



## Is muscle growth a mechanism for increasing strength?

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### ABSTRACT

Skeletal muscle hypertrophy commonly occurs with repeated bouts of resistance exercise as well as following the administration of exogenous drugs. This increase in muscle size is thought to be mechanistically important for the increase in muscle function. However, at present, there is no experimental evidence that would support any paradigm in which muscle hypertrophy is a mechanism for increasing strength with exercise. Therefore, it seems reasonable to also question the importance of changes in muscle size for changes in muscle strength (function) following exogenous drugs as well as aging, where both muscle size and strength decrease. The purpose of this paper is to discuss whether changes in muscle size contribute to changes in voluntary strength following exercise, pharmaceutical interventions, and aging. We also aim to provide potential mechanisms (central and peripheral) for the change in strength as well as outline study designs to better address this question. Herein, we suggest that there are dissociations between changes in muscle size and strength following exercise, anabolic drug administration, and aging (to a point). These dissociations occur throughout the literature, suggesting that these changes may be completely separate phenomena. We are not dismissing the potential importance of maintaining muscle mass, particularly in clinical populations. What we are suggesting, however, is that muscle function may not necessarily be improved by these exercise or pharmacological induced increases in muscle size. Exploring mechanisms and explanations beyond just changes in muscle size may improve therapy targeted at improving muscle function.

### Introduction

Skeletal muscle hypertrophy can occur with repeated bouts of resistance exercise as well as following the administration of exogenous drugs [1]. It has been suggested that increasing muscle size via resistance training and/or pharmacological compounds may produce a greater quality of life as an individual approaches senescence [2]. This topic is of particular interest to researchers investigating the mechanisms behind force production and clinicians studying and/or treating the age related decreases in muscle size and strength [3]. This is, in part, related to the direct relationships often observed between skeletal muscle size and function (and/or strength) [4,5]. However, it becomes difficult to discern whether muscle growth is important for the increase in strength because these changes sometimes occur together with exercise and/or pharmacological administration [1,6]. In other words, just because two things occur together does not necessarily mean that one (muscle size) caused the other (muscle strength). To address that question [7], a study would need to be designed to produce different effects on one variable (muscle size) and observe how this manipulation directly impacts the results of the other variable (muscle strength). This

study design could potentially be used for any variable thought to play a mechanistic role in strength gain but muscle growth is the variable of interest in the present manuscript.

We and others have questioned the influence that exercise induced muscle growth has on exercise induced increases in muscle strength [8,9]. Previous investigations specifically discussed this paradigm within exercise [10,11]; however, the use of muscle hypertrophy as a mechanism of strength change is not specific to exercise [1]. To be clear, our goal with this paper is not to exhaustively review this topic within each line of inquiry. The purpose of this paper is to discuss this concept in the context of exercise, pharmaceutical, and aging induced changes in muscle size and voluntary strength. Although not an exhaustive review, it is of note that a single well designed study can falsify a claim (in this case that muscle hypertrophy plays a causal role in determining strength changes) in the case that it has been specifically designed to test that claim; such that it is highly capable of finding flaws or discrepancies (i.e. a severe test). If no flaws or discrepancies are found, then it can be said that the claim has passed a severe test and thus the result is evidence for the claim. However, it cannot be said that a result provides evidence for the claim if little has been done to rule

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out ways the claim may be false. The data may agree with the claim, but may not constitute a severe test of the claim (i.e. bad evidence, no test) [12]. Herein, we propose a more general hypothesis regarding the role of changes in muscle mass for determining strength changes in conditions where growth or loss can occur. Having a greater understanding of the mechanisms behind these changes may improve therapy targeted at improving muscle function.

