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Fatigue Mechanisms and their Implications in Hypertrophy: A Review

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ABSTRACT

Mechanical tension, the force-velocity relationship, and high motor unit recruitment are all key factors in skeletal muscle fiber hypertrophy. Fatigue mechanisms can attenuate the hypertrophic response and can develop at any step during muscular contractions and in the post-workout period. These fatigue mechanisms can be split into central and peripheral nervous system. Fatigue physiology plays a key role in potentially modulating muscle fiber hypertrophy however they are seldom discussed together. This review aims to bridge the gap between the two domains and bring focus to the importance of appreciating and considering the role fatigue physiology can play in muscle fiber hypertrophy outcomes.

Keywords: Mechanical tension; motor unit recruitment; force-velocity relationship; length-tension relationship; central nervous system fatigue; peripheral fatigue.

INTRODUCTION

The various purported mechanisms of muscle fiber hypertrophy are well discussed in the literature. A comprehensive review article by Schoenfeld in 2010 discussed the three main purported drivers of muscle growth from exercise-induced activity (119). These are mechanical tension, muscle damage, and metabolic stress. There is contention as to whether all of these are contributors to muscle fiber hypertrophy rather than just mechanical tension alone (118, 54, 82, 135). However, seldom discussed alongside these are the mechanisms of fatigue which can play an impactful role in the decline of muscle fiber function during exercise (72, 139).

This review aims to bridge key concepts of the hypertrophic and fatigue literature and discuss these joint implications in hypertrophy outcomes. The approach of this paper is twofold: 1) review the key contributors of muscle fiber hypertrophy, and 2) review and discuss the involvement of fatigue in the key steps of muscular contractions, and their potential implications in hypertrophy outcomes.

As this review aims to bridge together muscle fiber hypertrophy and fatigue, many areas of physiology will be discussed, such as biomechanics, neurophysiology, and muscular biochemistry. Therefore, the following section will provide a summary of key terms to be discussed to provide the reader with some insight into these important topics, including muscle fiber hypertrophy, sarcomeres, fatigue, joint torques and internal moment arms.

Defining Muscle Fiber Hypertrophy

Hypertrophy refers to the increase of cross-sectional area of muscle fibers (132). Mechanisms of muscle fiber hypertrophy that have been proposed include existing muscle fiber splitting to create new daughter myofibrils or from additions of new myofilaments to the interior or exterior of existing myofibrils, making them larger (70). Muscle fibers can also grow lengthwise from the addition of sarcomeres in series (4). A sarcomere can be defined as the smallest functional unit of a muscle fiber and contains the molecular machinery to produce force via actomyosin cross bridges (for a comprehensive review, see 127).

Defining Fatigue

Fatigue can be defined as a temporary and reversible reduction in exercise performance due to a bout of previous exercise (13). There are

two types of neuromuscular fatigue: 1) Central Nervous System (CNS), which can be split into supraspinal (130) and spinal (47) fatigue, and 2) Peripheral Nervous System, which can be split into metabolite-related (74) and calcium-ion related (49) fatigue. Fatigue is an objective measurable phenomena and not simply the subjective feeling of lethargy experienced after a bout of exercise (60). Supraspinal fatigue can be measured by the use of maximum voluntary isometric contractions (MVIC) (46) and calcium-ion related fatigue can be measured by ratio of high/low frequency force measurements using the interpolated twitch technique, respectively (57). Both types of fatigue can have an impact on hypertrophic outcomes and can develop during exercise (134) and in the post-workout period (106).

Defining Joint Torque and Internal Moment Arm

A joint torque can be defined as the force needed to rotate a joint about its axis and is calculated as the product of force (newtons) and internal moment arm (metres). The internal moment arm is the perpendicular distance between the line of action of a force and the axis of rotation. For a given amount of muscle force, a longer internal moment arm results in a greater joint torque being produced (147). The internal moment arm represents a muscle's leverage in producing a joint moment and therefore its contribution to a particular joint motion, defining the role of the muscle (44).

Key Hypertrophy Considerations

The following will be introduced and discussed below as it pertains to muscle fiber hypertrophy: 1) mechanical tension, 2) the force-velocity relationship and, 3) the length-tension relationship.

