

Is There a Minimum Intensity Threshold for Resistance Training-Induced Hypertrophic Adaptations?

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Abstract

In humans, regimented resistance training has been shown to promote substantial increases in skeletal muscle mass. With respect to traditional resistance training methods, the prevailing opinion is that an intensity of greater than ~60% of 1 repetition maximum (RM) is necessary to elicit significant increases in muscular size. It has been surmised that this is the minimum threshold required to activate the complete spectrum of fiber types, particularly those associated with the largest motor units. There is emerging evidence, however, that low-intensity resistance training performed with blood flow restriction (BFR) can promote marked increases in muscle hypertrophy, in many cases equal to that of traditional high-intensity exercise. The anabolic effects of such occlusion-based training have been attributed to increased levels of metabolic stress that mediates hypertrophy at least in part by enhancing recruitment of high-threshold motor units. Recently, several researchers have put forth the theory that low intensity exercise ($\leq 50\%$ 1RM) performed without BFR can promote increases in muscle size equal, or perhaps even superior, to that at higher intensities provided training is carried out to volitional muscular failure. Proponents of the theory postulate that fatiguing contractions at light loads is simply a milder form of BFR and thus ultimately results in maximal muscle fiber recruitment. Current research indicates that low-load exercise can indeed promote increases in muscle growth in untrained subjects, and that these gains may be functionally, metabolically, and/or aesthetically meaningful. However, whether hypertrophic adaptations can equal that achieved with higher-intensity resistance exercise ($\leq 60\%$ 1RM) remains to be determined. Furthermore, it is not clear as to what, if any, hypertrophic effects are seen with low intensity exercise in well-trained subjects as experimental studies on the topic in this population are lacking. Practical implications of these findings are discussed.

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1. Introduction

Muscle tissue displays a high level of plasticity, allowing it to readily adapt to both acute and chronic imposed demands (1). Studies have clearly demonstrated that when subjected to functional overload, muscle tissue responds by increasing its cross sectional area (CSA). Animal models using passive stretch, synergist ablation (surgical removal of one muscle to cause increased overload of the synergists), and neuromuscular electrical stimulation produce hypertrophic increases of as much as 100% (2). In humans, regimented resistance training has been shown to promote marked increases in skeletal muscle mass (3, 4). Although hypertrophy occurs in all fiber types, fast-twitch (FT) fibers display an approximately 50% greater capacity for growth compared to their slow-twitch (ST) counterparts (2, 5). That said, there is a high degree of inter-individual variability with respect to the extent of hypertrophic adaptation across the full spectrum of fiber types (5).

Three primary factors have been proposed to mediate hypertrophic adaptations pursuant to resistance training: mechanical tension, metabolic stress and muscle damage (3). A number of researchers have surmised that tension is the primary driving force in this process (6, 7). However, assuming that a given level of mechanical tension is achieved, both metabolic stress and tissue damage may become increasingly important factors in optimizing a hypertrophic response (8, 9). Studies to date are inconclusive as to whether one particular parameter predominates with respect to activating the cellular and molecular mechanisms responsible for regulating muscle growth (2).

With respect to traditional resistance training methods, the prevailing opinion is that a concentric intensity of greater than ~60% of 1 repetition maximum (RM) is necessary to elicit significant increases in muscular size (10-12). It has been surmised that this is the minimum

threshold required to activate the complete spectrum of fiber types, particularly those associated with the largest motor units (MUs) (13). There is emerging evidence, however, that low-intensity resistance training performed with blood flow restriction (BRF) can promote significant increases in muscle hypertrophy, in many cases equal to that of traditional high-intensity exercise (14). Restriction of blood flow is achieved by wrapping an elastic implement (such as knee or elbow wraps) at the proximal portion of a limb so that circulation is occluded to working muscles during performance of resistance exercise. The anabolic effects of such occlusion-based training have been attributed to increased levels of metabolic stress--i.e. a buildup of metabolites pursuant to glycolytic energy production. It is theorized that metabolic stress mediates hypertrophy at least in part by enhancing recruitment of high-threshold MUs (15), but other mechanisms are also believed to play a role in the process including cell swelling, elevated hormonal levels, and increased production of reactive oxygen species (16, 17)

Recently, several researchers have put forth the theory that low intensity exercise ($\leq 50\%$ 1RM) performed without BFR can promote increases in muscle size equal, or perhaps even superior, to that at higher intensities provided training is carried out to volitional muscular failure (4, 18). Proponents of the theory postulate that fatiguing contractions at light loads is simply a milder form of BFR and thus ultimately results in maximal muscle fiber recruitment (19). It has been surmised that as long as progressive overload is employed, even the most serious lifters can realize significant increases in muscle hypertrophy from such low-intensity training (19). The purpose of this review therefore will be to evaluate the literature on the topic in an attempt to determine the minimum intensity required for optimal hypertrophic adaptations. Evidence-based recommendations will then be made to help guide program design when devising hypertrophy-oriented routines.

To carry out this review, English-language literature searches of the PubMed, EBSCO, and Google Scholar databases were conducted for all time periods up to December 2012. Combinations of the following keywords were used as search terms: "skeletal muscle"; hypertrophy"; "muscle growth"; "cross sectional area"; "intensity"; "loading"; "low load"; "repetition range"; "resistance training"; "resistance exercise". The reference lists of articles retrieved in the search were then screened for any additional articles that had relevance to the topic.

2. Theoretical Basis for Lower Intensity Hypertrophic Adaptations

Maximal muscle hypertrophy is predicated on recruiting as many MUs as possible in the target muscles and achieving high firing rates in these MUs for a sufficient length of time (11). The mechanisms by which mechanical forces lead to muscular adaptations are still not fully understood. Current theory proposes that the process is regulated by a phenomenon called mechanotransduction whereby sarcolemmal-bound mechanosensors, such as integrins and focal adhesions, convert mechanical energy into chemical signals that mediate intracellular anabolic and catabolic pathways, ultimately leading to a shift in muscle protein balance that favors synthesis over degradation (20). A summation of anabolic signals of an adequate magnitude is required to generate sustained responses that lead to muscle protein accretion (21).