## Lines of inquiry

### Exercise

Muscle hypertrophy and increased strength are two common occurrences when an adult undertakes a resistance training program [13,14]. This is perhaps why it seems intuitive to some that they must be mechanistically related [15]. A historical review of this topic suggests that muscle hypertrophy as a mechanism of strength change appeared quite questionable up until about the 1980s. For example in reference to strength gain, Schneider astutely pointed out in 1939 that “Casual observation is sufficient to prove that muscles do not make the similar gain in size [16].” Later in 1963 Morehouse stated “It has not been proved that hypertrophy is necessarily a desirable reaction. Some students are of the opinion that it may be simply a by-product of training, perhaps a noxious one [17].” From the mid to late 1980s on, however, the idea that muscle hypertrophy was a mechanism for strength change became almost axiomatic [18–20]. What changed? Evidence that muscle hypertrophy may be related to strength was provided in the early 1970s by Ikai and Fukunaga. They found that the change in maximum strength appeared to track with the increase in cross-sectional area following 100 days of isometric elbow flexion contractions [14]. Despite this early work from Ikai and Fukunaga, the study most textbooks cite as evidence for this mechanism is the within-subject experimental investigation completed by Moritani and DeVries in 1979. Participants completed an 8 week study in which one arm was exercised (elbow flexion) and the other arm did not exercise [21]. The investigators noted a change in voltage via surface electromyography and deduced that muscle hypertrophy was playing a significant role after the first few weeks. The authors supported this assertion by noting concomitant changes in arm circumference. One year later [22], using the same electromyography technique, they concluded that “Hypertrophy, on the other hand, undoubtedly contributed to the strength development in the young subjects, especially in the later stages of training while neural factors mainly contributed to the strength gain only at the initial stage of the training.”

After the 1980s, the story became “neural first, followed by hypertrophy” to explain why individuals increase voluntary strength following resistance exercise. Perhaps worth mentioning is that the commonly cited work of Moritani and DeVries did not actually measure muscle growth [21,22]. Nevertheless, it is more important to highlight that neither of those studies were designed to answer whether or not exercise induced muscle growth is important for changes in strength. For example, what would happen if both arms exercised (rather than exercise vs. non-exercise control) but one was designed to minimize muscle growth? When this is done, the strength change appears similar between arms [10], despite one arm having muscle hypertrophy and one arm not (elbow flexion exercise). When investigating different exercises (chest press, leg extension), similar findings emerge [11]. In other words, despite conditions having greater muscle growth, participants who experienced muscle growth were not any stronger than another group training in a situation designed to minimize hypertrophy (i.e. muscle growth was not necessary for changes in muscle strength).

What if the exercising groups had the same muscle growth but one group was designed to eliminate strength gain? Recently, two studies have been published which showed that bodyweight exercise (no external load lifted) was capable of increasing muscle size but not maximal voluntary strength [23,24]. Similar findings have been noted in

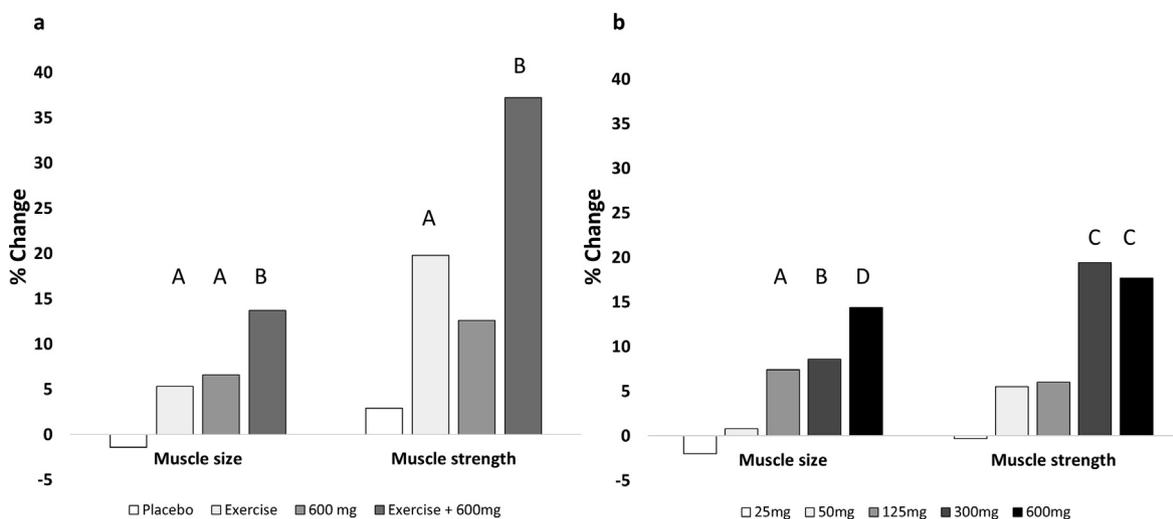
the blood flow restriction literature when very low loads (15% of maximum strength) are used [25,26] (i.e. muscle growth not sufficient for changes in voluntary muscle strength).