Mechanical Tension

Mechanical tension as a driver for muscle growth has been well understood since the 1970's. Goldberg and colleagues (50) discuss that tension, either active or passive, is critical in initiating muscle growth and can be defined as the force experienced by contracting or lengthening muscle fibers. Since then, further research confirms the importance of mechanical tension's role in driving muscle growth (51, 138). Although muscle damage and metabolic stress have been linked to hypertrophy outcomes (see Schoenfeld review 119 for in depth discussion) and mechanisms proposed, the role of mechanical tension is clearly defined (141).

Muscle fibers are distinguished typically by their myosin heavy chain isoform, and exist on a continuum from type I to type IIX ranging from several to thousands of micrometers in diameter (100), with maximal fiber size being limited by the ability to process sufficient oxygen; the more oxidative a muscle fiber the smaller its maximum potential size compared to more glycolytic muscle fibers (137).

Muscle fibers detect mechanical tension via mechanoreceptors which initiate the downstream anabolic signaling pathway mediators such as akt/mTOR (63), MAPK (7), and p70S6K (8). After a bout of resistance training, muscle protein synthesis (MPS) rates can be elevated up to 150% above baseline for ~24-48 hours (78, 25). MPS rates are also elevated above baseline after a muscle damaging workout in order to repair any damage to the muscle fibers or the surrounding ultrastructures (144), therefore MPS rate post-intervention must be interpreted with caution. Researchers currently measure muscle protein synthesis in a multitude of ways, including but not limited to mixed muscle protein fractional synthesis rates (FSR) (10), integrated muscle myofibrillar protein FSR (31), L-[ring–13C6] phenylalanine infusion (108) and oral deuterium oxide tracer (19). The same signaling pathways are activated during muscle fiber damage repair described earlier for muscle fiber hypertrophy (83). This illustrates the difficulty in accurately distinguishing between muscle fiber repair and muscle fiber growth if using mixed muscle protein synthesis.

A major limitation in measuring muscle fiber size from a resistance training intervention is that popular techniques such as CT, MRI and DXA measure muscle thickness to estimate muscle fiber cross-sectional area (43). These methods used to assess muscle fiber size cannot distinguish between lean body mass (LBM) and skeletal muscle tissue: for example, DXA uses a 3-compartment model which directly measures fat and bone content and estimates the remainder as LBM, with LBM being influenced by connective tissue, water, and fat (9). This is a potentially major limitation as muscle swelling appears to persist for numerous days after resistance training and may peak around 72-96 hours post-workout (112) and appears to be caused by increased muscle fiber intracellular fluid content with the more glycolytic type IIx fibers most affected (28, 64). If muscle fiber hypertrophy measures are taken within 72 hours post-resistance training intervention, this could present as an issue.

Muscle swelling appears to continue even after the first workout and therefore cannot be a phenomena attributed to untrained individuals only (42). This is explained by the 'repeated-bout effect' phenomena which affords protection against muscle damage from later exercise bouts after the initial (67). Several studies have reported the possible post-intervention muscle fiber size measurement issues due to edema (30, 94, 93). To summarize, mechanical tension's role is clearly defined as a stimulus for muscle fiber hypertrophy, with major limitations apparent in the methods used to determine muscle fiber hypertrophy.

The Force-Velocity Relationship

The concentric force-velocity relationship in skeletal muscle states an inverse relationship between muscle fiber shortening velocity and the force produced; the slower a muscle fiber shortens the greater the force it can produce (145). This is due to the number of actin-myosin cross-bridges that can be formed; the faster the movement velocity, the faster the rate of attachment and detachment, therefore a reduction in force (66). This force is the mechanical tension experienced by activated muscle fibers (50). It is worth noting this force experienced by muscle fibers differs from the whole muscle force required to overcome Newton's laws of motion and move the mass of the weight; overcoming the initial inertia, accelerating the weight against gravity, and deceleration towards the end of movement (45). The eccentric force-velocity relationship is much flatter than the concentric force-velocity relationship (2). The force produced during eccentric contractions is also far greater than those produced during concentric contractions in activated muscle fibers due to the involvement of the viscoelastic protein titin which produces greater force with increasing velocity of lengthening (107). However, as greater force can be produced, less motor unit recruitment is required for the same load lifted compared to concentric contractions (34).

