Exercise-induced muscle damage: mechanism, assessment and nutritional factors to accelerate recovery

Exercise induced muscle damage – mechanism, assessment and nutritional factors to accelerate recovery

Markus I[1], Constantini K[1*], Hoffman JR[2], Bartolomei S[3], Gepner Y[1]*

[1]Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, and Sylvan Adams Sports Institute, Tel-Aviv University, Tel-Aviv

[2]Department of Physical Therapy, Ariel University, Israel

[3]Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy

** Equal contribution*

Correspondence to:

Yftach Gepner, Ph.D.
Department of Epidemiology and Preventive Medicine
School of Public Health, Sackler Faculty of Medicine, and Sylvan Adams Sports Institute
Tel-Aviv University
Tel-Aviv, Israel
Tel: +972 733804726
Fax: +972 73 3804427
E-mail: gepner@tauex.tau.ac.il

Abstract

There have been a multitude of reviews written on exercise-induced muscle damage (EIMD) and recovery. EIMD is a complex area of study as there are a host of factors such as sex, age, nutrition, fitness level, genetics and familiarity with exercise task, which influence the magnitude of performance decrement and the time course of recovery following EIMD. In addition, many reviews on recovery from exercise have ranged from the impact of nutritional strategies and recovery modalities, to complex mechanistic examination of various immune and endocrine signaling molecules. No one review can adequately address this broad array of study. Thus, in this present review, we aim to examine EIMD emanating from both endurance exercise and resistance exercise training in recreational and competitive athletes and shed light on nutritional strategies that can enhance and accelerate recovery following EIMD. In addition, the evaluation of EIMD and recovery from exercise is often complicated and conclusions often depend of the specific mode of assessment. As such, the focus of this review is also directed at the available techniques used to assess EIMD.

Key words: muscle damage, exercise, nutrition, endurance, strength, inflammation

Author contribution:

YG, JRH and SB conceived and designed the idea. All authors wrote the manuscript. All authors read and approved the manuscript.

Abbreviations

4-HNE	4-hydroxynonenal
BDNF	Brain derived neurotrophic factor
CK	Creatine Kinase
CMJ	Counter movement jump
COX	Cyclooxygenase
DOMS	Delayed onset of muscle soreness
DTI	Diffusion tensor imaging
E-C	Excitation contraction
EIMD	Exercise induced muscle damage
FRAP	Ferric reducing/antioxidant power
H_2O_2	Hydrogen peroxide
HV	High volume
IL	Interleukin
Mb	Myoglobin
MDA	Malondialdehyde
MRI	Magnetic resonance imaging
mRNA	messenger RNA
NEFA	Non-esterified fatty acids
RBE	Repeated bout effect
RE	Resistance exercise
RM	Repetition maximum
SC	Satellite cells
TBARS	Thiobarbituric acid-reactive species
TNF	Tumor Necrosis Factor
VO_2max	Maximal oxygen uptake

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Introduction

Overload and progression are core training principles. Appropriately designed training programs using these core principles often result in feelings of soreness that are associated with myofibrillar damage. This is considered to be a normal response to exercise that is thought be part of the adaptation process (Pillon et al. 2013; Suzuki et al. 2020). With that, exercise-induced muscle damage (EIMD) and the subsequent inflammatory response is thought to be an integral part of the muscle repair process (Allen et al. 2015; Peake 2019) and is different from the inflammatory response reported from trauma-induced inflammation (Fehrenbach and Schneider 2006). EIMD is common to both prolonged and high intensity (e.g. interval or resistance training) training. EIMD can be separated into two phases. The initial phase, which results from the mechanical and metabolic stress brough about by an exercise bout leads to a damaging stimulus, while the secondary phase occurs post-exercise and involves an inflammatory response. During the secondary phase a temporary loss in muscle functional capacity is seen, and an increase in muscle soreness is common (see Figure 1). It is this latter phase, or recovery phase, that is thought to lead to favorable adaptions, including muscle remodeling and improvements in skeletal muscle performance (Roig et al. 2009; Peake 2019).