When the experimental evidence is considered together, this would seemingly provide justification for rethinking how we discuss exercise induced changes in muscle strength. However, proponents of the existing paradigm would disagree and appeal to the correlations between muscle cross sectional area and strength [27–29]. Though correlation is not causation is an obvious retort, another would be that these type of data provides no information for the current discussion; that is, whether the change in muscle size produces a change in muscle strength [4]. When looking at those changes, the correlations range from low to high depending on what correlational analysis is used [27–30]. Regardless of the method, there are a number of considerations that should be made; 1) these analyses cannot imply cause and effect, 2) these analyses use data from studies designed to maximize muscle growth, and 3) these analyses are likely correlating the error/random biological variability with muscle size with the error/random biological variability in muscle strength [4].

Is it any surprise that a study designed to increase muscle size and strength finds that they correlate with each other? Is the finding that two variables share variance compelling evidence that one causes the other? Is a change in voltage measured by surface electromyography, with no measurement of muscle size, sufficient to inform us about the importance of changes in muscle size for changes in muscle strength? The two studies designed to try and address this question fail to offer support for changes in muscle size leading to changes in muscle strength [10,11]. Even outside of those, there are many studies reporting dissociations at the group level between these two variables with exercise [31–34]. It is noted that dissociations do not completely rule out a cause and effect relationship between changes in muscle size and changes in muscle strength. Even so, the evidence of dissociation offers up the possibility that one variable is not contributing to the other (i.e. separate and potentially unrelated changes), as a true causal relationship would likely result in at least some magnitude of correlation present. We have noted previously [4] that the within subject correlation of a group increasing muscle size and strength was  $r = 0.68$ ; however, there was no within subject correlation between variables in another group that observed the same increase in strength without a change in muscle size. This highlights the limitations of correlations in answering this question and provides rationale for the inclusion of multiple groups in an effort to better study the impact of changes in muscle size for changes in muscle strength. In our opinion, the current story as it relates to exercise needs revision.

### Pharmaceutical

Pharmacological aids are used in clinical populations in an effort to increase muscle function, which is often attributed to the accretion of muscle mass [35–37]. However, based on the findings with exercise, it seems reasonable to question the physiologic importance of changes in muscle size for changes in muscle strength (function) following pharmacological aid (e.g. anabolic compounds). There are certainly studies that report statistically significant increases in muscle size and function following the administration of anabolic compounds [36,38]. Nevertheless, two things changing together does not necessarily mean one variable is causative for the next. For example, testosterone has been shown to increase motor neuron soma size and initiate electromyography activity when administered to rats [39], indicating that testosterone may augment strength by inducing neural adaptations independent of muscle hypertrophy. It is not uncommon to observe that the changes in muscle size are dissociated from the changes in measures of strength and physical function [40,41]. Some studies report increases in muscle mass without changes in function [42,43] (i.e. muscle growth not sufficient for increasing function), whereas others report an increase in function with no change in muscle mass [41] (i.e. muscle



