impact on skeletal muscle anabolism; and 3) to describe factors that we believe are more important for stimulating hypertrophy in human skeletal muscle. Clarifying both the role of hormones in regulating muscle mass as well as the underlying basis for adaptation of skeletal muscle to resistance exercise will hopefully enhance and support the prescription of resistance exercise as an integral component of a healthy lifestyle.

**Keywords:** testosterone; growth hormone; hypertrophy; muscle protein synthesis

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## Introduction

Repeat phases of positive net protein balance, which can be generated by the elevation of protein synthesis in response to repeated bouts of resistance exercise and protein ingestion, underpin muscle hypertrophy. In addition to the stimulus provided by loaded muscle contraction and amino acids, the hormone testosterone is considered highly anabolic. Training response in young men is attenuated when testosterone is pharmacologically suppressed to approximately one-tenth of normal levels.<sup>1</sup> Thus, testosterone contributes in some way to the anabolic processes that are initiated by resistance training in young men. Interestingly, women have testosterone levels that are approximately 10-fold lower basally (not unlike the levels seen in the study by Kvorning et al<sup>1</sup>), yet a recent large study reports comparable rates of hypertrophy in men and women after resistance training.<sup>2</sup> Does this mean, then, that testosterone is contributing to anabolic pathways in men but not in women? Or are women more efficient in using their inherently lower levels of systemic testosterone? Fundamental questions such as these remain unanswered as the role of hormones in regulating muscle mass continues to be elucidated.

Studies using pharmacological doses of testosterone and growth hormone (GH) help clarify these hormones' mechanisms of action on skeletal muscle and other bodily tissues. For example, it is apparent that supraphysiological testosterone is highly potent in stimulating muscle hypertrophy, whereas GH does not increase myofibrillar protein synthesis and instead directs anabolic action toward increasing whole-

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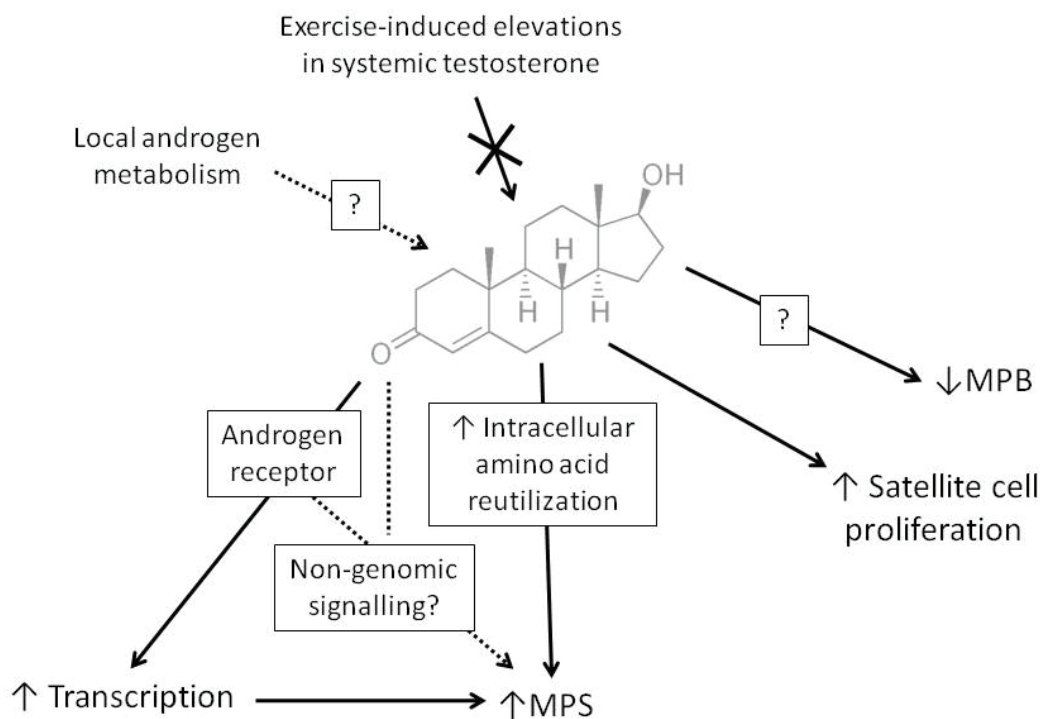
body protein synthesis (eg, connective tissue). In contrast, exercise-induced hormones, which have been characterized numerous times, have been poorly understood. In many cases, it has been assumed that the individuals with normal endocrine levels are bound with the same dependence on the circulating hormone concentrations to support training adaptations. Recently, however, it was demonstrated that muscle hypertrophy can occur in the absence of exercise-induced increases in endogenous anabolic hormone concentrations.<sup>3</sup> Furthermore, we have shown that exercise-induced increases in GH and testosterone do not enhance and are not necessary for muscle anabolism. Moreover, women can have hypertrophy to a similar degree to men in response to resistance training, despite having testosterone levels that are approximately 10-fold lower basally and with no exercise-induced testosterone response. These findings contribute to increasing evidence that support local regulation of skeletal muscle and

