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REVIEW ARTICLE

Is there Evidence for the Suggestion that Fatigue Accumulates Following Resistance Exercise?

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Abstract

It has been suggested that improper post-exercise recovery or improper sequence of training may result in an 'accumulation' of fatigue. Despite this suggestion, there is a lack of clarity regarding which physiological mechanisms may be proposed to contribute to fatigue accumulation. The present paper explores the time course of the changes in various fatigue-related measures in order to understand how they may accumulate or lessen over time following an exercise bout or in the context of an exercise program. Regarding peripheral fatigue, the depletion of energy substrates and accumulation of metabolic byproducts has been demonstrated to occur following an acute bout of resistance training; however, peripheral accumulation and depletion appear unlikely candidates to accumulate over time. A number of mechanisms may contribute to the development of central fatigue, postulating the need for prolonged periods of recovery; however, a time course is difficult to determine and is dependent on which measurement is examined. In addition, it has not been demonstrated that central fatigue measures accumulate over time. A potential candidate that may be interpreted as accumulated fatigue is muscle damage, which shares similar characteristics (i.e., prolonged strength loss). Due to the delayed appearance of muscle damage, it may be interpreted as accumulated fatigue. Overall, evidence for the presence of fatigue accumulation with resistance training is equivocal, making it difficult to draw the conclusion that fatigue accumulates. Considerable work remains as to whether fatigue can accumulate over time. Future studies are warranted to elucidate potential mechanisms underlying the concept of fatigue accumulation.

Key Points

The concept of long-term fatigue accumulation has appeared repeatedly in the literature without clear elucidation of what is accumulating and how/why this is occurring.

Due to the delayed appearance of muscle damage, it may be interpreted as accumulated fatigue.

Insufficient evidence exists on the presence of fatigue accumulation following resistance training, and future studies are warranted to elucidate potential mechanisms underlying the concept of fatigue accumulation.

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1 Introduction

Fatigue is a complex and multifactorial phenomenon and much is still unknown about why an individual becomes fatigued under various exercise conditions [1]. Research on resistance training is no exception, as mechanisms underlying fatigue following resistance exercise have not been fully delineated [2]. While a number of definitions of fatigue have been proposed [1, 3–5], a common tenet indicates that fatigue is the failure to maintain the required or expected force-generating capacity in response to voluntary effort. During resistance exercise, the extent of fatigue may be dependent on the level of effort [6], type of exercise selection [7], degree of active muscle mass [8], or volume of training [9]. Taking into consideration other variables such as sleep [10] and stress [11], the rate of recovery may dictate the readiness for the subsequent workout. Although less recovery time between each resistance training session (i.e., < 24 h between sessions vs. < 48–72 h between sessions) may not necessarily cause negative outcomes in muscle growth and strength within a short period of time (i.e., 12 weeks) [12], it has been suggested that improper

post-exercise recovery or sequence of training may result in an increase in accumulated fatigue [13, 14].

The concept of long-term fatigue accumulation has appeared repeatedly in the literature without clear elucidation of what is accumulating and how/why this is occurring [13–19]. Fatigue accumulation refers to the fatigue that summates over repeated bouts of training that is believed to be additive to pre-existing fatigue. Regardless of the lack of clarity on physiological aspects, the idea has been explained conceptually using the fitness-fatigue model originally proposed by Banister et al. [20]. This model is postulated as a way of explaining the interaction between two after-effects—fitness and fatigue—that may result from training. Fitness after-effect causes a positive physiological response that increases performance, whereas fatigue after-effect causes a negative physiological response that adversely influences performance. The fitness gain resulting from training is suggested to be moderate in magnitude but long-lasting (i.e., increases in muscle strength), while the fatigue effect is large in magnitude with a brief duration (i.e., reduction in force-generating capacity) [14, 21]. Consequently, the difference between these two antagonist effects is believed to describe performance and state of preparedness (preparedness = fitness − fatigue). Based on the assumption that fatigue would accumulate over the course of training [22], the concept is often reflected in the training structure (i.e., mesocycle) by creating a discrete period of deload (i.e., reduction in training volume and/or load). In addition, a tapering strategy is often structured in training to create a period of reduced training volume and/or load prior to a competition to express an athlete's current level of fitness by dissipating fatigue [18, 23, 24]. Mujika and Padilla have proposed that athletes who undergo tapering should achieve the expected improved performance level once accumulated fatigue fades away [23]. Of note, an increase in the testosterone/cortisol ratio during the taper has been suggested as one of the indices of enhanced recovery and elimination of accumulated fatigue [23, 25]. However, the endocrine responses to resistance training remain unclear due to the variability of the measurement results [26, 27].