**Fig. 1.** Relative change (%) in muscle size and strength with different doses of testosterone with or without exercise. Fig. 1a shows data from Bhasin et al. [1] which were calculated from Table 4 in that article. A = statistically significant differences from placebo; B = statistically significant differences from all other conditions. Fig. 1b shows data from Bhasin et al. [44] which were calculated from Tables 4 and 5 in that article. A = statistically significant differences from 25 mg; B = statistically significant differences from 25 and 50 mg doses; C = statistically significant differences from 25, 50 and 125 mg doses; D = statistically significant differences from all other groups.

growth is not necessary for increasing function). It is acknowledged that many of these studies are placebo-controlled drug trials that do not contain an exercise component. When clinical populations add in exercise with or without drug therapy, there is almost always an increase in strength/function but not always a change in muscle size [36,40].

In young healthy men [1], administering supraphysiologic levels of testosterone resulted in changes in muscle strength that were not statistically different between a group exercising with a placebo (19.8% change) and a group that just received 600 mg (12.6% change) of testosterone (Fig. 1a). When endogenous testosterone production was suppressed and exogenous testosterone was given at 5 different doses in otherwise healthy men [44], the changes in muscle strength did not necessarily follow changes in muscle size (Fig. 1b). However, looking at Fig. 1a, it would not be unreasonable to conclude that the pattern of change in muscle size tracks reasonably well with the change in muscle strength. This is particularly true when one considers that there is error associated with each measurement and that might make it difficult for the measurements to line up perfectly (i.e. an  $x$  amount of increase in one variable results in an  $x$  amount of increase in another variable). Nevertheless in Fig. 1b, one could just as easily conclude that the pattern of change in muscle size does not track well with the change in muscle strength. Although we can compare and contrast these two studies and other studies like them, they will never give definitive information about the importance of changes in muscle size for changes in muscle strength. This is not meant to be a criticism of those studies, but more of a suggestion to consider the methodological design of these papers when reading with this particular question in mind. Taken together, it seems reasonable to speculate that the testosterone induced increases in muscle function may also be occurring independently of the change in muscle size.

### Aging

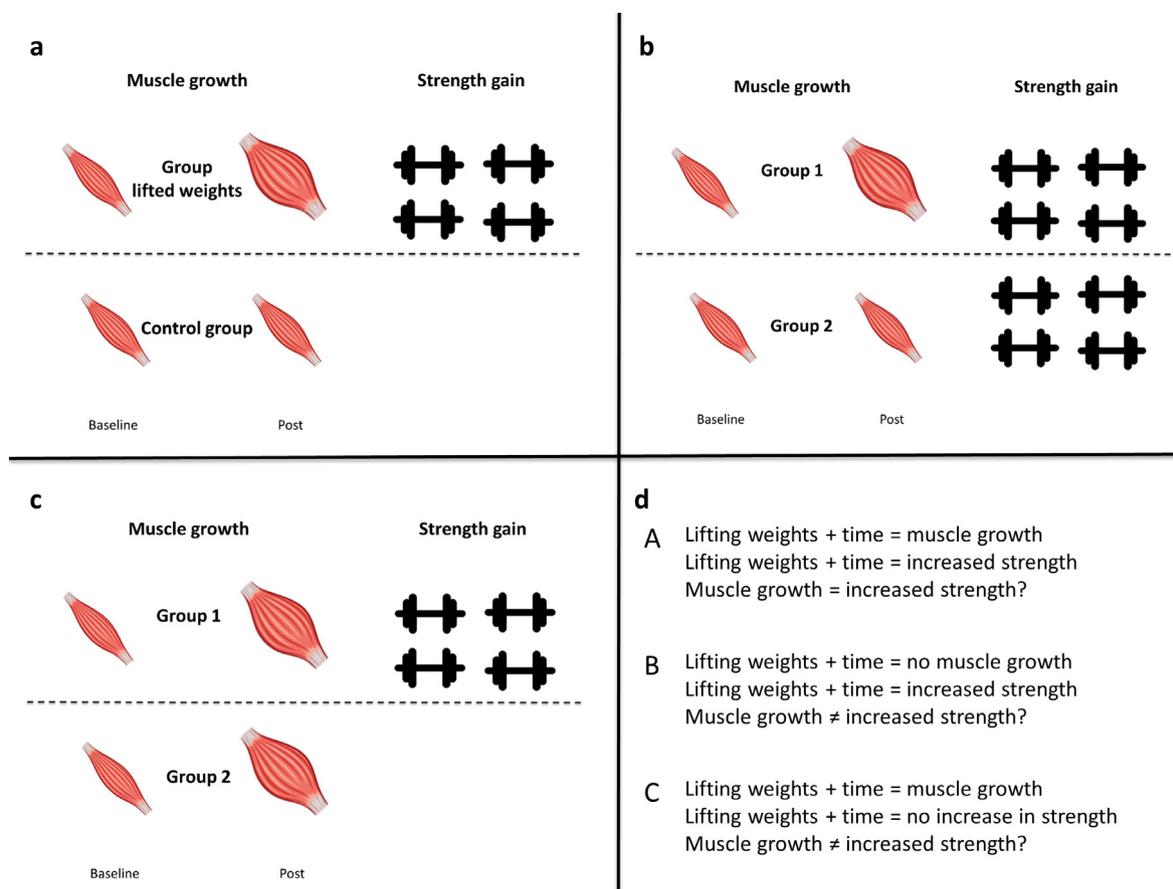
Muscle size and strength are commonly uncoupled with the aging process, with strength decreasing significantly more than that which could likely be attributed to changes in muscle size [45,46]. Because of the long lifespan of a human being, research on human aging is logistically difficult. Due to this, there has been a high reliance on cross-sectional data to inform researchers/clinicians about changes in muscle size and strength across a lifespan [47]. Based on the high correlations observed between muscle size and strength in these studies, it is easy to