Muscle damage occurs from the mechanical and metabolic stress within the fibers that are activated during the exercise stimulus (Tee et al. 2007; Kayani et al. 2008). The mechanical stress, resulting from muscle lengthening under tension, is thought to be the more dominant factor leading to muscle protein damage (Tee et al. 2007). Metabolic stress is thought to result from metabolic deficiencies within the activated fibers that may enhance the vulnerability of the fibers to the mechanical loading during exercise (Krisanda et al. 1988; Tee et al. 2007). During the recovery phase following exercise, a cascade of chemical events occurs that changes the chemical milieu of the activated cells. In response to damage of activated fibers, regardless if it is from endurance or resistance exercise, an increase in reactive oxygen species and inflammatory molecules will be seen as part of a signaling system that initiates the recovery process (Kayani et al. 2008; Radak et al. 2008; Webb et al. 2017) . An increase in both cell and vascular permeability results in an increase in proteolytic enzymes and proinflammatory immune cells that accumulate in the interstitial fluid compartment of the damaged and surrounding tissues (Hotfiel et al. 2018). This post-exercise chemical response is accompanied by intramuscular edema and is thought to be responsible for nociceptor activation and subsequent soreness sensations.

There have been a multitude of reviews written on EIMD and recovery. It is a complex topic of study as factors such as sex, age, nutrition, fitness level, genetics and familiarity with the exercise task determine the magnitude of performance decrements, muscle damage, and soreness, and the time course of recovery (Fatouros and Jamurtas 2016; Douglas et al. 2017; Owens et al. 2018). In addition, many reviews on recovery from exercise have ranged from the impact of nutritional strategies and recovery modalities to complex mechanistic examination of various immune and endocrine signaling molecules. No one review can adequately address this broad array of study. Thus, in this present review, we aim to examine EIMD emanating from both endurance exercise and resistance exercise training in recreational and competitive athletes and shed light on nutritional strategies that can enhance and accelerate recovery following EIMD. Lastly, we identify gaps in the literature regarding EIMD in females as well as comparisons between sexes and age groups.

[Place Figure 1 here]

From a performance perspective, recovery should be defined as a return to baseline performance measures. In the simplest of interpretations, if performance has not returned to baseline levels, then the athlete has still not recovered. In several studies, investigators assessed performance by asking participants to perform a certain number of repetitions at a specific intensity of their maximal strength (Hoffman et al. 2010; Gonzalez et al. 2014). The participants returned to the laboratory for several consecutive days and repeat the exercise protocol. The number of repetitions performed is used as an indicator of the extent of recovery. Other studies have used jump power, cycling performance or other quantifiable physical activities that provide a measure of recovery (Cooke et al. 2009; Bartolomei et al. 2017, 2019b; Gordon et al. 2017; Arroyo et al. 2017). Another perspective of recovery that has been used is a return of metabolic fuels to their pre-exercise levels. For an endurance athlete the ability of muscle glycogen to return to pre-exercise levels is an important indicator of the athlete's ability to be metabolically prepared to perform optimally (Van Loon et al. 2004; Roberts et al. 2016). Although there are many other factors that relate to recovery, if the athletes' fuel supply is not '*topped off*', they will be competing at a potential metabolic disadvantage. Sport and exercise scientists that focus on the biochemical perspective of exercise recovery assess various blood markers of muscle damage and inflammation over several time points to provide some measure

of the degree of recovery. Often, a decrease in the circulating concentrations of these markers, following an exercise-induced elevation, are believed to be indicative of recovery. Scientists have also used hormonal markers as a measure of recovery. For example, circulating concentrations of testosterone and cortisol and the ratio between these steroid hormones have been used as a marker of the anabolic/catabolic status of the body (Urhausen et al. 1995). A greater increase in testosterone and a lower cortisol concentration result in an increase in the testosterone:cortisol ratio indicating that protein synthesis exceeds protein catabolism and the body is "more recovered". On the other hand, if testosterone is lower and cortisol is higher, the ratio is low and there is a greater catabolic effect, impeding recovery.

The effects of endurance exercise, especially training programs that involve a heavy emphasis on eccentric muscle contractions (e.g. downhill running) on EIMD have been previously studied (Malm et al. 2004; Smith et al. 2007; Chen et al. 2009; Hayashi et al. 2019). During eccentric muscle contractions, force is generated by muscle lengthening (Sudo et al. 2015), which normally involves recruiting fewer motor units and requires less energy and oxygen compared to other forms of contraction such as concentric and isometric contractions (Abbott et al. 1952). A bout of eccentric exercise, performed at an intensity or volume that an individual is not accustomed to, can initiate a complex chain of events, resulting in myofibrillar damage, degradation of structural proteins, membrane damage and destruction of excitation contraction (E-C) coupling **(Figure 1)**. This cascade leads to an accumulation of calcium ions within the cytoplasm, attraction of inflammatory markers to the site of tissue damage and a temporary disruption of muscle regeneration (Peake 2019).