While several mathematical models have been proposed to quantify the training and performance relationship [28, 29], the commonly used fitness-fatigue equation presents that (Eq. 1) [30, 31]:

$$P(t) = p(0) + k1 \sum_{s=0}^{t-1} e^{-\frac{t-s}{\tau_1}} \cdot \mathrm{w(s)} - \mathrm{k2} \sum_{s=0}^{t-1} e^{-\frac{t-s}{\tau_2}} \cdot \mathrm{w(s)}, \quad (1)$$

where $p(t)$ is the performance at time t; p (0) is the initial performance level; k_1 and k_2 are the fitness and fatigue magnitude factors, respectively (i.e., how the training load impacts the fitness and fatigue effect on performance); τ_1 and τ_2 are the fitness and fatigue decay time constant, respectively; and w is the known training load per week (or day) from the first week of training to the week (or day) preceding the performance. These parameters are interpreted as individual response profiles, and the mathematical model may predict the effects of training on physical capability [30, 32].

Furthermore, the model suggests that fatigue has a cumulative effect, and when fatigue accumulates to the point where fatigue after-effects significantly exceed fitness after-effects (i.e., depletion of the individual's adaptive abilities), overtraining occurs [14]. Although the model may conceptually give some insights, the criticism has been made in regard to the discrepancies between the predicted and measured time course of physiological adaptations [32]. Thus, it seems that there is a gap between the model and the underlying physiology, certainly with regard to the physiological aspects of fatigue accumulation (i.e., what is accumulating and how/why is this occurring). Currently, the majority of investigations on fatigue or overtraining have been conducted in aerobic-oriented activities [33–36]. Furthermore, the mechanisms that underlie overtraining in resistance exercise largely remain uncertain [17], and further investigation on this mode of training is warranted. Therefore, the purpose of this review was to evaluate the time course of the changes in various fatigue measures in response to resistance exercise with an aim to elucidate some of the potential mechanisms that may contribute to accumulating fatigue in resistance training.

2 Types of Fatigue

One of the most well-accepted models for explaining the causes of neuromuscular fatigue involves the concept of task dependency. The task dependency model of muscle fatigue implies that the cause of the fatigue is dependent on characteristics of the exercise that is being performed, meaning that dominant fatigue-inducing mechanisms involved in limiting performance may differ in various conditions [37]. Although the specificity of the impairments that contribute to the development of muscle fatigue (i.e., contraction mode, muscles involved, type of exercise) [38] and the approaches to study fatigue (i.e., muscle in vivo, isolated muscle, isolated single fiber) [39] would make a causal mechanism of muscle fatigue difficult to decipher, it has been suggested that the mechanisms underlying fatigue can be of central or peripheral origin [40]. In essence, central fatigue occurs proximal to the neuromuscular junction (i.e., within the motor neurons and central nervous system), whereas peripheral fatigue includes the neuromuscular junction and muscle fibers themselves [39, 41, 42]. As proposed in the task dependency model, the cause of fatigue is dictated by the characteristics of

the exercise task that is being performed. For example, peripheral fatigue contributes relatively more to maximum voluntary contraction (MVC) reduction during short, high-intensity exercise, and central fatigue contributes relatively more during longer duration, moderate-intensity exercise [40]. In resistance training, a different acute neuromuscular fatigue profile was observed between a maximal strength loading protocol (15 sets of 1 repetition maximum) and a hypertrophic loading protocol (5 sets of 10 repetition maximum) [43]. The results indicated that the hypertrophic loading protocol resulted in greater losses in post-loading maximum isometric force accompanied by reduced neuromuscular efficiency (force/electromyography [EMG] amplitude), reduced median frequency, and maintained EMG amplitude, which was related to the greater degree of peripheral fatigue [43]. On the other hand, a maximal strength loading protocol led to decreased concentric and isometric force in conjunction with reduced EMG amplitude and maintained median frequency [43]. Based on the lack of change in median frequency, the authors speculated that the same motor units were active throughout the exercise protocol. Furthermore, when considering the decrease in concentric and eccentric EMG amplitudes, the authors suggested that a reduction in firing frequency may occur as a consequence of maximal strength loading. The difference in the degree of peripheral fatigue during these loadings may imply that there were different neuromuscular responses between conditions [44]. Within the scope of complexities that cause fatigue, subsequent sections will discuss the potential mechanisms of neuromuscular fatigue to present knowledge of the peripheral and central factors of muscle fatigue that are related to resistance exercise. In addition, the time course of the changes in fatigue phenomenon will be evaluated to help determine whether fatigue 'accumulates' over time.

3 Peripheral Fatigue

Potential sites of peripheral fatigue occur in the peripheral nerve, neuromuscular junction, muscle cell membrane, calcium release machinery, and sliding filaments [41, 42]. Within these structures, perturbations of neuromuscular transmission, propagation of the muscle action potential, excitation–contraction coupling, and contractile mechanisms correspond to the decline in tension development [39, 41, 45]. In regard to the mechanisms underlying peripheral fatigue, it has been proposed that fatigue could be due to the depletion of energy substrates or to the accumulation of metabolites [42].