Motor unit recruitment is governed by Henneman's size principle (59). Motor units are recruited in size order from low-threshold to high-threshold depending on the demands; the heavier the external load, the greater the external force required to overcome, the greater the motor unit recruitment required and the more muscle fibers that are activated (39). As the largest, more glycolytic type II muscle fibers are most susceptible to growth compared to smaller, lower-threshold motor units (137) the focus should be on achieving high motor unit recruitment in a resistance training programme (58).

Interestingly both high velocity movements (140) such as vertical jumping, and strength training with 'heavy' loading, which is about 85% of a 1 repetition maximum (35) achieve high motor unit recruitment, yet different hypertrophy outcomes (98). Explosive movements by virtue of being high velocity means low muscle fiber force due to the faster actin-myosin detachment rate (101), therefore low degrees of mechanical tension experienced per muscle fiber. On the contrary, 'heavy' loads (>~85% 1RM) also require full motor unit recruitment (55) but have an involuntarily slow movement speed (due to a high degree of effort being required from the first repetition). This suggests high degrees of force and high mechanical tension per activated muscle fiber. Velocity-loss based training studies illustrate the importance of the force-velocity relationship in providing the mechanical tension stimulus required for muscle fiber hypertrophy (99).

'Lighter' loads (~30% 1RM) can also be used to attain a high level of motor unit recruitment and therefore similar hypertrophy outcomes to using 'heavy' loading (115). However, there is an important distinction to be made when 'lighter' loads are used; as mentioned above, when heavy loads (~85% 1RM) are used, which is about a 5-6 repetition maximum, full motor unit recruitment is achieved from the first repetition, however when lighter loads are used (~30% to <85% 1RM), the motor unit recruitment is built up over the course of the working set as lower-threshold motor units fatigue and higher-threshold motor units must be recruited to continue to produce the required force (35).

Loads that are less than ~20% of a 1 repetition maximum ('very light' loads) are too light to produce meaningful hypertrophy (81). The use of blood flow restriction (BFR) techniques such as occlusion cuffs can achieve similar hypertrophy outcomes with 'very light' loads compared to 'light' loads (123). Interestingly, venous occlusion does not occur with 'very light' loads as the contractile force is too little (114), therefore metabolites cannot be trapped inside the muscle. These metabolites are key to slowing the muscle fiber shortening velocity (143). Evidence suggests it is not the accumulation of metabolites such as lactate and growth hormone that is directly causing the hypertrophic effects seen with BFR (146) nor is it the associated hypoxia in absence of exercise with BFR (95), providing

evidence against the idea that metabolic stress causes hypertrophy.

As motor unit recruitment is high from the beginning of a set with 'heavy loads', these sets may not necessarily need to be taken to failure, whereas lighter loads which require the gradual recruitment of higher threshold motor units may need to be taken closer to failure (88). This is reflected in the idea that a large rep range exists for skeletal muscle hypertrophy with proximity to task failure considered important (56). To summarize, the force-velocity relationship is a key factor determining the amount of mechanical tension an activated muscle fiber can experience. Concomitantly, a high-degree of motor unit recruitment is equally important to gain access to the muscle fibers most susceptible to growth (glycolytic type II).

Length-Tension Relationship

The length-tension relationship describes the tension that can be produced by an individual sarcomere at a particular length (53). The length-tension relationship has two components; active and passive; the active length-tension relationship describes the contractile components of the sarcomere and the actin-myosin interactions during a concentric muscle action (111). The passive length-tension relationship describes the tension experienced during an eccentric muscle action due to the major contributions of the viscoelastic protein titin and some smaller contributions from the parallel and series elastic components (110).

Sarcomeres, the smallest functional unit of a muscle fiber, produce their greatest tension where there is greatest overlap between actin and myosin filaments which is described as the plateau of the length-tension relationship (21). At extremely short (ascending limb) or long (descending limb) sarcomere lengths, little force can be produced due to either too much or too little overlap of actin-myosin filaments, respectively (110). Different training styles can affect the length-tension relationship of muscle: eccentric-only training shifts the angle of peak torque to longer muscle lengths due to the addition of sarcomeres in series (62), whereas concentric-only training does not (136).