In the first section of this review, we will discuss processes associated with muscle damage induced specifically by prolonged, endurance exercise, while the second part will focus on resistance training. In each of these sections we will attempt to identify sex differences, as well as differences between younger and older individuals. Lastly, nutritional interventions that may enhance recovery following exercise will also be discussed.

Exercise-Induced Muscle Damage Following Prolonged Endurance Exercise

As a result of physical damage to muscle fibers and the subsequent inflammatory response, muscle pain and soreness are often experienced (Fatouros and Jamurtas 2016). EIMD can be assessed indirectly using a variety of methods including blood markers (Baird et al. 2012), pain scales (Black and Dobson 2013), measurement of range of motion (Hayashi et al. 2019), or directly by using muscle biopsies (**Table 1**). The latter, however, is an invasive

procedure and therefore serial measurements within a short time frame (e.g. to assess recovery) may not be feasible (Marqueste et al. 2008). Indication of tissue injury/damage can also be obtained, non-invasively, with magnetic resonance imaging (MRI). An advantage of MRI is its ability to detect early changes in muscle structure and muscle edema using measures termed T1 and T2 imaging, which identify a variety of medical states such as fat infiltration and muscular dystrophy (Radunsky et al. 2019; Klemt et al. 2020). However, MRI T1-T2 imaging methods are limited, as muscle damage usually occurs at the cellular to fascicular level, which is beyond T1-T2 capabilities (Oudeman et al. 2016). In recent years, a more sensitive and complex MRI technique to assess changes in muscle integrity has been developed. Diffusion tensor imaging (DTI) allows for the evaluation of microstructural muscle damage by detecting anisotropic restricted diffusion of water in damaged skeletal muscle tissues (Berry et al. 2017) (**Figure 2**). DTI-MRI enables in-depth assessment of damage after intense exercise (Froeling et al. 2015; Hoffman et al. 2016; Gepner et al. 2017). DTI-MRI enables in-depth assessment of damage after intense exercise (Froeling et al. 2015; Hoffman et al. 2016; Gepner et al. 2017). Moreover, a recent study found that both T2 and DTI measurements have the ability to track muscle-healing processes following muscle injury (Biglands et al. 2020). Although DTI-MRI could potentially provide highly sensitive assessment of EIMD, to date, a limited number of studies have used this advanced method.

[Place Table 1 and Figure 2 here]

Inflammatory and muscle protein responses: mechanisms & assessment

Prolonged endurance exercise can lead to micro-structure damage of muscle tissue, resulting in an inflammatory response, which is primarily aimed at regenerating and healing damaged muscle fibers (Millet et al. 2011; Baird et al. 2012; Baumert et al. 2016). As muscle damage occurs, a variety of immune cells (e.g., acute-phase proteins, cytokines, leukocytes, and lymphocytes) are recruited to the site of injury and accumulation of these cells results in muscle edema and an increase in muscle temperature. EIMD also results in an increase in muscle membrane permeability causing leakage of muscle proteins (e.g. creatine kinase (CK) and myoglobin (Mb)) into the circulation (Millet et al. 2011; Sudo et al. 2015). This post-exercise inflammatory response is a normal physiological process that is thought to have a vital

role in repairing tissue damage and enhancing muscle adaptation (Millet et al. 2011; Sudo et al. 2015).

Blood markers, specifically those related to inflammation, are a useful tool to evaluate muscle damage and provide information about recovery status (Bessa et al. 2016) (**Table 1**). During the first 24h post-exercise, macrophages and neutrophils act to clear cellular debris that accumulated in the muscle as a result of micro-structural damage (Castiglioni et al. 2015). An accumulation of neutrophils observed at the injured areas (Paulsen et al. 2010) leads to activation of myeloperoxidase (MPO), which promotes the inflammatory response (Arnhold and Flemmig 2010). For example, one study showed that following 60 min of high intensity cycling exercise, neutrophil expression peaked 3h post exercise, with a return to baseline 48h post exercise (Neubauer et al. 2013). Interestingly, systematic elevation of bioactive substances may determine neutrophil mobilization and functional status, which may then affect local muscular tissue damage (Suzuki et al. 1999).