3.1 Depletion Hypothesis

The depletion or exhaustion hypothesis largely involves the depletion of energy substrates: phosphagens (adenosine triphosphate [ATP] and phosphocreatine) and skeletal muscle glycogen [42]. In the broad sense, fatigue can be viewed as the net balance between the ATP utilization of muscle cells and their ATP-resynthesizing capacity. Since there is a limited supply of readily available intramuscular ATP stores, a sustained contractile activity is hindered for an extended period of time [46]. Thus, to prevent muscle fibers from exhausting their ATP stores, other metabolic pathways, substrate-level phosphorylation (or anaerobic) and oxidative phosphorylation (aerobic), must be activated to produce ATP. ATP resynthesis that is predominantly involved in intense anaerobic exercise includes the breakdown of phosphocreatine and glycogen. These ATP-generating pathways have a greater rate of ATP production with a smaller capacity (total ATP produced) compared with aerobic pathways [46]. Although it is less studied relative to aerobic and other anaerobic activities, it has been demonstrated that depletion of muscle phosphocreatine and glycogen plays a role, in some part, in inducing fatigue during resistance exercise [47, 48].

Phosphocreatine is the high-energy phosphagen that provides the immediate energy in the initial stages of intense exercise by donating its phosphate molecule to adenosine diphosphate to resynthesize ATP [49]. During resistance exercise, it has been reported that the concentration of phosphocreatine is significantly depleted at the point of fatigue [48]. For instance, when resistance-trained individuals performed either one or three sets of a biceps exercise to failure at 80% of one-repetition maximum (1RM), the phosphocreatine concentration was lower by a mean value of 62% in the 1-set group and 50% in 3-sets group [48]. The fact that performing 3 sets did not lead to greater depletion of phosphocreatine indicated that the 3 min rest period between sets was long enough to restore phosphocreatine. In line with this finding, sustaining isometric contraction at 66% of MVC until force declined to approximately 50% of MVC resulted in a rapid recovery of phosphocreatine resynthesis [50]. It was reported that approximately 67% of phosphocreatine was restored following 2 min of recovery and approximately 84% of phosphocreatine was recovered after 4 min of recovery, demonstrating that the majority of resynthesis completed immediately after the exercise [50].

Simultaneously, as the stores of available phosphocreatine deplete, the rate of ATP regeneration from the breakdown of glycogen will be augmented. Skeletal muscle glycogen is the major readily available energy source that plays a role in muscular contractile activity, demonstrated by the inability to sustain a high-intensity exercise when glycogen stores are depleted [51]. Glycogen is also

differently distributed within a muscle and is located in the subsarcolemmal region, intermyofibril, and intramyofibril, with possible distinct functions [52]. It has been suggested that glycogen located between the myofibrils close to the longitudinal sarcoplasmic reticulum (intermyofibrillar glycogen) powers the release of sarcoplasmic stored calcium (Ca^{2+}) and activates tropomyosin binding sites, whereas the glycogen located inside the myofibrils (intramyofibrillar glycogen) is preferably depleted during high-intensity exercise and plays a role in excitability and/or sarcoplasmic reticulum Ca^{2+} release properties [53, 54]. It is generally accepted that impaired sarcoplasmic reticulum Ca^{2+} release is a major factor in fatigue after performing exercise due to disruptions of the excitation–contraction coupling process [39]. Furthermore, one of the relevant potential mechanisms involving a glycogenolytic complex is associated with the sarcoplasmic reticulum. This was portrayed in the work of Ørtenblad et al., who reported that the depletion of glycogen during exhausting exercise was associated with impaired muscle ability to release sarcoplasmic reticulum Ca^{2+} [55]. While the reduction in muscle glycogen may be dictated by the duration, intensity, and volume of performed exercise, a typical resistance exercise bout has been shown to reduce glycogen levels by approximately 25–40% [47, 48, 56–58]. For instance, Hokken et al. reported that muscle glycogen decreased by 38% when 10 male weightlifters performed resistance exercises consisting of four sets of five repetitions (4 × 5) at 75% of 1RM back squats, 4 × 5 at 75% of 1RM deadlifts, and 4 × 12 at 65% of 1RM rear foot elevated squats [57]. Although skeletal muscle glycogen can be resynthesized with no calorie/carbohydrate (CHO) intake during the post-workout period [59], immediate provision of CHO to the muscle cell is recommended to initiate effective refueling as glycogen depletion provides a strong drive for its own enhanced resynthesis rates during the early phase (0–4 h) after exercise [60]. When 1.5 g CHO/kg body weight was ingested immediately after and 1 h after the resistance exercise, the muscle glycogen content was restored to 91% of the pre-exercise level following 6 h of training bout [56]. Similar results were reported by Roy and Tarnopolsky in which the rate of muscle glycogen synthesis was significantly higher at a dose of 1 g CHO/kg body weight over the first 4 h of the recovery period compared with a placebo group [58]. The glycogen resynthesis and degradation rates following resistance exercise may range from 1.9 to 11.1 mmol/kg/h and 40.6 to 46.9 mmol/kg wet weight, respectively [56, 59]. A complete glycogen restoration might occur within 4–5 h if glycogen depletion is only around 40 mmol/kg wet weight and sufficient CHO is provided [61]. If glycogen depletion is 150 mmol/kg wet weight following resistance training [57], a complete glycogen restoration might take up to 24 h, with the maximal glycogen resynthesis rates occurring after exercise (10 mmol/kg/h) for 4 h and a mean glycogen storage rate of 4–6 mmol/kg/h [60, 61]. Taken together, the consideration of the time course of glycogen resynthesis may be particularly important for an individual who undertakes multiple training sessions within the same day (i.e., < 12 h recovery from the first session). To summarize, resistance exercise predominantly involves the breakdown of muscle phosphocreatine and glycogen to sustain ATP resynthesis. The depletion of phosphocreatine and glycogen plays a role in inducing fatigue during resistance exercise, yet the time course of depletion appears to be short-lived. For muscle phosphocreatine, the majority of resynthesis occurs immediately after the completion of exercise. Similarly, the greater part of the recovery of glycogen storage takes place within a 24-h period.