The length-tension relationship of each activated muscle fiber dictates sarcomere operating lengths (SOL); muscle fibers with SOLs that reach the descending limb (long lengths) are able to experience stretch-mediated hypertrophy (SMH) which can be measured as an increase in muscle fascicle length (4). An example would be the quadricep sarcomeres which operate on the descending limb (125) and therefore can experience sufficient passive tension to experience SMH, similar to the Biceps femoris hamstring muscle (4). However, the triceps brachii whose sarcomeres do not reach the descending limb, and appear to exist mainly on the plateau, do not appear to benefit from being trained in the stretched position (128).

The large muscle groups that contribute the greatest to the force requirement of movements are known as prime movers, which are also the muscle groups that likely experience a hypertrophic response during exercise. Prime movers are dictated by the relevant biomechanical leverages of the muscle(s) involved throughout the exercise range of motion (65). An example is the glute bridge for the gluteus maximus muscle; the internal moment arm length of the gluteus maximus is longer at higher degrees of hip extension contributing a large joint torque (89). To summarize, the length-tension relationship is a key consideration when programming resistance training and choosing what range of motion to take exercises through.

To review, mechanical tension describes the force experienced by an activated individual muscle fiber. The force-velocity relationship describes the slow movement speed required for an activated muscle fiber to experience high degrees of force (mechanical tension). Motor unit recruitment dictates the amount of activated muscle fibers and the length-tension relationship describes the amount of tension a sarcomere can produce depending on its length. Therefore, it appears that high motor unit recruitment at involuntarily slow movement velocities (due to the force-velocity relationship) is required to create a hypertrophic stimulus.

This hypertrophy can be achieved with the use of both 'heavy' and 'light' loads (and 'very light' loads with the use of occlusion training, for example BFR). However, only the highest threshold motor units accessible under voluntary control are capable of experiencing a hypertrophic response (103). Therefore, if the goal is to build skeletal muscle tissue, it seems to be pertinent to strive for full recruitment of all available motor units during resistance training.

However, in order to achieve high motor unit recruitment, fatigue must be appropriately managed. Below the various types of neuromuscular fatigue

will be discussed and their potential implications in achieving high degrees of motor unit recruitment and hypertrophic outcomes.

FATIGUE MECHANISMS DURING A MUSCULAR CONTRACTION

Central Nervous System Fatigue Mechanisms

Supraspinal Fatigue

The muscular contraction sequence begins in the motor cortex. A central motor command (CMC) is generated for a required action, such as carrying out daily tasks or performing resistance training exercises, and is akin to motor unit recruitment (131).

Supraspinal fatigue affects the amount of CMC that can be produced in the motor cortex (134). This in turn reduces the amount of motor unit recruitment capable of being achieved and therefore the highest threshold motor units are not activated (in accordance with Henneman's size principle). The CMC is under voluntary control and is directly linked to effort (32); a greater effort voluntarily produced induces a greater level of CMC and therefore a larger recruitment of motor units. Therefore it can be reasoned that when experiencing supraspinal fatigue, this can lead to a reduction in the CMC and thus motor unit recruitment.

The size of the CMC generated in the motor cortex is linked to our perceived effort and how much we can tolerate (124). Marcora (86) proposed the psychobiological model of fatigue which centers around the corollary discharge theory: a copy signal of the CMC is produced in the sensory cortex and any afferent feedback causing discomfort such as burning or cardiovascular sensations from metabolite and inflammatory mediator accumulation will increase our perception of effort without increasing our CMC. This will reduce corollary discharge (17), and subsequently reduce the CMC. This suggests that our maximum tolerable perception of effort is reached at a lower level of CMC and therefore involves lower motor unit recruitment.

Spinal Fatigue

The extent of spinal fatigue is linked to the duration of the motor unit firing; the longer the firing, the greater the spinal fatigue (47). As motor units repeatedly fire, they become increasingly desensitized to the CMC. This reduced motor neuron excitability can be observed in sustained isometric contractions with low and high levels of muscle activation (20).