Many signaling pathways have been identified as playing a part in the regulation of muscle mass, with certain pathways acting in a permissive role and others providing direct mediation of cellular processes that influence messenger RNA translation and hypertrophy (22). Signaling pathways that have been identified include phosphatidylinositol 3-kinase-protein kinase B-mammalian target of rapamycin (PI3K-Akt), mitogen-activated protein kinase (MAPK), and various calcium- (Ca^{2+}) dependent pathways, amongst others. Although these

pathways may overlap at key regulatory steps, evidence suggests that they are interactive rather than redundant (23). For example, although Akt and MAPK/extracellular signal-related kinase (ERK) both have been shown to stimulate mammalian target of rapamycin (mTOR) to a similar extent, the combined effects of both lead to an even greater stimulation compared to either pathway alone (24). A complete discussion of these signaling pathways and their functions is beyond the scope of this article. For further information, interested readers are referred to recent reviews by Bassel-Duby and Olson, (25), Miyazaki and Esser (26), and Glass (27)..

Claims for a hypertrophic effect of low-intensity resistance exercise are based on the premise that recruitment of the full spectrum of MUs is achieved at virtually any intensity provided training is carried out to the point of concentric muscular failure (18). It remains questionable, however, whether this belief holds true in practice. There is evidence that fatiguing contractions result in a corresponding increase in electromyography (EMG) activity, presumably resulting from an increased contribution of high-threshold MUs recruited to maintain force output (28), but it is not clear what level of intensity is required to initiate activation of these high-threshold MUs. Furthermore, beyond a certain intensity level the resistive exercise would become more reliant on aerobic metabolism and thus could be continued for extended periods of time in the upper levels of steady state. This shift in energy system contribution would conceivably result in a competitive interaction between anabolic and catabolic signaling pathways that leads to adaptations associated more with endurance than strength (29).

Studies corroborating the supposition that low-intensity training to failure equates to a milder form of BFR are lacking. Wernbom et al. (4) demonstrated that peak EMG activity was similar between 3 sets of low intensity (30% 1-RM) unilateral knee extensions performed with and without BFR to muscular failure. Mean values were not reported thereby prohibiting analysis

of the effects on muscle recruitment over the course of the entire range of sets. Further research is necessary to better determine the relationship between muscle recruitment and low-intensity exercise with and without blood flow restriction.

There is evidence that muscle recruitment is indeed greater in high-intensity exercise compared to low-intensity blood flow restricted exercise. Employing a model that examined inorganic phosphate splitting via ^{31}P -magnetic resonance spectroscopy, Suga et al (30) displayed that FT fiber recruitment occurred in only 31% of subjects who performed BFR training at 20% 1RM compared with 70% of those who trained at 65% 1RM. This finding is consistent with other research showing that exercise performed at high-intensities produces substantially greater EMG activity compared to BFR exercise at 20% 1RM, indicating an attenuated recruitment at the lower training intensity (31, 32). Follow up work by Suga et al.(33) showed that splitting of P_i peaks at 30% 1RM approached those of higher intensity exercise, but nevertheless did not reach levels indicative of equal muscle fiber recruitment. Only when blood flow restricted exercise was carried out at an intensity of 40% 1RM did P_i peaks equate to, and actually exceed, those associated with traditional high-intensity training. Lending further support to these findings, Cook et al. (34) recently demonstrated that EMG amplitude of the vastus lateralis, vastus medialis and rectus femoris during knee extension exercise to failure was significantly greater at a high intensity (70% 1RM) than at low intensity (20% 1RM) both with and without BFR. The aforementioned studies are limited to the use of the knee extension; further research is needed using a variety of single- and multi-joint movements with varying percentages of 1RM performed to failure to provide a better understanding of the subject.

3. Acute Responses to Varying Resistance Exercise Intensities

Several animal studies have evaluated the effects of different intensities on acute signaling responses. Using an in situ model, Martineau et al. (35) subjected rat plantaris muscles to peak concentric, eccentric, and isometric actions via electrical stimulation. Results showed tension-dependent phosphorylation of c-Jun N-terminal kinase (JNK) and ERK, with higher mechanical tension resulting in progressively greater phosphorylation. This suggests that peak tension is a better predictor of MAPK phosphorylation than either time-under-tension or rate of tension development. Interestingly, follow-up work by the same laboratory found a linear relationship between time under tension and signaling of JNK whereas rate of tension change showed no effect, highlighting the importance of time under tension in anabolic signaling (36). Taken together, these findings point to the importance of overall training volume for maximizing the acute molecular responses related to skeletal muscle hypertrophy irrespective of training intensity.

In an attempt to qualify the acute effects of resistance training intensity in humans, Kumar et al. (37) investigated the acute exercise responses at 20-90% 1 RM in healthy young and old men. The protocol was designed so that volume of training was approximately equal between training intensities. Thus, at 20% intensity participants performed 3 sets of 27 repetitions; at 40% intensity 3 sets of 14 repetitions were performed; at 60% intensity, training consisted of 3 sets of 9 repetitions; at 75% intensity, 3 sets of 8 repetitions were performed; and 90% intensity involved performing 6 sets of 3 repetitions. Increases in myofibrillar muscle protein synthesis (MPS) were minimal after exercise at 20 and 40% 1RM but values significantly and markedly increased at 60% 1RM, plateauing thereafter. Similarly, phosphorylation of p70S6K was maximized at intensities of 60-90% 1RM, peaking just prior to the maximal rise in MPS. These results held true in both younger and older subjects, suggesting that the stimulatory

effect on muscle protein synthesis (MPS) reaches a maximum at ~60%-75% 1RM of isotonic exercise. The authors did not state whether low-load training was carried out to muscular failure, but based on the study design this does not appear to be the case. This is an important limitation as research indicates the hypertrophic response to low-load training is predicated on lifting to the point of voluntary muscular failure (38-40).