challenge the common perception that systemic changes in anabolic hormones are required for the stimulation of muscular hypertrophy that occurs with resistance training. Clarifying both the role of hormones in regulating muscle mass as well as the underlying basis for adaptation of skeletal muscle to resistance exercise will promote resistance exercise as an integral component of a healthy lifestyle.

## Testosterone

Evidence is undisputed that anabolic steroids are extremely potent in inducing muscle hypertrophy. Indeed, the capability of testosterone to increase muscle cross-sectional area, both solely and in combination with resistance exercise, has been demonstrated in a study of testosterone supplementation in young men.<sup>4</sup> The highly anabolic nature of testosterone is likely interdependent to some extent (Figure 1). Firstly, the nature of testosterone as a steroid allows it to cross the

**Figure 1.** The multiple mechanisms by which testosterone can act in a myofiber.



**Abbreviations:** MPB, muscle protein breakdown; MPS, muscle protein synthesis.

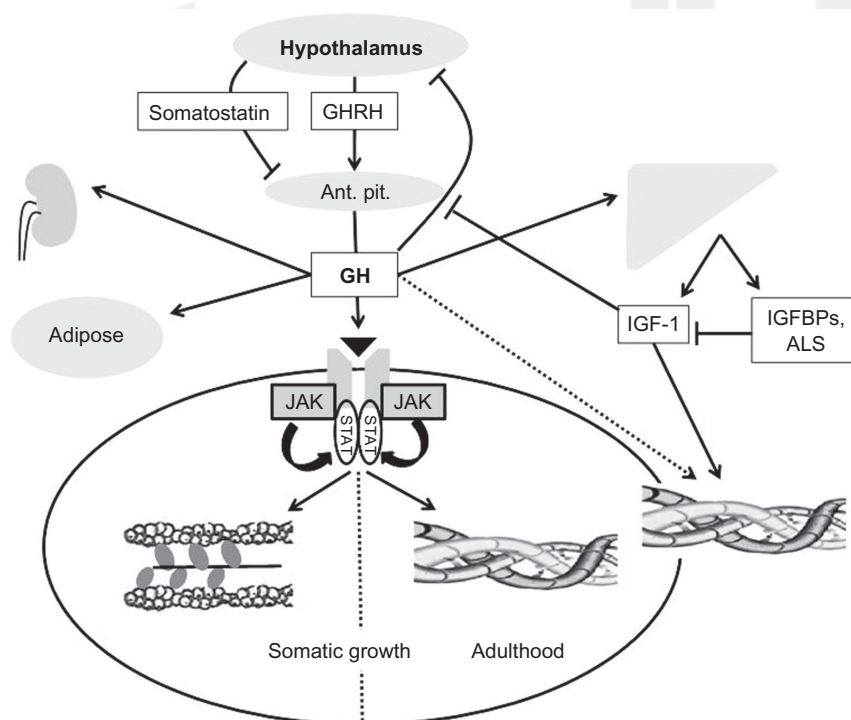
lipid bilayer of the sarcolemma where it can form a complex with cytosolic or nuclear<sup>5</sup> androgen receptors to ultimately enhance gene transcription. The androgen receptor contains > 3 important subunits: 1) a C-terminal domain, which binds ligands (eg, testosterone); 2) a central domain, which binds DNA; and 3) an N-terminal domain, which regulates transcription.<sup>6</sup> On ligand binding, androgen receptors transform, dimerize, translocate to the nucleus, and bind to androgen-response elements as a homodimer.<sup>6</sup> Activation of androgen response elements stimulates the transcription of protein targets directly related to protein accretion (eg, MHC). In addition, testosterone may also enhance transcription of other anabolic systems, such as the local production of insulin-like growth factor 1 (IGF-1).<sup>5</sup> Secondly, pharmacological doses of testosterone increase the rate of muscle protein synthesis.<sup>7,8</sup> Testosterone has been shown to increase the intracellular reutilization of amino acids to stimulate muscle protein synthesis<sup>8</sup> as well as decrease muscle protein breakdown,<sup>9</sup> the latter of which is attributed to decreased ubiquitin-proteasome activity or antagonism of glucocorticoid-based mechanisms either by ligand-receptor interference or by interfering with DNA