Peripheral Fatigue Mechanisms

As the action potential arrives at the NMJ, the neurotransmitter acetylcholine (ACh) binds to its receptor and transmits the action potential towards the muscle fiber (79). The propagation of this action potential across the muscle cell membrane can be reduced which in turn reduces the amount of muscle fibers which are activated; the disruption of this signal may be due to structural cellular damage: ion channels which would otherwise maintain appropriate polarity may be damaged by reactive oxygen species and phospholipase-induced degradation (6).

The action potential depolarizes the muscle fiber membrane triggering the release of calcium- ions from the sarcoplasmic reticulum (SR), representing the conversion of an electrical signal into a chemical signal. The process of excitation contraction coupling (ECC) occurs at the triadic junction (121). Calcium-ions bind to troponin C located on Actin filaments, inducing a conformational change in the troponin complex by pulling tropomyosin away revealing the actin binding site to allow myosin to bind and form cross-bridges (52).

If the electrical signal above is impaired and does not convert to this chemical signal then reduced cross-bridges will be formed, and this in turn reduces muscle force. This is called ECC Failure (ECCF) (129). The release and reuptake of calcium-ions occurs many times per second, as muscle fibers are switched on and off during contractions. This is a leaky process (80), and although the mitochondria can aid in removal of some calcium-ions (36), especially in oxidative type I muscle fibers which have greater mitochondrial density compared to the more glycolytic type II muscle fibers, not all can be recovered. The mitochondria are particularly important during this process and the uptake of these calcium-ions helps support the energy requirements of muscular contraction by stimulating the krebs cycle and ATP generation (71). The importance of the mitochondria in calcium-ion uptake during skeletal muscle contractions is demonstrated by the loss of the mitochondrial calcium uniporter gatekeeping protein MICU1 which causes impaired calcium-ion uptake during ECC, muscle weakness and fatigue, and myofiber

damage repair (33). Due to the build up of calcium-ions, calpain enzymes are released and can degrade the triadic junction, causing the voltage sensor to lose structural integrity and separate from the SR (11).

The cross-bridge is formed when a myosin head binds to actin and the cross-bridge cycle is reviewed in depth (77). To summarize, the cross-bridge cycle begins with ATP binding to a myosin head. This causes the detachment from actin and subsequent ATP hydrolysis to ADP and Pi. The ADP- myosin head binds to a new site on the actin filament. The ADP is released causing the myosin filament to pull on the actin filament, making the sarcomere shorten, leading to a muscular contraction. This action continues until calcium-ions are no longer available to bind to troponin C.

Muscle fiber shortening velocity can also be impacted (142) as myosin must form cross-bridges with actin repeatedly to sustain a muscular contraction. Actin to myosin binding and unbinding can be affected by the presence of H+ ions (acidosis) and inorganic phosphates (from ATP cycling) (41), thus slowing this process down. However, importantly, a reduction in muscle fiber shortening velocity means an increase in muscle fiber force production due to the force-velocity relationship discussed above, and thus an increase in mechanical tension. Acidosis appears primarily responsible for the shortening velocity whilst inorganic phosphate accumulation from ATP cycling affects muscle force to a greater degree. Interestingly, even with a plentiful supply of ATP, the build up of phosphates can stop the cross-bridge cycling from forming and both metabolites are free to dissipate once blood flow is no longer occluded by muscular contractions and can freely flow out of the muscle (1).

Fatigue Post-Workout

Muscle Damage Induced Post-Workout Fatigue

Although muscle damage as a driver of hypertrophy is contentious (118) it is well documented that muscle damaging workouts such as heavy, sustained eccentric contractions (126) correlates with post-workout muscle soreness and leads to post-workout fatigue (5). Muscle damage is caused by calcium-ion accumulation and subsequent increase in calpain activity which degrade the structures of the cell (48). This process is similar to the process of ECCF discussed above. The use of eccentric contractions also opens up stretch -activated ion channels which allow for additional calcium-ion influx (90). Muscle damage creates a local and a systemic inflammatory response which is fundamental to the repair process leading to an increase in supra-spinal CNS fatigue due to afferent feedback. CNS and peripheral fatigue within a workout are highly transitory and will typically dissipate after 2-5 minutes with force restitution apparent (23). However, muscle damage can lead to supraspinal CNS fatigue that lasts for days and can have impacts on the following workouts if the muscle damage is severe enough; Prasartwuth et al, (2006) demonstrated that voluntary activation had still not recovered 8 days after muscle damaging eccentric work (104), with another study finding that it took 48 hours to recover from high-volume heavy resistance training in a study conducted on 10 strength-trained male athletes (133).