Burd et al. (39) sought to determine whether resistance exercise intensity had a differential effect on MPS and anabolic signaling. A quasi within-subject design was used where 15 young, recreationally active men performed 4 sets of unilateral knee extension at 30% and 90% 1RM to volitional muscular failure. A third condition involved performing the exercise at 30% 1RM with external work (repetitions x load) matched to the 90% condition. At 4-h post-exercise, measures of MPS were elevated at all conditions studied, but levels in the 30% work-matched condition were approximately half that of the other 2 conditions. Interestingly, myofibrillar MPS remained elevated at 24-h post-exercise only in the 30% to failure condition. Phosphorylation of p70S6K was significantly increased at 4-h only in the 30% to failure condition, and this elevation was correlated with the degree of stimulation of myofibrillar MPS. These findings suggest that low-intensity exercise performed to volitional fatigue induces greater acute muscular responses compared to high intensity exercise. The fact that volume was substantially greater in the 30% condition versus the 90% condition confounds the ability to isolate the impact of intensity on the variables studied.

Although these studies provide relevant clues as to the anabolic effects of various intensities of exercise, their findings are not necessarily predictive of long-term changes in lean body mass. Evaluation of measures of MPS following an acute bout of resistance exercise do not always occur in parallel with chronic upregulation of causative myogenic signals (41) and may

not reflect hypertrophic responses experienced pursuant to regimented resistance training carried out over a period of weeks or months (42). Moreover, the acute responses of subjects with minimal training experience, in particular, must be viewed with caution as results may be primarily a function of the unfamiliarity of exercise and thus not applicable to the response of well-trained individuals (2, 43). Given these inherent limitations, any attempt to extrapolate findings from such data to hypertrophic adaptations is speculative, at best.

4. Chronic Adaptations to Varying Resistance Exercise Intensities

A number of studies have attempted to directly evaluate long-term hypertrophic adaptations along the strength-endurance intensity continuum. Findings between these studies are inconsistent and discrepant. Table 1 summarizes the relevant research to date.

Campos et al. (44) was the first to investigate the topic in a well-controlled experimental fashion. Thirty-two untrained males (mean \pm SD age 22.5 ± 5.8 years) were randomly assigned to 1 of 3 lower body training protocols: a low repetition group (n=9) that performed 3-5 RM for 4 sets of each exercise with 3 minute rest intervals between sets; an intermediate repetition group (n=11) that performed 9-11 RM for 3 sets with 2 minute rest intervals, or; a high repetition group (n=7) that performed 20-28 RM for 2 sets with 1 minute rest intervals. A control group (n=5) performed no resistance exercise. The exercise regimen consisted of the leg press, squat, and knee extension with total volume load approximately equal between groups. Training was carried out 2 days a week for the first 4 weeks and 3 days a week for the final 4 weeks. Resistance was progressively increased throughout the training period to maintain repetition ranges and all sets were performed to momentary concentric muscular failure. Muscle biopsy was used to assess changes in fiber CSA of the vastus lateralis. After 8 weeks, both the high and intermediate repetition groups displayed significant increases of 12.5%, 19.5%, and 26% in CSA

for type I, IIA, and IIX fibers, respectively. Increases in muscle fiber CSA for the high repetition group did not reach statistical significance for any of the fiber types, indicating that lower-intensity exercise is substandard for promoting increases in hypertrophy.

Employing the same basic training program as Campos et al. (44), Leger et al. (45) divided 25 healthy males into either a low or high repetition group--an intermediate group was not included as part of the study design. Subjects were older than in the Campos et al. (44) study (age 36 ± 4.9 years) and had not participated in a resistance training program for at least 1 year. Muscle volume was assessed by computerized tomography (CT). After 8 weeks, an approximately 10% increase in quadriceps CSA was noted in both groups with no significant differences found between training protocols. Follow-up work by this laboratory (46) in a similar population demographic also reported 10% increases in quadriceps hypertrophy with no significant differences between groups using the same training protocol. The researchers attributed the discrepancy between their results and that of Campos et al. (44) to the detrained status of the somewhat older subjects, theorizing that any type of resistance training in this population would promote a sufficient overload stimulus to elicit increases in muscle growth.

Tanimoto and Ishii (40) evaluated the muscular response of low-intensity exercise performed with slow movement and tonic force generation to a traditional higher-intensity routine in 24 untrained men. Subjects were randomly assigned to perform repetitions of the leg extension at either 50% RM with a 6 second cadence (3 seconds for both concentric and eccentric actions) and no relaxing phase between repetitions (LST; n=8) or 80% RM at a tempo of 1 second for both concentric and eccentric actions with 1 second relaxation between repetitions (HN; n=8). Both of these groups performed ~8 repetitions per set until failure and the intensity was progressively adjusted based on performance in the previous session. A third group

(LN; n=8) performed low-intensity exercise (50% RM) using the normal tempo employed in the high-intensity protocol and thus did not work to volitional failure. Training was carried out 3 days a week for 12 weeks. At the end of the study period, muscle CSA as determined by magnetic resonance imaging (MRI) increased significantly in both LST and HN ($5.4 \pm 3.7\%$ versus $4.3 \pm 2.1\%$, respectively), with no significant differences noted between groups. The LN group did not significantly increase muscle mass. These results again emphasize the importance of training to muscular failure for eliciting a hypertrophic response during low load training.

This study design was subsequently replicated by the same laboratory (47) using a total-body resistance training program consisting of 3 sets of the squat, chest press, lat pull-down, abdominal bend, and back extension. Intensity was slightly higher for both groups (55%-60% in LST and 80%-90% in HN) as necessitated by the multi-joint nature of the exercises. Again, significant increases in muscle size were detected in both LST and HN (‘mean \pm SD = $6.8 \pm 3.4\%$ versus $9.1 \pm 4.2\%$, respectively), with no significant differences noted between groups. While these findings are intriguing, they are confounded by the altered repetition cadence thereby making it impossible to draw relevant conclusions as to traditional intensity recommendations. Moreover, although results did not reach statistical significance in the total-body protocol, high-intensity exercise produced an approximately 34% greater absolute increase in hypertrophy. Thus, it seems likely that the small sample size resulted in a type II error.