binding to improve fasting net protein balance.<sup>5,10</sup> Thirdly, testosterone may facilitate the accumulation of DNA that is normally required for muscle growth by activating satellite cells.<sup>11</sup> Figure 3 places exogenous testosterone at the bottom of the hypertrophy pyramid, indicating that it is highly potent in producing increases in skeletal muscle cross-sectional area.

## Growth Hormone

Growth hormone acts both directly through its receptor and indirectly through systemic IGF-1 to regulate a variety of tissues (Figure 2). It is well established that growth and maturation of the musculoskeletal system is mediated by systemic changes in the GH/IGF-1 axis.<sup>12</sup> For example, a deficiency or excess of GH during growth can result in overt musculoskeletal changes (eg, slowed or accelerated changes in stature, respectively). Furthermore, GH plays an important role in regulating body composition in adult life; rhGH supplementation in clinically GH-deficient individuals restores “normal” fat to lean tissue distribution through decreased fat mass and increased lean tissue assimilation. In addition, GH and muscle mass are reduced in tandem with age, which can

**Figure 2.** A basic overview of the effects of growth hormone (GH) on multiple tissues in the body.



Clockwise from top right: hepatic insulin-like growth factor I (IGF-I) production, indirect and direct stimulation of connective tissue synthesis, intramuscular connective tissue synthesis in adulthood, myofibrillar synthesis during phases of rapid growth and maturation, lipolysis, fluid retention.



lead to an inaccurate interpretation that there is a cause-and-effect relationship. Based on this logic, GH could be viewed as an attractive ergogenic aid to maintain strength and muscle mass in elderly populations. Although GH replacement can be used to recover lean body mass in individuals with clinical GH deficiency, studies by Taaffe et al<sup>13,14</sup> revealed that rhGH supplementation did not augment gains in strength or muscle fiber hypertrophy following resistance training in elderly men. These findings are in agreement with studies by Yarasheski et al,<sup>15,16</sup> who found that while whole-body protein synthesis was increased, there was no augmentation of muscle protein synthesis with rhGH supplementation in both young and old men. Moreover, in sedentary elderly men, 16 weeks of GH and resistance exercise conferred no added strength gains across 9 exercises versus resistance exercise plus placebo.<sup>16</sup> Not surprisingly, there was no difference observed between groups in muscle protein synthesis. Although increases in fat-free mass were greater in the GH group, the authors demonstrated that a disproportionate amount of the mass was because of increased total body water,<sup>16</sup> which may be partly due to a hydrating process of newly synthesized connective tissue that equilibrates with extracellular fluid. This is also not surprising because GH acutely and chronically alters the regulation of water and electrolytes by the kidneys, resulting in an expanded extracellular volume.<sup>17</sup>