The inflammatory response appears to have two phases, which include activation of both anti- and pro-inflammatory mediators, having antagonistic roles. Upon initial tissue insult from the exercise stimulus, pro-inflammatory cytokines are activated. This response then leads to an increase in anti-inflammatory cytokines. The anti-inflammatory markers inhibit the expression of pro-inflammatory cytokines, thus controlling the magnitude of the inflammatory process (Dinarello 2000). During the pro-inflammatory phase, cytokines such as interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF)-α are activated (Ostrowski et al. 1998; Dinarello 2000). TNF-α is involved in muscle regeneration and has a pro-inflammatory role at the site of cellular damage (Opal and Depalo 2000). IL-6 is a prominent cytokine that has been shown to increase during and following exercise (Ostrowski et al. 1998; Pedersen and Fischer 2007). It has both local (i.e. muscular) and systematic effects not only on mediating the local inflammatory response, but also on energy metabolism (Febbraio and Pedersen 2002; Pedersen and Fischer 2007). It has been demonstrated that during 2.5h of treadmill running at 75% VO_2max, IL-6 concentrations begin to increase after 30 min of running and peaks immediately post-exercise (Ostrowski et al. 1998). IL-6 concentrations gradually decrease thereafter, returning to baseline between 6h to 5 days post-exercise (Ostrowski et al. 1998; Pedersen et al. 2001; Peake et al. 2017).

One of the more well-known and important blood markers of muscle damage and indicator of muscle membrane permeability is CK, whose serum concentrations are often elevated 24-48h post-EIMD. The magnitude of increase in CK reflects the extent of muscle

damage and cellular necrosis. Both CK and Mb are normally found in skeletal muscle tissue, and when muscle integrity is disrupted, as occurs during EIMD, these molecules leak into the circulation (Pedersen and Fischer 2007). Yet, timing of appearance of these muscle damage markers in the circulation appears to differ. Since Mb is a smaller molecule, its elevation is generally seen immediately after repeated eccentric contractions, whereas CK is a larger molecule and therefore takes longer (24-48 hours) to leak out of the cell (Pedersen and Fischer 2007). Despite the different timeline regarding peak appearance in the circulation, changes in both CK and Mb similarly reflect the extent of muscle damage and are positively correlated to each other (Febbraio and Pedersen 2002).

A variety of external factors, such as type of contraction (eccentric vs. concentric), duration and intensity of exercise and age can influence the magnitude of the inflammatory response and release of muscle proteins into the circulation following EIMD caused by aerobic exercise (Pedersen et al. 2001; Peake et al. 2005, 2017; Peake 2019) . Considering the type of muscle contraction, the prevalent belief is that eccentric lengthening contractions cause greater sarcomere damage that subsequently leads to a more severe inflammatory response than concentric or isometric contractions (Faulkner et al. 1993; Nosaka et al. 2001; Pokora et al. 2014; Peake et al. 2017). For example, Pokora et al. (2014) compared the cytokine and CK response to 60-min of downhill (i.e. predominantly eccentric) vs. uphill (i.e. predominantly concentric) running in recreationally active men. The investigators indicated that CK concentrations were significantly increased immediately and 24h post-exercise only in the uphill/eccentric group (Pokora et al. 2014). Moreover, although the pro-inflammatory cytokines IL-1b and TNF-α demonstrated a similar response between groups, IL-6 was substantially elevated immediately and 24h post-downhill running while only a modest response was reported following uphill running (Pokora et al. 2014). With regard to exercise intensity, it has been shown that in men, concentrations of anti-inflammatory cytokines such as IL-receptor antagonist 1 (1ra) and IL-10 are greater following high intensity running compared to low intensity running, and these results have also been found after downhill running (Peake JM et al. 2005). The influence of exercise intensity on the primary inflammatory response was demonstrated in another study reporting that total circulating leukocytes and neutrophils were higher in trained runners who ran 60 min at a high intensity workload (85% maximal oxygen consumption; VO_2max) in comparison to low intensity (60% VO_2max) running immediately and one hour post-exercise (Peake et al. 2004).