Holm et al. (48) studied the effects of light-load resistance exercise in 11 sedentary young men. A within-subject design was employed whereby subjects performed 10 sets of unilateral leg extensions, training one leg at 70% 1RM and the contralateral leg at 15.5% 1RM in a randomized, counterbalanced fashion. Training was carried out 3 days-a-week for a total of 12 weeks. Muscle CSA of the quadriceps as determined by MRI was greater by threefold in the

high-intensity leg compared to the leg that performed low-intensity exercise. It should be noted that the low-intensity exercise involved performing one repetition every 5 seconds for 3 minutes, calling into question the extent of fatigue experienced during exercise performance and thus obscuring the ability to extrapolate conclusions to low-load training to failure. Interestingly, a subsequent study using the same protocol in healthy, young males showed a significant 18% increase in satellite cell number associated with the low-load protocol after 12 weeks of training, indicating that low-intensity exercise has a favorable effect on early-stage myogenesis (49).

In a follow-up to their previously mentioned acute training study (39), Stuart Phillips' laboratory employed a quasi within-subject design to test the hypothesis that these results would translate into long-term gains in muscle hypertrophy (50). Eighteen untrained males (mean \pm SD age 21 ± 1 years) were randomly assigned to perform 2 of 3 different resistance training protocols involving unilateral knee extension exercise for each leg to momentary concentric muscular failure as follows: 3 sets of low-intensity exercise at 30% RM; 3 sets of high-intensity exercise at 80% RM; 1 set of high-intensity exercise at 80% RM. Training was carried out 3 days per week for 10 weeks. Muscular adaptations of the vastus lateralis was assessed by magnetic resonance imaging and muscle biopsy. At the end of the study period, both the low- and multi-set high-intensity groups realized significant increases in muscle volume (mean \pm SD = $6.8 \pm 1.8\%$ versus $7.2 \pm 1.9\%$, respectively), with no differences found between groups. The single set high-intensity group also showed significant increases in hypertrophy, although the gains were less than half that of the other 2 groups (mean \pm SD = $3.2 \pm 0.8\%$). Interestingly, fiber analysis by muscle biopsy showed that the low-intensity group displayed greater hypertrophy of type I fibers while the high-intensity group displayed greater hypertrophy of type II fibers, suggesting a fiber type-specific adaptive response along the strength-endurance continuum. The study was limited

by the sole use of the leg extension exercise, which is not representative of training routines normally employed in a hypertrophy-oriented program.

A recent study by Schuenke et al. (51) investigated both the effects of intensity as well as tempo on muscle hypertrophy. Thirty-four untrained women were randomly divided into 1 of 3 groups: A traditional strength (TS) group that performed sets of 6-10RM at a cadence of 1-2 seconds on the concentric and eccentric portion of the repetition; a traditional muscular endurance (TE) group that performed 20-30 repetitions at the same speed as TS, and; a slow-speed (SS) group that performed 6-10 repetitions at a tempo of 10 seconds on concentric action and 4 seconds on the eccentric action. Both TE and SS trained at an intensity of ~40-60% 1RM while TS trained at ~80-85% 1RM. The longer duration of cadence in the SS routine is associated with a reduced momentum and a greater consistency in average force (versus peak force) over a complete repetition compared to training with TE. Training consisted of 3 sets of the leg press, squat, and knee extension to momentary muscular failure with ~2 minutes rest intervals afforded between sets. Training was carried out 2 days/week for the first week and 3 days/week for the remaining 5 weeks. Muscle biopsy was used to assess CSA of the vastus lateralis. After 6 weeks, significant increases were noted in TS for type I, type IIA, and type IIX fiber area (‘mean \pm SD 26.6 \pm 22.7%, 32.9 \pm 20.4%, and 41.1 \pm 32.7% respectively) whereas no significant differences were seen in TE. Interestingly, SS displayed significant increases in both type IIA, and type IIX CSA, although these changes were less than half that of that experienced by TS. It remains conceivable that hypertrophy might manifest more gradually in lower intensity exercise and, if so, would therefore not have been evident in this study given its short duration.

Most recently, Ogasawara et al. (52) found similar increases in CSA of the pectoralis major and triceps brachii in subjects performing free-weight bench press exercise at 75% 1RM

versus 30% 1RM to concentric muscle failure. The study employed a within-subject design whereby 9 previously untrained subjects performed the higher intensity exercise for the initial 6 weeks of the study and then, after a 12-month washout period of detraining, performed 6 weeks of the low-load exercise in non-randomized fashion. Although intriguing, these findings must be viewed with caution as "muscle memory" via neural mechanisms and/or satellite cell accretion may have influenced results (5, 53, 54)

The mixed and conflicting results between these studies is hard to justify and likely a function of the varied study designs and methods of assessment. One issue of note is the use of different techniques for measuring muscular adaptations including biopsy, MRI, ultrasound, and/or CT. Each of these techniques has various inherent strengths and weaknesses, causing difficulties when attempting to reconcile research findings (2).

The use of different exercise protocols serves to further confound results. Some of the studies involved only a few sets of single-joint exercise while others employed multi-set routines consisting of combinations of single- and multi-joint exercises more representative of traditional hypertrophy training practices. In addition, some studies equated volume between training conditions while others did not. These confounding issues hinder the ability to draw relevant comparisons between studies.

Another major limitation of the current body of literature is a lack of statistical power due to small sample sizes. Studies to date have generally involved fewer than ~30 exercising subjects with ≤ 12 subjects per group studied. This substantially raises the possibility of a type II error, whereby significant differences cannot be determined when in fact they do exist. Greater statistical power could be achieved by pooled analysis of data, however the disparate methods employed in existing studies to date make such meta-analysis problematic.

Finally and importantly, all studies to date have been carried out in untrained or minimally trained subjects. It is well-established that highly trained individuals respond differently than those who lack training experience (55). A "ceiling effect" makes it progressively more difficult for trained individuals to increase muscular gains, thereby necessitating more demanding resistance training protocols to elicit a hypertrophic response. Moreover, there is emerging evidence that consistent resistance exercise can alter anabolic intracellular signaling in rodents (56) and humans (57), indicating an attenuated hypertrophic response. As such, current findings cannot necessarily be generalized to a well-trained population. Future research should therefore focus on the hypertrophic effects of training intensity in those with at least 1 year or more of regular, consistent resistance training experience.