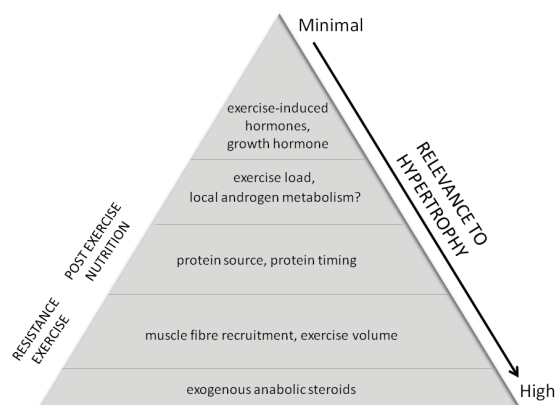
There is good evidence that GH can favorably affect body composition by stimulating lipolysis<sup>18</sup> and increasing lean body mass. For example, in a 6-month randomized controlled trial in healthy elderly men, administration of low-dose GH significantly increased lean body mass by approximately 2 kg.<sup>19</sup> However, the increased mass did not translate into strength changes, implying that GH can promote fluid retention, but not affect functional (ie, strength-promoting) muscle protein accretion. Indeed, GH-induced increases in lean body mass can be misinterpreted as muscle growth, but instead are primarily related to body water retention<sup>16</sup> that accompanies the accretion of lean tissue that arises from elevated whole-body protein synthesis. Thus, while using GH as a therapeutic agent in cases of clinical deficiency can help recover muscle mass and strength<sup>20</sup> at normal or even supraphysiological levels, anabolic effects are directed toward the synthesis of collagen, not contractile myofibrillar proteins.<sup>21</sup> For example, Wallace et al<sup>22</sup> reported large increases in markers of bone and soft tissue formation with GH supplementation after acute endurance exercise. These findings are in agreement with the report that

7 days of GH administration stimulated collagen-producing osteoblasts and activated bone remodelling.<sup>23</sup> Circulating GH and IGF-1 are thought to also increase collagen synthesis by fibroblasts and increased fibroblast cell division in the extracellular matrix and tendons.<sup>24</sup>

In summary, there is little support for GH having an effect on muscle hypertrophy. Rather, accumulating evidence suggests that GH functions primarily to increase the synthesis of whole-body proteins and connective tissue, in particular increasing water retention and altering body composition. Accordingly, GH supplementation does not increase myofibrillar protein synthesis or muscle strength in healthy individuals. Thus, Figure 3 places GH at the top of the pyramid of factors regulating hypertrophy, indicating that its contribution is negligible.

## Exercise-Induced Anabolic Hormones

Resistance exercise program variables can be manipulated to alter the acute postexercise blood concentration profile of testosterone and GH. Specifically, bouts of resistance exercise that are high in volume, activate a large muscle mass, and require a high degree of effort transiently (~40 min) to elevate the circulating levels of testosterone and GH. We recently measured the muscle protein synthetic and signaling responses to an acute bout of arm exercise in the presence of divergent hormonal environments.<sup>25</sup> In one condition, arm exercise alone was performed; this resulted in GH and testosterone concentrations that remained near basal levels. In the other condition, the performance of identical arm exercise was immediately followed by a high volume of leg exercise at a moderate-to-heavy load, which activated a large muscle mass. Arm exercise was selected to precede leg exercise so that there would be no possible confounding influence of central fatigue (ie, participants would be able to exert maximal effort during arm exercise in both conditions without any residual fatigue from the leg exercises). The leg exercise stimulated a large increase in endogenous GH and testosterone, which peaked approximately 15 minutes after exercise. These hormones returned to basal levels by 60 minutes after exercise. As expected, the rate of muscle protein synthesis was elevated after exercise (ie, a main effect was observed); however, despite drastic differences in the postexercise concentrations of testosterone and GH, there were no differences between conditions. Therefore, acute increases in the availability of GH and testosterone did not enhance the rate of muscle protein synthesis in the biceps muscle exercised.