assume that the two are mechanistically related. Longitudinal data tell a somewhat different story, with strength decreasing much more than muscle size. In fact, a longitudinal study found that a group that increased muscle size over a 5 year period still lost muscle strength [45]. This suggests that changes in muscle size across time may not necessarily be driving the declines in muscle strength/function. However, some may point to “muscle quality” decreasing in the aforementioned group that maintained muscle mass. Muscle quality in that study was defined as strength divided by muscle size. We are of the opinion that this is a somewhat misleading variable, because it assumes that those two are mechanistically related. We do wish to highlight that, contrary to the changes observed with exercise, there is likely a point at which the loss of muscle mass begins to meaningfully affect muscle strength and function [48]. The decrease in the contractile machinery needed for muscle size to become a limiting factor in strength with age is presently unknown. Nevertheless, we felt it of merit to at least mention this commonly observed dissociation in muscle size and strength with age.

### Rodent models

Although our question of interest is how humans increase voluntary strength, there is still likely something to be learned from rodent models. To avoid deviating too far from the purpose of this paper, we will be brief. Similar to humans, resistance type exercise in rodents also produces dissociations between muscle size and strength [49]. Some prefer these resistance exercise models to genetic manipulation or synergist ablation, because it is thought that these exercise models (e.g. ladder climbing, plantar flexion exercise, squat movements) may better imitate human exercise. For example, the loading patterns are intermittent and the amount of growth produced may be more similar to a human partaking in an exercise training programs. In other words, muscle size changes or does not change [49,50], but muscle strength almost always increases.

With genetic manipulation, muscle size can increase to levels much greater than that observed with exercise. Myostatin knockout is one example where the removal of a negative regulator of growth has a profound impact on the size of the animal [51,52]. Interestingly, the increase in strength is not always as impressive. Absolute levels of strength are greater than [52], similar to [53], or less than controls [54]. While we are open to the possibility that some models exist where muscle size increases substantially enough to increase strength, we