5. Conclusions

Although it is evident that a minimum intensity threshold exists to promote increases in muscle mass, the precise level of intensity needed to achieve hypertrophic adaptations has yet to be elucidated. Based on current research, it does appear that low-load exercise can indeed promote increases in muscle growth in untrained subjects, and that these gains may be functionally, metabolically, and/or aesthetically meaningful. However, whether hypertrophic adaptations can equal that achieved with higher-intensity resistance exercise ($\leq 60\%$ 1RM) remains dubious. Furthermore, it is not clear as to what, if any, hypertrophic effects are seen with low intensity exercise in well-trained subjects as experimental studies on the topic in this population are lacking.

The preponderance of evidence indicates that blood flow restricted resistance exercise at intensity levels $\leq 20\%$ 1RM do not result in recruitment of the full spectrum of MUs, making it

highly unlikely that non-occluded resistance exercise at similar intensities would achieve comparable muscle activation to high-intensity exercise. Recruitment of FT fibers with blood flow restricted resistance exercise at 30% has been shown to approach, but not equal, that of high-intensity exercise (33). Given these findings, it would appear that intensities above 30% are needed for complete muscle fiber recruitment. It therefore stands to reason that if traditional resistance exercise $\leq 30\%$ 1RM does in fact promote muscular gains equal to that of high intensity exercise as has been found in a limited number of studies (45, 46, 50), the differences in protein accretion seemingly would have to be made up by a greater degree of hypertrophy in type I and perhaps type IIA fibers. It is conceivable that other factors attributed to metabolic stress (cell swelling, autocrine/paracrine factors, systemic hormonal elevations, etc) may allow for such enhanced adaptations. This appears to be the case with BFR, as marked hypertrophy is routinely seen at intensities $\leq 30\%$ 1RM (14), presumably mediated by a heightened metabolic buildup (16, 58). Whether similar effects are realized in low-load training without BFR remains to be elucidated. Moreover, some exercises may lend themselves well to promoting BFR and thus heightening metabolic stress at lower loads (those with consistent torques) while others may not (those with torque curves that considerably drop off during the lift). Further research is needed to investigate these issues.

Another consideration that needs to be taken into account is the necessity to train to fatigue during low intensity training. It has been hypothesized that persistently training to volitional muscular failure increases the potential for overtraining and psychological burnout (59). Indeed, Izquierdo, et al. (60) found that training to failure caused reductions in resting insulin-like growth factor (IGF)-1 concentrations and a blunting of resting testosterone levels over a 16 week protocol, suggesting that subjects may have been overtrained by the end of the

study. The negative effects of overtraining generally take time to manifest and thus likely would not have been evident in the current studies on training intensity given their relatively short duration (≤ 12 weeks). In practice, however, this would necessitate the implementation of more frequent unloading periods over the course of a periodized training program compared to higher intensity exercise. It is not clear how such alterations might affect long-term hypertrophic gains.

Research seems to suggest that a moderate repetition range (6-12 RM) using a controlled lifting cadence may be optimal for maximizing gains in muscle hypertrophy (7, 61, 62), although evidence is far from conclusive on the subject. This so-called "hypertrophy range" may conceivably provide an optimal combination of mechanical tension, metabolic stress, and muscle damage, thereby generating a sustained anabolic response that maximizes muscle protein accretion (3). Regardless of the existence of an ideal hypertrophy range, however, a strong case can be made for incorporating the use of a variety of training intensities into a hypertrophy-oriented program. Low repetition resistance training (1-5 RM) enhances neuromuscular adaptations necessary for the development of maximal strength (61). These adaptations allow the use of heavier loads, and thereby greater mechanical tension, at a given moderate intensity. On the other hand, higher-repetition training (15+ RM) can help to attenuate the exercise-induced rise in blood lactate (63), delaying the onset of fatigue and thus leading to a greater inroad of fibers during hypertrophy-type training. This varied approach would seem to be of particular importance for those with considerable training experience as greater degree of overload is necessary for continued adaptation in these individuals.

It is also conceivable that people may respond differently to exercise intensity based on individual muscle morphology. There is clear evidence that men and women exhibit large variations in their response to the same resistance training protocol, with some subjects

displaying little to no muscular gains and others showing profound increases in muscle mass (64, 65). These variances may be due, at least in part, to differences in muscle fiber type distribution. Studies show a large genetic variability between individuals in the percent of FT versus ST fibers for a given muscle (66), and these disparities can have implications in the response to exercise (67). This raises the possibility that adaptations to low and high training intensities may be specific to the fiber-type profile of the target muscle. For example, there is evidence that the predominantly ST soleus muscle is much less responsive to traditional resistance exercise compared to primarily FT muscles such as the vastus lateralis and the biceps brachii (68). Might the soleus respond better to a high-repetition protocol given its high percentage of slow twitch fibers? Although this concept is intriguing in theory, however, a fiber-type exercise prescription based on training intensity has not been confirmed through research and thus remains speculative. Moreover, given the inter-individual variability of fiber-type composition, it would be difficult if not impossible to non-invasively determine fiber-type ratios of each muscle, thus making application impractical for the vast majority of people.

In conclusion, there is evidence that low-load training can increase muscle mass in untrained subjects. Therefore, low-load training to failure appears to be an effective strategy to increase muscle mass during early-stage training. This may have particular relevance in populations such as the elderly and others who may not be able to perform resistance exercise at higher intensities. It remains questionable, however, as to whether the extent of hypertrophy in low-load training is comparable with what can be achieved through heavy resistance exercise. Based on recruitment data, it would appear that intensities above 30% RM are needed to optimize type II fiber activation in the absence of active BFR. Moreover, research evaluating the effects of such training in promoting hypertrophic benefits in experienced lifters is lacking at this

time. Future research should seek to clarify the extent of hypertrophic effects along the intensity continuum using realistic training programs, as well as elucidating these effects in those with considerable training experience.