**Figure 3.** From essential to extraneous: factors that influence skeletal muscle hypertrophy.

It is understood that these factors often work in concert and not in isolation; furthermore, the relative positions of certain components are somewhat speculative. However, continued research will identify new components as well as facilitate upward and downward mobility of components of the pyramid in order to define the biggest players and strongest signals that regulate hypertrophy. Finally, genetic predisposition to hypertrophy will determine the potential of skeletal muscle to respond to factors noted on the pyramid. Exercise = resistance exercise.

We have recently confirmed these acute findings in a training study in which these 2 different hormonal conditions were elicited repeatedly after bouts of elbow flexor exercise. In agreement with the findings of our acute study, we report that exercise-induced elevations of testosterone and GH do not enhance gains in muscle hypertrophy or strength in young men with training.<sup>3</sup>

As outlined previously, elevated hormone concentrations after exercise bouts are a result of changes in secretion, clearance, and/or hemoconcentration. The biological implications of postexercise hormonal changes remain to be elucidated, but elevated GH and testosterone appear to respond to various signals associated with the exercise bout (eg, increased lactate concentration, neural feedback, hypoxia<sup>26</sup>); as such, it is possible that they are responding as part of a concerted effort to mobilize fuel. Interestingly, the acute GH response after exercise appears to be associated with an increase in the rate of glycerol appearance, a measure of lipolysis.<sup>27</sup> The finding that carbohydrate provision blunts the elevation in cortisol<sup>28,29</sup> (an exercise-responsive hormone involved in glucose release) appears to support this notion. Furthermore, while exercise is a well-established stimulator of GH release, it appears that the exercise-induced GH release is relatively nonspecific and is released in response to both resistance exercise and moderate intensity aerobic exercise (eg, 60% maximum oxygen uptake [ $\text{VO}_{2\text{ max}}$ ]),<sup>26</sup> the latter of

which is not associated with hypertrophy. This is in contrast to the specific nature of various muscular adaptations that occur in response to exercise, as demonstrated by Wilkinson et al.<sup>30</sup> Perhaps it makes more sense that GH would exert more general metabolic effects such as substrate mobilization and connective tissue remodeling in response to an exercise stimulus.<sup>31</sup>

## Factors That Drive Hypertrophy

In general, there are numerous inputs contributing to the signaling milieu that takes place in each muscle cell that is stimulated from loaded contractions. We know that these loaded contractions activate signaling cascades that increase mRNA translation, which is thought to be the rate-limiting step to increasing muscle protein synthesis.<sup>32,33</sup> However, the locus of control for the regulation of muscle mass remains to be fully elucidated because a similar early activation of proteins involved in translational control was recently observed after both aerobic and resistance exercise,<sup>34</sup> which are known to produce divergent phenotypes, leading the authors to suggest gene transcription may be more important than originally thought.

We have recently observed that exercise load is not a primary variable in determining response to protein synthesis. Specifically, light loads (30% of 1 repetition maximum [RM]) can stimulate muscle protein synthesis to a similar extent as heavy loads (90% of 1RM) provided light loads are lifted to failure.<sup>35</sup> This finding challenges the recommendation<sup>36</sup> that lifting heavy loads provides a superior anabolic stimulus. Instead, it supports a thesis underpinned by the size principle, whereby type II fibers, which are highly hypertrophic,<sup>37</sup> are activated during the repetitions preceding muscle failure despite the relatively light load. The occlusion that develops with this type of training likely plays an important role in the type II fiber recruitment and overall muscle hypertrophy at light loads.<sup>38,39</sup>

Although load does not appear to be a crucial factor in creating an acute anabolic response, we have recently observed that 3 sets of resistance exercise enhance both the intracellular signals and the rate of myofibrillar protein synthesis versus 1 set.<sup>40</sup> In other words, certain regulatory anabolic signaling proteins (ie, p70S6K1) appear to remain active for a longer duration following 3 sets versus 1 set of resistance exercise at 70% of 1RM. Specifically, p70S6K1, whose activation is correlated with increases in myofibrillar protein synthesis<sup>41</sup> and hypertrophy,<sup>42,43</sup> appears to be rejuvenated by protein ingestion 24 hours after exercise, particularly if 3 sets were performed.