3.2 Accumulation Hypothesis

The accumulation hypothesis relates to the build-up of a number of metabolites within muscle fibers [42]. Although not exhaustive, two end products of anaerobic metabolism, hydrogen ion (H^+) and inorganic phosphate (P_i), have received the most attention in this regard [62–65]. In the context of the accumulation hypothesis, if fatigue accumulates in response to resistance exercise, potential scenarios would be that either the exercise-induced metabolic byproducts accumulate acutely but dissipate shortly after training, or the exercise-induced metabolic byproducts accumulate acutely and also exacerbate over time (prolonged accumulation of metabolic byproducts). Indeed, if the latter case is supported, it may serve as a partial explanation for the purported fatigue accumulation that may cause prolonged impairments in muscular function. Intense muscular contraction creates an increased intramuscular pressure condition that causes a partial occlusion of the blood flow [66, 67]. Accordingly, impairment of oxygen availability may result in a more rapid accumulation of metabolites and interference in contractile function (i.e., cross-bridge cycling) [68, 69]. When considering the major potential sites of peripheral fatigue, including sarcolemma excitability, excitation–contraction coupling, contractile mechanisms, metabolic energy supply, and metabolic accumulation, a diminished contractile function corresponding to the decline in tension development may occur if any of these sites are disrupted by intense muscular contractions [70]. Muscle contractions depend on electrical excitation of the muscle fibers in such a way that neuromuscular transmission initiates an action potential and propagates along the sarcolemma, leading each action potential to an efflux of potassium (K^+) (i.e., an increase in extracellular K^+) [39, 71]. As such, alternation in excitability at the sarcolemma might be the site of fatigue due to the inability to maintain electrical gradients (sodium [Na^+] and K^+) during repeated stimulation [39]. When K^+ channels open up due to a drop in ATP concentration, K^+ floods out

and causes an extracellular K^+ accumulation and depolarizes the cell membrane, which in turn inactivates the Na^+ channel and reduces membrane excitability [72, 73]. This may reduce the action potential of the T-tubules and limit Ca^{2+} release from the sarcoplasmic reticulum [39, 45]. However, under normoxic conditions, the K^+ channels do not seem to contribute significantly to the decrease in force during fatigue [73].

Other potential sites of peripheral fatigue include the cross-bridge's ability to 'cycle'. The cross-bridge cycle is initiated with a sequence of events leading to the release of Ca^{2+} from the sarcoplasmic reticulum [74]. Thus, at the cellular level, force production may depend on (1) the concentration of Ca^{2+} surrounding the myofilaments; (2) the Ca^{2+} sensitivity of the myofilaments; and (3) the maximum Ca^{2+} activated force (force produced by the cross-bridge) [4]. In the case of fatigue associated with H^+, accumulation of H^+ resulting from ATP catabolism and glycolysis has shown a correlation between the extent of acidosis (increase in H^+) and impairment in contractility [63]. Specifically, acidosis caused by elevated H^+ (reduced intracellular pH) has been proposed to induce fatigue by suppressing myofibrillar Ca^{2+} sensitivity [75]. Furthermore, the elevated H^+ reduces the affinity of the binding sites on troponin C [76], and indirectly impairs contractile function by inhibiting the key glycogenolytic enzyme activities such as phosphorylase [51]. However, the role of H^+ in fatigue is the current topic of debate as to whether H^+ plays a central role in skeletal muscle fatigue [77, 78] since the effect of acidosis on reduced maximum shortening velocity of mammalian muscle has been shown to be small at physiological temperature (i.e., 30 °C) [79]. The time course of changes in the accumulation of H^+ is also acute in nature, as Degroot et al. reported that the clearance of H^+ was mostly completed in the first 15 min following a maximal isometric foot plantar flexion sustained for 4 min [64]. The authors further noted the dissociation between changes in pH and MVC at the onset of both exercise and recovery, suggesting that H^+ might not be a primary regulator of muscle fatigue [64]. In addition, resistance training appears to improve muscle H^+ regulatory capacity over time. It was found that bodybuilders who performed static handgrip exercise at 30% of MVC had significantly less H^+ accumulation (attenuated pH response) compared with untrained individuals [80]. Taken together, these findings suggest that intracellular accumulation of H^+ per se may not be a major contributor to muscle fatigue.