Table 1: Summary of Long-Term Studies Evaluating the Effects of Training Intensity on Muscle Hypertrophy

Study	Subjects	Design	Volume Equated?	Train to Failure?	Measurement	Findings
Campos et al. (44)	32 untrained young men (5 served as non-exercising controls)	Random assignment to either low intensity (3-5 RM), intermediate intensity (9-11 RM) for 3 sets with 2 minute rest intervals, or; high intensity (20-28 RM) exercise. Exercise consisted of 2-4 sets of squat, leg press and leg extension, performed 3 days a week for 8 weeks.	Yes	Yes	Muscle biopsy	Significant increases in CSA for high-intensity exercise; no significant increase in CSA for low-intensity exercise
Leger et al. (45)	24 untrained middle-aged men	Random assignment to either low intensity (3-5 RM) or a high intensity (20-28 RM) exercise. Exercise consisted of 2-4 sets of squat, leg press and leg extension, performed 3 days a week for 8 weeks.	Yes	Yes	CT	No differences in CSA between low- and high-intensity exercise
Lamon et al. (46)	25 untrained middle-aged men	Random assignment to either low intensity (3-5 RM) or a high intensity (20-28 RM) exercise. Exercise consisted of 2-4 sets of squat, leg press and leg extension, performed 3 days a week for 8 weeks.	Yes	Yes	CT	No differences in CSA between low- and high-intensity exercise
Tanimoto and Ishii (40)	24 untrained young men	Random assignment to either 50% RM with a 6 second tempo and no relaxing phase between repetitions, 80% RM with a 2 second tempo and 1 second relaxation between repetitions, or 50% RM with a 2 second tempo and 1 second relaxation between repetitions. Exercise consisted of 3 sets of knee extensions,	No	Yes	MRI	No differences in CSA between low- and high-intensity exercise

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		performed 3 days a week for 12 weeks.				
Tanimoto et al. (47)	36 untrained young men (12 served as non-exercising controls)	Random assignment to either 55-60% RM with a 6 second tempo and no relaxing phase between repetitions or 80-90% RM with a 2 second tempo and 1 second relaxation between repetitions. Exercise consisted of 3 sets of squat, chest press, lat pulldown, abdominal bend, and back extension, performed 2 days a week for 13 weeks.	No	Yes	B-mode ultrasound	No differences in CSA between low- and high-intensity exercise
Holm et al. (48)	11 untrained young men	Random, counterbalanced performance of 10 sets of unilateral leg extensions, training one leg at 70% 1RM and the contralateral leg at 15.5% 1RM, performed 3 days a week for 12 weeks.	Yes	No	MRI	Significantly greater increases in CSA in high intensity versus low intensity exercise
Mitchell et al. (50).	18 untrained young men	Randomly assignment to perform 2 of 3 unilateral leg extension protocols: 3 sets at 30% RM; 3 at 80% RM; 1 set at 80% RM. Training was carried out 3 days per week for 10 weeks.	No	Yes	MRI, muscle biopsy	No differences in CSA between low- and high-intensity exercise
Schuenke et al. (51)	34 untrained young women	Randomized assignment to either moderate intensity (80-85% RM) at a tempo of 1-2 seconds, a low intensity (~40-60% RM) at a tempo of 1-2 seconds, or slow-speed (~40-60% RM) at a tempo of 10 seconds concentric and 4 seconds eccentric. Exercise consisted of 3 sets of squat, leg press, and leg extension, performed 2-3 days a week for 6 weeks	No	Yes	Muscle biopsy	Significant increases in CSA for high-intensity exercise; no significant increase in CSA for low-intensity exercise
Ogasawara et al. (52)	9 untrained young men	Non-randomized crossover design to perform 4 sets of bench press exercise at 75% 1RM. Training was carried	No	Yes	MRI	No differences in CSA between low- and high-intensity exercise

		out 3 days a week for 6 weeks. After a 12 month washout period, the same protocol was performed at 30% 1RM.				
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Abbreviations: RM (repetition maximum); CSA (cross sectional area); CT (computerized tomography), MRI (magnetic resonance imaging)

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References

1. Fluck M, Hoppeler H. Molecular basis of skeletal muscle plasticity--from gene to form and function. *Rev Physiol Biochem Pharmacol.* 2003;146:159-216.
2. Adams G, Bamman MM. Characterization and regulation of mechanical loading-induced compensatory muscle hypertrophy. *Comprehensive Physiology.* 2012;2829(2970).
3. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. *J Strength Cond Res.* 2010 Oct;24(10):2857-72.
4. Wernbom M, Jarrebring R, Andreasson MA, Augustsson J. Acute effects of blood flow restriction on muscle activity and endurance during fatiguing dynamic knee extensions at low load. *J Strength Cond Res.* 2009 Nov;23(8):2389-95.
5. Kosek DJ, Kim JS, Petrella JK, Cross JM, Bamman MM. Efficacy of 3 days/wk resistance training on myofiber hypertrophy and myogenic mechanisms in young vs. older adults. *J Appl Physiol.* 2006 Aug;101(2):531-44.
6. Goldberg AL, Etlinger JD, Goldspink DF, Jablecki C. Mechanism of work-induced hypertrophy of skeletal muscle. *Med Sci Sports.* 1975 Fall;7(3):185-98.
7. Fry AC. The role of resistance exercise intensity on muscle fibre adaptations. *Sports Med.* 2004;34(10):663-79.
8. Schoenfeld BJ. Does exercise-induced muscle damage play a role in skeletal muscle hypertrophy? *J Strength Cond Res.* 2012 May;26(5):1441-53.
9. Schoenfeld BJ. Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. *Sports Med.* In Press.
10. McDonagh MJ, Davies CT. Adaptive response of mammalian skeletal muscle to exercise with high loads. *Eur J Appl Physiol Occup Physiol.* 1984;52(2):139-55.
11. Wernbom M, Augustsson J, Thomee R. The influence of frequency, intensity, volume and mode of strength training on whole muscle cross-sectional area in humans. *Sports Med.* 2007;37(3):225-64.
12. American College of Sports Medicine. American college of sports medicine position stand. progression models in resistance training for healthy adults. *Med Sci Sports Exerc.* 2009 Mar;41(3):687-708.
13. Schuenke MD, Herman J, Staron RS. Preponderance of evidence proves "big" weights optimize hypertrophic and strength adaptations. *Eur J Appl Physiol.* 2012 Oct 25.
14. Loenneke JP, Wilson JM, Marin PJ, Zourdos MC, Bembien MG. Low intensity blood flow restriction training: A meta-analysis. *Eur J Appl Physiol.* 2011 Sep 16.
15. Loenneke JP, Fahs CA, Wilson JM, Bembien MG. Blood flow restriction: The metabolite/volume threshold theory. *Med Hypotheses.* 2011 Nov;77(5):748-52.