Thus, it appears that repeat exercise sets may allow for the repeated activation of type II fibers, which may be responsive to either unknown volume-sensitive mechanisms, or may simply require multiple sets to be recruited and anabolically active.

The inherent biological purposes of the increase in GH and testosterone that results from high-volume, high-intensity exercise that uses a large muscle mass are not clear. These hormone elevations appear to be a metabolic byproduct that may contribute to fuel mobilization and tissue remodeling or repartitioning as opposed to a direct stimulator of contractile tissue anabolism. Indeed, the complete lack of a relationship between the exercise-induced hormone response and either the acute or chronic phenotypical outcome has led to the question of where or how a hormone such as testosterone, which is anabolic in nature, could be occurring. Recent work in rodents has investigated the prospect of locally produced testosterone as the result of increased activity of steroidogenic enzymes. Aizawa et al<sup>44,45</sup> suggest exercise-induced activation of local androgen metabolism and report increases in androgen receptor content and intramuscular testosterone. Thus, as we have found that systemic hormone changes are not intrinsically reflective of an effect in the muscle, we are aware that intramuscular hormone concentrations (while manipulated by exercise) were not controlled, and there is therefore no definitive indication that they are having an effect. However, when considering that intramuscular steroidogenic enzymes are upregulated in concert with the intramuscular hormone concentrations, this suggests that androgens are being produced locally where they are spatially and readily available for ligand-receptor interaction. Furthermore, local androgen production appears reasonable because intramuscular testosterone concentrations increase with exercise in female rats, which have low systemic levels. Although these data are intriguing, however, human data did not show an increase in intramuscular testosterone levels with resistance training.<sup>46</sup> Changes in intramuscular androgen metabolism need to be corroborated with a phenotypical outcome (eg, muscle protein synthesis) and in human skeletal muscle to determine if there is a local hormone component that is contributing to other known signaling pathways initiated by loaded contractions.

Lastly, our laboratory has produced data that show both the acute and chronic anabolic response to resistance exercise is markedly influenced by postexercise nutrition. We have shown that milk protein confers a greater anabolic advantage (ie, elevates muscle protein synthesis and enhances hypertrophy to

a greater degree) than soy protein or an isocaloric carbohydrate drink.<sup>47,48</sup> Placement of protein source and protein timing<sup>49</sup> on the middle platform of Figure 3 denotes the interaction of postexercise nutrition with training-induced hypertrophy phenotypes. A review by Tang and Phillips<sup>50</sup> provides a more detailed description of different protein sources. Despite claims that exercise-induced hormones could synergistically interact with postexercise nutrition, it has never been demonstrated, and currently there is no plausible mechanism by which these hormones enhance amino acid transport into the muscle and enhance skeletal muscle protein accretion.

## Conclusion

Adaptations to exercise are both exercise- and muscle-specific, suggesting local factors are of primary importance. The many local events that are observed in response to weightlifting are being integrated into coherent mechanisms that continue to improve our understanding of the regulation of human skeletal muscle. What is becoming clear is that exercise-induced GH and testosterone responses are not suitable surrogate measures of skeletal muscle anabolism and do not reflect the mechanisms that underpin hypertrophy. Adverse events associated with the prescription of testosterone continue to be reported in the literature.<sup>51</sup> In contrast, resistance exercise is a safe and simple activity, and has the dual benefit of actively expending energy while increasing lean body mass and basal metabolic rate, as well as reducing risk for chronic diseases. Future studies need to systematically characterize and quantify the effect of resistance exercise to disease risk. It may be time for head-to-head comparison of the health benefits of resistance exercise versus aerobic exercise versus pharmacology-based interventions; perhaps then the prescription of resistance exercise would be more prevalent, which would undoubtedly benefit the public health profile.

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## Conflict of Interest Statement

Daniel W. D. West and Stuart M. Phillips, PhD, FACSM disclose no conflicts of interest.



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