By the same token, during high-intensity exercise, the concentration of P_i increases due to the breakdown of phosphocreatine [63]. This can occur rapidly with maximum activation, and P_i accumulation contributes to the changes in cross-bridge behavior. According to the current cross-bridge action model, P_i is released in the transition from a weakly bound (low-force) state to a strongly attached (high-force) state at the actin-myosin binding sites. This indicates that the transition to the high-force cross-bridge states is hindered by increased P_i, and force production would decrease as a consequence of fewer cross-bridges in high-force states [74, 81]. Furthermore, the rise in P_i induces fatigue by acting on sarcoplasmic reticulum Ca^{2+} handling. The amount of Ca^{2+} released from the sarcoplasmic reticulum is reduced when P_i diffuses from the myoplasm into the sarcoplasmic reticulum through a P_i permeable channel and binds to Ca^{2+} to form calcium phosphate (CaP_i) [4, 69]. Similar to the discussion on H^+, the time course of recovery from accumulated P_i completes quickly. To illustrate, Baker et al. compared two exercise protocols that produced similar levels of moderate fatigue, to examine the role of metabolic and non-metabolic factors [65]. The short-duration exercise (SDE) group consisted of 2 min of sustained MVC of the ankle dorsiflexor muscles with blood flow restriction (anaerobic exercise), and the long-duration exercise (LDE) group performed 15–20 min of intermittent ankle dorsiflexion exercise without applying blood flow restriction (aerobic exercise). The major finding of the study was that for SDE, fatigue correlated with increased inorganic phosphate, and, importantly, both force and inorganic phosphate recovered within 5 min following exercise. For LDE, recovery of force took over 15 min following exercise, but the recovery of inorganic phosphate was not slowed (recovered within 5 min). Thus, the results of the study indicated that fatigue caused by short-duration anaerobic exercise might be more due to a metabolic inhibition of the contraction, whereas the fatigue caused from long-duration aerobic exercise may involve a contribution from non-metabolic factors, such as an impaired excitation–contraction coupling [65]. In closing, the data on the accumulation hypotheses suggest that the build-up of two end products of anaerobic metabolism, H^+ and P_i, may only last a short period of time (i.e., < 1 h), corresponding to acute fatigue within a single training session.

4 Central Mechanisms of Fatigue

Exercise-induced reductions in maximal voluntary force cannot be solely explained by the mechanisms related to peripheral fatigue. This is illustrated by the coexistence of central and peripheral fatigue during resistance exercise [82, 83]. For example, when the magnitude of both central and peripheral fatigue was measured following 10 sets of 5 repetitions of the high bar back squat at 80% of 1RM, the reduction in voluntary activation (indicative of central fatigue) and twitch force (indicative of peripheral fatigue) persisted, with a faster recovery of central compared with peripheral fatigue [83]. Thus, part of exercise-induced fatigue is related to modifications within the central aspects. Any breakdown in muscular activation within the motor neurons and central