**Fig. 2.** Models for the relationship between changes in muscle size and changes in muscle strength. Fig. 2a shows the model that is traditionally used to test the importance of changes in muscle size to changes in muscle strength (see also Fig. 2d). We propose two additional models (Fig. 2b and c) which may provide better designs for experimentally testing the importance of changes in muscle size to changes in muscle strength. In Fig. 2b, group 1 is a traditional training group increasing muscle size and strength; group 2 increases strength without increasing muscle size (see also Fig. 2d). In Fig. 2c, group 1 is a traditional training group increasing muscle size and strength; group 2 increases muscle size without increasing strength (see also Fig. 2d). Muscle image used courtesy of creativecommons.org. Dumbbell image used courtesy of clipartstation.com.

were surprised that the myostatin knockout literature did not lend more support to that idea. We acknowledge that there is some discussion that while manipulating myostatin increases muscle size, it also decreases the overall quality of the intracellular components [53,54]. Interestingly, one study found that exercising these animals was able to lead to increases in the force generating capacity of the tissue [54]. However, it should be noted that the increase in strength was concomitant with a decrease in muscle size. Though these rodent models are potentially dissimilar to that of a human, the dissociations observed between increases in muscle size and strength are quite similar.

**Hypothesized mechanisms of strength gain**

The proposed mechanisms for changes in muscle strength have traditionally consisted of neural adaptations followed by contributions from muscle hypertrophy [55,56]. This is not to say that other peripheral mechanisms have not been hypothesized [57], but changes in muscle size as a mechanism of strength change is ubiquitous in the muscle physiology literature. We do acknowledge that we cannot definitively rule out changes in muscle size as a mechanism for changes in strength; however, there is experimental evidence against this mechanism [10,11] and no experimental evidence for it. Given this, we are left to only speculate as to what the cause(s) of changes in strength may be. An obvious candidate to explain changes in strength would be neural adaptations but it is likely that there are also adaptations occurring within the muscle (independent of muscle growth). Adaptations in the nervous system could include changes in the primary motor

cortex [58], spinal cord [59], and/or alterations in the motor neuron [60]. It may even be that exercise, anabolic steroids, and aging may affect each of these differently. With respect to exercise, one of the limitations that may exist is that many of these studies make the assumption that any strength gain beyond 3–4 weeks is driven predominantly by hypertrophy. Because of this, many (not all) of the studies investigating the neural adaptations to strength training last only four weeks [55]. This potentially limits our understanding of the full capacity of the nervous system to adapt in response to exercise.

The muscle fiber itself may also undergo changes that can increase strength which we hypothesize could be completely independent of the change in muscle size. A recent meta-analysis on fiber level changes concluded that neural adaptations likely play a large role with increasing strength but also noted some fiber level alterations [61]. Notably, authors suggested that some mechanism intrinsic to the muscle fiber, and independent of muscle growth, may be contributing to strength increases in response to resistance exercise. For example, there could be a change in the composition of the myosin motors [62], modifications in the pattern of calcium release [63], and/or changes in the major components involved in the excitation contraction coupling process (i.e. neuromuscular junction, surface membrane, transverse tubules, ryanodine receptor, calcium pumps, etc.) [64]. Following the signal from the nerve, there could be alterations to affect strength at any of these points along the chain of events to muscle contraction [65]. Though we commonly think of these mechanisms with respect to fatigue (acute decrease in strength), it seems reasonable to speculate that they may also be involved in increasing voluntary strength. However,

these mechanisms are currently speculative and will need to be verified through experiment.

### Recommendations for future research

We acknowledge that the question of what increases voluntary strength is difficult to answer experimentally but it is not impossible. Papers currently being published often determine the mechanistic importance of muscle growth based solely on whether or not a change was detected. Importantly, that change is often compared to nothing [66,67], a non-exercise control group [13,68], or another group which may have also observed increases in muscle size [69–71]. This often leads researchers to make the following claims 1) if muscle growth occurs and the individual gets stronger (Fig. 2a), then muscle growth is playing a role as a mechanism of strength gain and 2) if muscle growth does not occur and the individual gets stronger, then neural adaptations are the cause of the increased strength. It is likely that any proposed method to address this question will have strengths and limitations inherent to each model. However, efforts to isolate effects through study design may be one way to address the importance (or lack thereof) of muscle growth for strength. For example, the experimental model used could be a protocol in which muscle growth is eliminated in one group and the strength change is compared to another group that experienced muscle growth (Fig. 2b). If muscle growth is present in one group but there are no differences in strength, this might suggest that muscle growth is neither necessary (nor additive) for changes in strength. There is some experimental evidence for this model [10,11].