Glycogen Depletion

There are strong correlations between glycogen availability and cardiovascular exercise performance, particularly during lengthy sessions at 60-80% maximal oxygen uptake (15, 61). Low glycogen availability is associated with impaired calcium-ion release and reuptake via the SR (91, 97). This suggests calcium-ion related fatigue mechanisms (37, 38) which can induce muscle damage affecting glycogen repletion rates (27). In one particular study glycogen repletion rates were slowed for up to 10 days later after eccentric-induced muscle damage (96). This suggests a means by which fatigue can potentially accumulate, not from metabolic-related mechanisms, rather impaired calcium-ion functioning during a muscular contraction.

DISCUSSION

The key considerations of skeletal muscle hypertrophy and the fatigue mechanisms that develop during resistance exercise and in the post-workout period have been discussed in-depth in this article. The presence of substantial CNS fatigue, both supraspinal and spinal, will reduce motor unit recruitment, as measured by voluntary activation, therefore impacting our ability to recruit the highest threshold motor units. The presence of peripheral fatigue mechanisms can be attributed to both calcium-ion related fatigue and metabolite-related fatigue. These in turn reduce muscle fiber force and muscle fiber shortening velocity, respectively.

If metabolite-related fatigue is the predominant fatigue mechanism present during high levels of motor unit recruitment, this can be beneficial as this causes a slowing of muscle fiber shortening velocity. Therefore, supraspinal and calcium-ion related fatigue mechanisms appear to be where the most attention should be paid with regards to fatigue management.

Supraspinal fatigue affects motor unit recruitment. High motor unit recruitment is needed for activating the muscle fibers most responsive to grow in size (103). Afferent feedback reduces voluntary activation (122) and lifting light loads to task failure creates metabolite-induced afferent feedback with less motor unit recruitment compared to heavier loads (88). In addition, a study showed that light load unilateral training demonstrated post-workout fatigue still apparent 48 hours later in the trained leg, and 24 hours later in the non-trained leg, compared to recovery after 24 hours in the trained leg using moderate loads and no measurable fatigue in the non-trained leg (40).

A large aerobic demand, which may be observed during high repetition multi-joint compound movements such as back squats and deadlifts, produces afferent feedback via group III/IV muscle afferents via spinal motor neuron output restriction and subsequent voluntary activation reduction (3). This reduction in voluntary activation can be linked to earlier discussions regarding increased perception of effort due to afferent feedback affecting corollary discharge processing. This is supported by the observation that people disengage from a task after they cannot tolerate any more effort where physiological failure is not apparent (85, 29, 105, 92).

After a bout of high-intensity exercise, central fatigue is recovered in ~2 minutes (23). Some evidence suggests longer rest periods (3 minutes per set) can be more hypertrophic than shorter rest periods (1 minute per set) in young resistance-trained men (117). A separate study using the same rest periods demonstrated greater muscle damage markers, creatine kinase and increased inflammatory cell activity, in the 1 minute rest period compared to 3 minute rest period due to increased calcium-ion related fatigue and therefore increased post-workout supraspinal fatigue (120), which was the same outcome as a much earlier study using the same rest periods and muscle damage marker measurements (87). A study investigating lower repetition heavier loading with longer rest (3 minutes) vs higher repetition shorter rest (1 minute) in resistance trained men (33 men, 5.7 2.2 years training experience) concluded the former group demonstrated greater improvements in hypertrophy and strength measures at study end (84). The use of less muscle mass for a task may also involve less CNS fatigue, i.e., unilateral variations (113). Supraspinal fatigue in a workout can therefore be appropriately managed by paying attention to rest period lengths and afferent feedback producing stimuli such as discomfort experienced when performing aerobically demanding exercises and light load/ higher repetition loading.