nervous system is generally considered central, and central fatigue is the degradation of the muscle voluntary activation attributed to a decline in motoneuronal output [84]. A number of mechanisms may contribute to the development of central fatigue, such as inhibition of motoneuron excitability by afferent feedback from the muscle (i.e., groups III and IV muscle afferents), a decline in motor neuron firing rate, and a reduction in the number of motor units recruitment [85, 86]. Notably, peripheral factors are also implicated in central fatigue. During muscle contraction, the group III and IV afferent nerve fibers contribute to motor command and sense both mechanical and metabolic stimuli, respectively [87]. Accordingly, information about contractile events at the periphery is delivered to the central nervous system, leading to altered efferent output. Of note, release of cytokines, especially interleukin (IL)-6, has been suggested to initiate afferent signals to the brain during exercise, and may contribute to feelings of fatigue and decreased efferent drive to the muscles [88]. Ultimately, a feedback loop from group III and IV nerve fibers to the central nervous system potentially leads to (1) a decrease in the firing frequency of the motor neuron; (2) an inhibition or facilitation of the motor neuron; and/or (3) an inhibition of the motor cortex neuron [41]. The extent of central fatigue that appears after resistance exercise may be dictated by factors such as the type of exercise [7] and intensity of the load [89]. For instance, Yoon et al. demonstrated that a low-force contraction using 20% of MVC induced greater central fatigue than a high-force contraction using 80% of MVC for both men and women when exercising to task failure [89]. The authors suggested that the difference in voluntary activation likely resulted from a reduced descending drive and excitability of the motor neuron pool at spinal sources for the low-force contraction. The finding that low-load training elicited greater central fatigue than a high-load condition was also illustrated by Farrow et al., who compared the fatigue responses to low- and high-load dynamic knee extension exercise (40% and 80% MVC, respectively) to momentary failure in both an exercised and non-exercised limb [90]. It was demonstrated that low-load exercise induced greater fatigue in both exercised and non-exercised limbs compared with the high-load group. A presence of greater fatigue found in the non-exercised leg indicates that central mechanisms predominately mediated the exercise-induced fatigue produced by low-load exercise. The authors suggested that performing low-load training accompanied with a longer time under load likely resulted in greater acto-myosin cross-bridge cycling and a greater accumulation of metabolites, leading to a greater influence of group III/IV afferent motor unit firing rates and the need for greater central motor command [90].

Central fatigue can be quantified as voluntary activation, as estimated using twitch interpolation during an MVC [91]. In essence, the additional force elicited by supramaximal electrical stimulation is delivered to a nerve or muscle during a voluntary contraction, and, correspondingly, an increase in the amplitude of the interpolated twitch during maximal efforts is established as evidence of decreasing voluntary drive that is demonstrative of central fatigue [92]. Transcranial magnetic stimulation (TMS) can also investigate the human motor cortex by measuring corticospinal excitability with motor evoked potentials (MEPs), which are used to evaluate the existence of central fatigue [82]. Here, an important consideration is the discrepancy in the time course of central fatigue with different types of measurement. For example, Latella et al. conducted an acute training study where participants completed a single session of heavy strength training of the biceps curl (5 sets of 3 repetitions maximum). Acute changes in corticospinal excitability were measured, and MEP response from TMS showed an immediate reduction in corticospinal excitability, which returned to baseline in 30 min [93]. While studies have demonstrated that the changes in cortical excitability may not necessarily be the direct cause of central fatigue [94], the development of central fatigue is accompanied by changes in the excitability of the motor cortex [84]. Conversely, unlike the reduction in corticospinal excitability which returned to baseline within 1 h, a reduction in voluntary activation persisted for 48 h when a heavy resistance exercise session of the back squat (10 sets of 5 repetitions at 80% of 1RM) was performed [83]. Prasartwuth et al. also noted that voluntary activation was impaired for more than 24 h after eccentric exercise when measured with motor nerve stimulation, but when assessed with TMS, there was only a trend toward a decline in voluntary activation immediately after eccentric exercise [95]. The authors posited that reduced voluntary activation seemed to contribute to the force loss in the first 24 h after eccentric exercise, and this may be attributed to inhibition in the motor cortex and/or the motor neurons. Besides the limitations of measurement [92], these results illustrate that the discrepancies of time course changes of central fatigue may in part be explained by the methodologies employed to measure central fatigue. As such, different types of measurements provide varied information about the limits of voluntary drive to muscles, and the postulate that central fatigue requires prolonged recovery may be an oversimplification. Furthermore, the time course in the recovery of central fatigue may be positively modified in the long-term. When examined with an isokinetic dynamometer, it has been demonstrated that a repeated bout of eccentric training elicited a faster recovery period of reduced voluntary activation compared with the initial bout of eccentric exercise [96]. The authors noted a modification in neural drive (i.e., motor corticospinal drive) and an attenuated degree of supraspinal fatigue following the repeated bout of exercise, suggesting that a protective mechanism following a repeated bout of damaging exercise (repeated bout effect) may be partly explained by a modification in the central nervous system [96]. Nonetheless, the common assessment of central

fatigue only involves a single bout of exercise [82, 83, 89, 97] and the question remains as to whether long-term repeated exposures of resistance exercise (i.e., in the form of dynamic or isotonic exercise) accumulate or exacerbate central fatigue over time. Even when individuals experience central fatigue, a smaller relative contribution of central-mediated fatigue compared with peripheral-mediated fatigue during voluntary contractions also raises concerns regarding the relevance of central factors in fatigue accumulation. Acutely, a larger part of the force reduction seems to be attributed to peripheral factors (i.e., 89%) [97], and the reduction in voluntary drive is typically low (i.e., 20%) [98], suggesting a minor influence on muscle fatigue. Furthermore, a model simulating motor unit firing behavior and muscle force during MVC that involves only peripheral factors of muscle fatigue was able to explain the modifications in force behavior commonly attributed to central fatigue [92]. This is not to refute the concept of central fatigue but presents data that raise important concerns about the discrepancy in the time course of central fatigue with different types of measurement, and interpretation of central fatigue in relation to the contribution of accumulated fatigue.