16. Loenneke JP, Fahs CA, Rossow LM, Abe T, Bemben MG. The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. *Med Hypotheses*. 2012 Jan;78(1):151-4.
17. Pope ZK, Willardson JM, Schoenfeld BJ. A brief review: Exercise and blood flow restriction. *J Strength Cond Res*. 2013 Jan 28.
18. Burd NA, Mitchell CJ, Churchward-Venne TA, Phillips SM. Bigger weights may not beget bigger muscles: Evidence from acute muscle protein synthetic responses after resistance exercise. *Appl Physiol Nutr Metab*. 2012 Jun;37(3):551-4.
19. Burd NA, Moore DR, Mitchell CJ, Phillips SM. Big claims for big weights but with little evidence. *Eur J Appl Physiol*. 2012 Oct 20.
20. Zou K, Meador BM, Johnson B, Huntsman HD, Mahmassani Z, Valero MC, et al. The alpha(7)beta(1)-integrin increases muscle hypertrophy following multiple bouts of eccentric exercise. *J Appl Physiol*. 2011 Oct;111(4):1134-41.
21. Adams G. The molecular response of skeletal muscle to resistance training. *Deutsche Zeitschrift für Sportmedizin*. 2010;61(3):61-7.
22. Mayhew DL, Hornberger TA, Lincoln HC, Bamman MM. Eukaryotic initiation factor 2B epsilon induces cap-dependent translation and skeletal muscle hypertrophy. *J Physiol*. 2011 Jun 15;589(Pt 12):3023-37.
23. Tidball JG. Mechanical signal transduction in skeletal muscle growth and adaptation. *J Appl Physiol*. 2005 May;98(5):1900-8.
24. Winter JN, Jefferson LS, Kimball SR. ERK and akt signaling pathways function through parallel mechanisms to promote mTORC1 signaling. *Am J Physiol Cell Physiol*. 2011 May;300(5):C1172-80.
25. Bassel-Duby R, Olson EN. Signaling pathways in skeletal muscle remodeling. *Annu Rev Biochem*. 2006;75:19-37.
26. Miyazaki M, Esser KA. Cellular mechanisms regulating protein synthesis and skeletal muscle hypertrophy in animals. *J Appl Physiol*. 2009 Apr;106(4):1367-73.
27. Glass DJ. Skeletal muscle hypertrophy and atrophy signaling pathways. *Int J Biochem Cell Biol*. 2005 Oct;37(10):1974-84.
28. Spiering BA, Kraemer WJ, Anderson JM, Armstrong LE, Nindl BC, Volek JS, et al. Resistance exercise biology: Manipulation of resistance exercise programme variables determines the responses of cellular and molecular signalling pathways. *Sports Med*. 2008;38(7):527-40.
29. Atherton PJ, Babraj J, Smith K, Singh J, Rennie MJ, Wackerhage H. Selective activation of AMPK-PGC-1alpha or PKB-TSC2-mTOR signaling can explain specific adaptive responses to endurance or resistance training-like electrical muscle stimulation. *FASEB J*. 2005 May;19(7):786-8.

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30. Suga T, Okita K, Morita N, Yokota T, Hirabayashi K, Horiuchi M, et al. Intramuscular metabolism during low-intensity resistance exercise with blood flow restriction. *J Appl Physiol*. 2009 04;106(4):1119-24.
31. Manini TM, Clark BC. Blood flow restricted exercise and skeletal muscle health. *Exerc Sport Sci Rev*. 2009 Apr;37(2):78-85.
32. Cook SB, Murphy BG, Labarbera KE. Neuromuscular function following a bout of low-load blood flow restricted exercise. *Med Sci Sports Exerc*. 2012 Aug 14.
33. Suga T, Okita K, Morita N, Yokota T, Hirabayashi K, Horiuchi M, et al. Dose effect on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *J Appl Physiol*. 2010 Jun;108(6):1563-7.
34. Cook SB, Murphy BG, Labarbera KE. Neuromuscular function after a bout of low-load blood flow-restricted exercise. *Med Sci Sports Exerc*. 2013 Jan;45(1):67-74.
35. Martineau LC, Gardiner PF. Insight into skeletal muscle mechanotransduction: MAPK activation is quantitatively related to tension. *J Appl Physiol*. 2001 08;91(2):693-702.
36. Martineau LC, Gardiner PF. Skeletal muscle is sensitive to the tension-time integral but not to the rate of change of tension, as assessed by mechanically induced signaling. *J Biomech*. 2002 May;35(5):657-63.
37. Kumar V, Selby A, Rankin D, Patel R, Atherton P, Hildebrandt W, et al. Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. *J Physiol*. 2009 Jan 15;587(Pt 1):211-7.
38. Burd NA, West DW, Moore DR, Atherton PJ, Staples AW, Prior T, et al. Enhanced amino acid sensitivity of myofibrillar protein synthesis persists for up to 24 h after resistance exercise in young men. *J Nutr*. 2011 Apr 1;141(4):568-73.
39. Burd NA, West DW, Staples AW, Atherton PJ, Baker JM, Moore DR, et al. Low-load high volume resistance exercise stimulates muscle protein synthesis more than high-load low volume resistance exercise in young men. *PLoS One*. 2010 Aug 9;5(8):e12033.
40. Tanimoto M, Ishii N. Effects of low-intensity resistance exercise with slow movement and tonic force generation on muscular function in young men. *J Appl Physiol*. 2006 Apr;100(4):1150-7.
41. Coffey VG, Shield A, Canny BJ, Carey KA, Cameron-Smith D, Hawley JA. Interaction of contractile activity and training history on mRNA abundance in skeletal muscle from trained athletes. *Am J Physiol Endocrinol Metab*. 2006 May;290(5):E849-55.
42. Timmons JA. Variability in training-induced skeletal muscle adaptation. *J Appl Physiol*. 2011 Mar;110(3):846-53.
43. Atherton PJ, Smith K. Muscle protein synthesis in response to nutrition and exercise. *J Physiol*. 2012 Mar 1;590(Pt 5):1049-57.