Although muscle growth is not necessary and appears to not provide an additive response to muscle strength, the change in muscle size could still be contributory to changes in strength [30]. While possible, a complete loss of training induced increases in leg lean mass and fiber cross sectional area had no effect on the exercise induced change in muscle strength [72]. In other words, practicing the strength test one time per month maintained maximal strength despite a complete loss of the exercise induced change in muscle mass. Any contributory cause of muscle growth for increasing strength would appear small. However, some individuals may be capable of increasing muscle size to a much greater extent than the group mean. Do these hyper-responders experience the largest changes in strength? To address this question, a non-exercise control group would be important to account for the error of the tester as well as the error associated with random biological variability within a given time frame [73,74]. However, this might be more informative about differences in adaptability than whether or not muscle growth is important for changes in muscle strength (i.e. hyper responders may just change more across all variables). When studying trained participants, a non-exercise control group could still be implemented within the design. This control group could not be composed of trained individuals because having them not exercise would lead to a detraining response. However, a non-exercise control group of similar age would still provide useful information for the error of the tester as well as the error associated with random biological variability within a given time frame.

Another model could be one that produces growth within each condition but in a manner that seeks to eliminate strength in one of them (Fig. 2c). If muscle growth is present in both groups but strength is eliminated in one of the groups, this might suggest that muscle growth is not sufficient for changes in strength. There is some experimental evidence for this model [23,24,26]. One point to consider with this approach is to be cognizant of the number of strength tests implemented across the duration of the study. This is because it is not possible to measure voluntary strength without practicing the strength test. If a strength test was performed too often, adaptation could occur. The test used to determine changes in strength is also an important consideration. The test that would provide the most information on the effects of training are the strength tests that are the closest to the movements completed during the training period. An isotonic one

repetition maximum test in the knee extensors would more closely resemble the strength adaptations of isotonic knee extensor exercise than an isometric strength test. Lastly, although we acknowledge the principle of diminishing returns, it would be useful to investigate these mechanisms over longer durations (> 8 weeks) of time. Of note, a previous paper hypothesized that muscle growth as a mechanism of strength may become more important with continued training (i.e. years) [56]. This idea remains to be experimentally tested.

With exercise it is methodologically difficult but possible to experimentally investigate this mechanistic question; however, with pharmacological and aging research it may be more difficult due to the goals of those types of studies. For example, anabolic compounds are often given to clinical patients with the goal of increasing both muscle bulk and strength/function. With disease and aging, as mentioned in Sections “Pharmaceutical and Aging”, there is likely a point where the loss of contractile machinery begins to have a meaningful impact on strength and function. Nevertheless, the model of testing this question would seemingly be similar to that used with exercise.

### Conclusions

In closing, we are not dismissing the potential importance of maintaining muscle mass, particularly in clinical populations. We also acknowledge that exercise and/or pharmacological compounds are capable of increasing muscle size and strength. What we are suggesting, however, is that muscle function may not necessarily be driven by these exercise or pharmacological induced increases in muscle size. Perhaps it is time for the field to take another look at what increases muscle strength and function? Exploring mechanisms and explanations beyond just changes in muscle size may be fruitful for improving our ability to augment muscle strength and function.

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#### Conflicts of interest

Jeremy P. Loenneke, Scott J. Dankel, Zachary W. Bell, Samuel L. Buckner, Kevin T. Mattocks, Matthew B. Jessee, and Takashi Abe declare that they have no conflicts of interest relevant to the content of this review.

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