5 Complexity of Interpreting Prolonged Impairments of Muscle Function

The different states of preparedness within training have been described as overreaching or overtraining. The former is defined as an accumulation of training and/or non-training stress resulting in a short-term decrement in performance capacity with or without related symptoms of maladaptation, whereas the latter is defined as an accumulation of training and/or non-training stress resulting in a long-term decrement in performance capacity with or without related symptoms of maladaptation [35]. The process of recurrent training leading to overreaching and/or overtraining is often viewed as a continuum where overreaching is believed to precede overtraining if high levels of training persist and/or recovery is inadequate [99], yet the overtraining continuum may be an oversimplification [17, 100]. Indeed, a substantial amount of work is required to elicit overtraining in a controlled scientific setting for resistance exercise (i.e., 10 sets of 1 repetition at 100% 1RM, every day for 2 weeks) [101–103], and many studies have not followed up the length of recovery and time course of changes in physical performance, which makes it challenging to investigate the manifestation of overtraining [27, 104, 105]. These findings can also be difficult to interpret due to the lack of clear guidelines or established diagnostic tools other than a sustained decrease in performance (i.e., 1RM strength) for overreaching and overtraining in resistance exercise [17]. In particular, the magnitude of the performance decline required to diagnose overreaching or overtraining varies depending on the specific performance assessment. Currently, the development of overtraining is determined when long-term decrements in measured performance (i.e., 1RM strength) are detected relative to nothing [103] or a control group with a substantially lower workload compared with the overtraining group (i.e., 10×1 at 100% 1RM, every day for 2 weeks vs. 3×5 at 50% 1RM, twice weekly for 2 weeks) [101, 102]. Within such studies, it is uncertain if the proclaimed state of 'accumulated' fatigue is a reflection of a single bout of training or repeated exposures of training over time. The feelings of weakness and exhaustion or the decline in performance that individuals experience following the series of training bouts may be perceived as accumulated fatigue, but, without establishing an appropriate assessment means, it is also reasonable to claim that a single bout of training is enough to induce fatigue accumulation as long as individuals experience prolonged impairments of muscle function.

One of the potential candidates that has been interpreted interchangeably as 'accumulated fatigue' might be muscle damage, which also induces prolonged impairments in muscle function (i.e., prolonged strength loss [106]). Muscle damage is typically caused by predominantly eccentric activity, and prolonged loss of maximal voluntary force after exercise is considered to be one of the most reliable indirect measures of muscle damage [107]. Damage may be manifested in the sarcolemma, T-tubules, myofibrils, and cytoskeletal system [108]. Potential mechanisms that cause prolonged reductions in force production include ionic changes and disruption of calcium homeostasis and mechanical stress to the cells [109]. For example, lengthening contractions causes disruption in the sarcomeres and Z-disk streaming [110]. The most prevalent intermediate filament protein in skeletal muscle, desmin, attaches to the Z-disk and eccentric contraction involves disruptions to the intermediate filament system [111]. Desmin is also a target of calpain, which is involved in muscle damage following eccentric contractions, causing an elevation of cytosolic Ca^{2+}concentrations [112]. Consequently, an unregulated influx of Ca^{2+} leads to a disruption of normal homeostasis within a muscle cell. Elevations of cytosolic Ca^{2+} concentrations seem to be a key event for activation of calpain proteolytic activity, and calpain promotes muscle damage regulated by calpastatin [113]. Furthermore, increased activity of calpain promotes the activation of neutrophils and macrophages, leading to reactive oxygen species (ROS) production [111]. Notably, the interaction between neutrophils and macrophages promotes an inflammatory response of muscle damage. In addition, mechanical stress may damage the excitation–contraction coupling complex by deforming the connection between the T-tubules and the ryanodine receptors of the sarcoplasmic reticulum (known as junctophilin). It has been demonstrated that the level of junctophilin was significantly reduced after 50 eccentric contractions, and the

damage to junctophilin was associated with the decline in force [114]. A sustained increase in Ca^{2+} levels also activates phospholipase, particularly phospholipase A2, which is the mechanism independent of calpain-mediated proteolysis [112]. Phospholipase produces arachidonic acid and lysophospholipids, both of which are known to cause membrane structural damage [112]. Importantly, these biochemical changes of the cell indicate that much of the damage is caused by factors that are secondary to mechanical loading. If mechanical loading predominantly causes membrane damage (i.e., rupture of the membrane) to a greater extent, the increased level of extracellular markers in damaged muscle would appear immediately after exercise. However, an indirect marker of muscle damage (i.e., creatine kinase) gradually increases over days and may peak a few days (i.e., 4 days) after resistance exercise is performed [115]. This delayed nature of the appearance of muscle damage may therefore be interpreted as fatigue accumulation.