44. Campos GER, Luecke TJ, Wendeln HK, Toma K, Hagerman FC, Murray TF, et al. Muscular adaptations in response to three different resistance-training regimens: Specificity of repetition maximum training zones. *Eur J Appl Physiol.* 2002 11;88(1-2):50-60.
45. Leger B, Cartoni R, Praz M, Lamon S, Deriaz O, Crettenand A, et al. Akt signalling through GSK-3beta, mTOR and Foxo1 is involved in human skeletal muscle hypertrophy and atrophy. *J Physiol.* 2006 Nov 1;576(Pt 3):923-33.
46. Lamon S, Wallace MA, Leger B, Russell AP. Regulation of STARS and its downstream targets suggest a novel pathway involved in human skeletal muscle hypertrophy and atrophy. *J Physiol.* 2009 Apr 15;587(Pt 8):1795-803.
47. Tanimoto M, Sanada K, Yamamoto K, Kawano H, Gando Y, Tabata I, et al. Effects of whole-body low-intensity resistance training with slow movement and tonic force generation on muscular size and strength in young men. *J Strength Cond Res.* 2008 Nov;22(6):1926-38.
48. Holm L, Reitelseder S, Pedersen TG, Doessing S, Petersen SG, Flyvbjerg A, et al. Changes in muscle size and MHC composition in response to resistance exercise with heavy and light loading intensity. *J Appl Physiol.* 2008 Nov;105(5):1454-61.
49. Mackey AL, Holm L, Reitelseder S, Pedersen TG, Doessing S, Kadi F, et al. Myogenic response of human skeletal muscle to 12 weeks of resistance training at light loading intensity. *Scand J Med Sci Sports.* 2011 Dec;21(6):773-82.
50. Mitchell CJ, Churchward-Venne TA, West DD, Burd NA, Breen L, Baker SK, et al. Resistance exercise load does not determine training-mediated hypertrophic gains in young men. *J Appl Physiol.* 2012 Apr 19.
51. Schuenke MD, Herman JR, Gliders RM, Hagerman FC, Hikida RS, Rana SR, et al. Early-phase muscular adaptations in response to slow-speed versus traditional resistance-training regimens. *Eur J Appl Physiol.* 2012 Oct;112(10):3585-95.
52. Ogasawara R, Loenneke JP, Thiebaut RS, Abe T. Low-load bench press training to fatigue results in muscle hypertrophy similar to high-load bench press training. *Int J Clin Med.* 2013;4:114-21.
53. Staron RS, Leonardi MJ, Karapondo DL, Malicky ES, Falkel JE, Hagerman FC, et al. Strength and skeletal muscle adaptations in heavy-resistance-trained women after detraining and retraining. *J Appl Physiol.* 1991 Feb;70(2):631-40.
54. Bruusgaard JC, Johansen IB, Egner IM, Rana ZA, Gundersen K. Myonuclei acquired by overload exercise precede hypertrophy and are not lost on detraining. *Proc Natl Acad Sci U S A.* 2010 Aug 24;107(34):15111-6.
55. Peterson MD, Rhea MR, Alvar BA. Applications of the dose-response for muscular strength development: A review of meta-analytic efficacy and reliability for designing training prescription. *J Strength Cond Res.* 2005 Nov;19(4):950-8.

56. Ogasawara R, Kobayashi K, Tsutaki A, Lee K, Abe T, Fujita S, et al. mTOR signaling response to resistance exercise is altered by chronic resistance training and detraining in skeletal muscle. *J Appl Physiol*. 2013 Jan 31.
57. Coffey VG, Zhong Z, Shield A, Canny BJ, Chibalin AV, Zierath JR, et al. Early signaling responses to divergent exercise stimuli in skeletal muscle from well-trained humans. *FASEB J*. 2006 Jan;20(1):190-2.
58. Nishimura A, Sugita M, Kato K, Fukuda A, Sudo A, Uchida A. Hypoxia increases muscle hypertrophy induced by resistance training. *Int J Sports Physiol Perform*. 2010 Dec;5(4):497-508.
59. Fry AC, Kraemer WJ. Resistance exercise overtraining and overreaching. neuroendocrine responses. *Sports Med*. 1997 Feb;23(2):106-29.
60. Izquierdo M, Ibanez J, Gonzalez-Badillo JJ, Hakkinen K, Ratamess NA, Kraemer WJ, et al. Differential effects of strength training leading to failure versus not to failure on hormonal responses, strength, and muscle power gains. *J Appl Physiol*. 2006 May;100(5):1647-56.
61. Hulmi JJ, Walker S, Ahtiainen JP, Nyman K, Kraemer WJ, Hakkinen K. Molecular signaling in muscle is affected by the specificity of resistance exercise protocol. *Scand J Med Sci Sports*. 2012 Apr;22(2):240-8.
62. Sale D, MacDougall D, Alway S, Sutton J. Effect of low vs high repetition weight training upon strength, muscle size and muscle fiber size. *Can J Spt Sci* 1985; 10: 27. 1985;10(27).
63. Harber MP, Fry AC, Rubin MR, Smith JC, Weiss LW. Skeletal muscle and hormonal adaptations to circuit weight training in untrained men. *Scand J Med Sci Sports*. 2004 Jun;14(3):176-85.
64. Hubal MJ, Gordish-Dressman H, Thompson PD, Price TB, Hoffman EP, Angelopoulos TJ, et al. Variability in muscle size and strength gain after unilateral resistance training. *Med Sci Sports Exerc*. 2005 Jun;37(6):964-72.
65. Bamman MM, Petrella JK, Kim JS, Mayhew DL, Cross JM. Cluster analysis tests the importance of myogenic gene expression during myofiber hypertrophy in humans. *J Appl Physiol*. 2007 Jun;102(6):2232-9.
66. Simoneau JA, Bouchard C. Genetic determinism of fiber type proportion in human skeletal muscle. *FASEB J*. 1995 Aug;9(11):1091-5.
67. Costa AM, Breitenfeld L, Silva AJ, Pereira A, Izquierdo M, Marques MC. Genetic inheritance effects on endurance and muscle strength: An update. *Sports Med*. 2012 Jun 1;42(6):449-58.
68. Trappe TA, Raue U, Tesch PA. Human soleus muscle protein synthesis following resistance exercise. *Acta Physiol Scand*. 2004 10;182(2):189-96.