Calcium-ion related fatigue is particularly problematic as this reduces mechanical tension, a key driver of muscle fiber hypertrophy and can cause muscle damage which produces supraspinal CNS fatigue. Eccentric training and working at longer muscle lengths causes an increase in calcium-ion related fatigue due to the opening of stretch-activated ion channels (12). The following also leads to increased calcium ion-related fatigue: training closer to task failure due to the increased involvement of the more glycolytic fast-twitch fibers at higher motor unit recruitment levels measured by low frequency fatigue (109), the use of lighter loads over heavier loads due to longer muscle activation time (57) and the use of larger training volumes (24).

Session/ weekly resistance training volume, defined as the amount of sets taken to task failure, is a key consideration. A study of 8 trained men showed that MPS rates were elevated 210% above baseline after 3 sets to failure compared to 130% after 1 set to failure 5 hours after exercise cessation, with the 3 sets groups still 130% above baseline 29 hours later (22). This suggests 3 sets is far superior to just 1 set to failure for hypertrophic outcomes. A dose-response relationship of volume for hypertrophic outcomes performed by Schoenfeld et al (2017) demonstrated that 3 sets per week produced substantial hypertrophy also, however to double the amount of hypertrophy achieved from this volume would require 18 sets per week (116). This suggests that a 'unit of hypertrophy' is not achieved with each subsequent set after the first and there are diminishing returns on the hypertrophic stimulus with each subsequent set in a workout. This provides valuable insight into effectively programming volume according to the individual's needs versus arbitrarily applying volume.

CONCLUSION

Fatigue development during a workout is inescapable and will be incurred to varying degrees, however the type and extent of this fatigue appears dependent on how resistance training programmes are written. Progressive overload is a key variable that is important in continued progression during resistance training (76), therefore programming in a manner that allows the continuation of progressive overload seems most reasonable.

The use of deload periods to try to manage fatigue accumulated in a resistance training programme are common (14). One study concluded that the addition of a 1 week deload period at the midpoint of a 9 week resistance training programme actually had negative outcomes with reference to lower body muscle strength and zero effect on lower body measures of hypertrophy, power, and local muscular endurance (26). MPS rates are elevated for ~24-48 hours after a bout of resistance training with the newest adaptations being lost if no new stimulus is achieved to either maintain or increase muscle fiber size once this inflated MPS period ends. This has been clearly demonstrated in the maintenance training (16), detraining (68, 102) and atrophy (69) literature with evidence even suggesting that dietary protein intake alone does not have any measurable effect on myofibrillar protein synthesis rates in the absence of a mechanical tension stimulus (75) and muscle fascicle length increases alongside concomitant decreases in muscle fiber cross-sectional area have been observed in lengthed position limb immobilization studies (18, 73) If the purported use of deload periods is used to ameliorate accumulated fatigue, it could be suggested based on the deload, maintenance, detraining, and atrophy data that managing programme volume could be more beneficial than the use of planned deloads, if there appears to be no net benefit on hypertrophic outcomes by using deloads.

The topics discussed in this report are not binary; a hypertrophic stimulus can still be achieved in the presence of fatigue and incomplete recovery. However, to maximize the value gained from hypertrophic-focused workouts these applications can be taken into consideration. As training status advances and the pool of growable motor units shrink, these factors may prove most useful for continued progress. This review aims to bridge together the fatigue and muscle physiology as it pertains to hypertrophy. Future studies measuring hypertrophic outcomes from various training style interventions could benefit from the inclusion of fatigue physiology in order to paint a more specific picture of what is happening at the mechanistic level, and therefore how resistance training programmes can be better designed. Furthermore, more effort is needed in considering and discussing the fundamental principles of hypertrophic mechanisms such as the force-velocity relationship, length-tension relationship, and Henneman's size principle as they relate to hypertrophy outcomes, as these principles are seldom discussed in the hypertrophic literature.

CONFLICTS OF INTEREST

There are no relationships to be mentioned as no beneficial endorsement is to be gained from this review.

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ETHICAL APPROVAL

Not Applicable.

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