Nonetheless, the muscle damage also does not seem to accumulate following a resistance training program per se [116]. Twenty untrained women performed two bouts of eccentric exercise consisting of 70 maximum eccentric contractions where one 2–3 s action was performed every 15 s. Subjects were randomly divided into group A or group B, in which the second bout was performed on days 5 and 14 following the first bout, respectively. The purpose of the study was to examine whether the second bout of exercise in an unrecovered state would exacerbate performance decrements and elevation of the muscle damage marker in the blood [116]. Perceived soreness, elbow joint angles, isometric strength, and creatine kinase were measured. No measure had returned to initial values by day 5 post-exercise. Thus, when group A performed the second bout of exercise, the subjects did not fully restore muscle function from the first bout of training. On the contrary, group B restored measured values to the baseline level after 14 days. The isometric strength of both groups A and B significantly decreased following the first bout of training and produced only 45% and 40% of initial strength, respectively. When the second bout was performed, group A had regained 66% of initial strength, whereas group B regained 87% of baseline strength. The peak activity of serum creatine kinase was observed on days 4 and 5 but did not become significant until day 3. After performing the second bout, creatine kinase activity steadily decreased in group A and reached the baseline level by day 3 post-exercise. Creatine kinase activity level in group B remained stable following the second bout and there was no significant difference between values. The results of the study demonstrated that recovery time following the repeated bout was faster compared with following the initial bout whether or not muscle functions were fully restored. Similar results were reported in a follow-up study where a bout of eccentric exercise was repeated 3 and 6 days after the initial bout, and no indication of increased muscle damage or slowed recovery were documented [117]. Granted, isometric strength measured before eccentric exercise at days 3 and 6 was still lower than the baseline measures but repeated bouts did not exacerbate the strength loss; rather, strength gradually recovered over the 9 days. Although the question remains as to whether a repeated bout of exercise with a shorter recovery (i.e., 24 h) would change this relationship, these instances indicated that the repeated bout effect was powerful enough to cause adaptations in the absence of complete muscle function restoration and further mitigate muscle damage. Overall, what is perceived as accumulated fatigue may be more accurately interpreted as muscle damage per se. Whether it is caused by a single bout or series of training, the overlap area of muscle damage and fatigue causes difficulty when interpreting what may 'accumulate' following resistance training. An exhaustive coverage of what is currently known about the physiological processes of fatigue following resistance exercise is beyond the scope of this paper, but other potential mechanisms that may accumulate or induce prolonged force reduction after exercise include psychological changes [11, 102], inflammatory responses (i.e., leukocytes) [118], neuromodulators (i.e., cytokines) [119], and neurotransmitters (i.e., epinephrine) [101].

6 Conclusion

Despite the substantial advancement in fatigue research, a significant gap still remains in understanding the mechanisms that mediate long-term fatigue symptoms. Regardless of the lack of clarity on physiological mechanisms, it has been suggested that improper post-exercise recovery or sequence of training may result in greater accumulated fatigue. This idea has been explained conceptually using the fitness-fatigue model. Within the current model, it is believed that fatigue has a cumulative effect, and when fatigue accumulates to the point where fatigue after-effects significantly exceed fitness after-effects, overtraining occurs. However, due to the lack of evidence regarding the exact role of biochemical, physiological, and psychological markers in overtraining in resistance training, questions remain whether a change in any aspect of acute fatigue reflects the contribution to fatigue accumulation in the long-term, which is proposed to precede overtraining. In the current paper, the time course of fatigue was evaluated to help determine whether fatigue accumulates over time.

For peripheral fatigue, both depletion and accumulation hypotheses suggest that potential mechanisms of fatigue may be acute (i.e., < 24 h), by which the depletion of these energy substrates and accumulation of metabolic byproducts correspond to fatigue within a single session. A discrepancy in the time course of central fatigue among different types of

measurements and a smaller relative contribution of central-mediated fatigue compared with peripheral-mediated fatigue during voluntary contractions also raises concerns regarding the role of central factors in fatigue accumulation. A potential candidate that may be interpreted as accumulated fatigue is muscle damage, which shares similar characteristics with fatigue. Overall, considerable work remains to determine whether fatigue accumulates over time. Insufficient evidence exists on the presence of fatigue accumulation following resistance training and future studies are warranted to elucidate potential mechanisms underlying the concept of fatigue accumulation.

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