Evidence examining differences in the inflammatory response following aerobically-based EIMD between sexes is limited. However, there do appear to be differences in the recovery response among women during different phases of the menstrual cycle as estrogen appears to enhance membrane stability, thus minimizing, or at least reducing the extent of muscle damage (Enns and Tiidus 2010). A study examining circulating cytokine and CK concentrations in female athletes running for 90 min at 70% VO_2max reported that IL-6 and CK concentrations were greater during the mid-follicular phase of the menstrual cycle when sex hormones (e.g. estrogen and progesterone) are low compared to the mid-luteal phase (Hackney et al. 2019), however this finding was not specific to EIMD. Clearly, there is gap in the literature regarding sex differences in the inflammatory response associated with muscle damage induced by aerobic exercise. In the scant number of studies that assessed EIMD following aerobic exercise and included both men and women, the results of both sexes were combined either because the number of women was small (n=1-3; Kyrolainen et al. 2000; Malm et al. 2004) or because no significant differences were found between sexes (Hayashi et al. 2019). It should be mentioned that none of these studies (Kyrolainen et al. 2000; Malm et al. 2004; Hayashi et al. 2019) examined the expression of inflammatory markers. With regards to rate of recovery following EIMD caused by prolonged/aerobic exercise, future studies should directly compare the response between men and women, as it has been suggested that estrogen increases muscle permeability to leukocytes, which, in addition to blunting the extent of muscle damage, could accelerate muscle healing (Enns and Tiidus 2010).

Aging is accompanied by a decline in immune function that is associated with chronic low-grade inflammation and higher susceptibility for chronic disease, which could negatively influence the rate of recovery (Chung et al. 2009). Although it has been suggested that resting cytokine and TNF-α concentrations of elderly athletes are higher in comparison to young athletes (Tieland et al. 2018), a recent study by Lavin et al. (2020) demonstrated that lifelong aerobic exercise can negate these age-related effects by enhancing anti-inflammatory and reducing pro-inflammatory levels at rest and following acute exercise. It still remains to be determined whether the inflammatory (i.e. cytokine and white blood cell) response to muscle damage induced by *aerobic* exercise is age dependent. Interestingly, a recent study found that CK and Mb levels increased to a similar extent in both young and middle-aged trained individuals after 45 min of downhill running at 65% VO_2max (Hayashi et al. 2019). However, this study did not assess inflammatory markers.

Pain and Soreness

EIMD is often associated with muscle soreness, reflected by pain or discomfort of activated muscles after a novel training stimulus or intense training session (Hody et al. 2019). Muscle soreness is often characterized by stiffness, muscle sensitivity and local pain (Lewis et al. 2012). It is thought to be a consequence of micro-trauma to the muscle caused by the strain and breakdown of the sarcomere (Lewis et al. 2012). The intracellular damage activates an inflammatory response that may heighten pain receptors, thus causing feelings of soreness, though the complete mechanism of muscle soreness remains unclear. Most of the research has focused on exercise in novice populations, which generally results in a heightened level of soreness, often referred to as delayed onset of muscle soreness or DOMS. This response likely differs from that seen following an intense exercise session in competitive athletes or even recreational individuals (Hotfiel et al. 2018). The scientific literature on the mechanisms associated with DOMS suggests two main pathways for this phenomenon. One mechanism involves activation of B2-bradykinin receptors, which are released during exercise resulting in mechanical hyperalgesia (Hody et al. 2019), while the second relates to cyclooxygenase (COX)-2 and glial cell line-derived neurotrophic factor (Paulsen et al. 2010). When COX-2 inhibitors are provided orally after lengthening (i.e. eccentric) contractions, this treatment blunts the severity of muscle soreness, supporting the second hypothesis (Murase et al. 2013). Interestingly, the appearance and severity of DOMS appears to be independent of other markers of EIMD, including histological changes (Nosaka et al. 2002a). While strength studies commonly agree that perceived pain is greater after the first bout or resistance exercise versus a second bout, there is still lack of research regarding endurance/aerobic based EIMD and reduced muscle soreness in subsequent exercise bouts. In a study by Smith et al. (2007) it was shown that along with a blunted inflammatory response, participants experienced less severe soreness and that soreness peaked earlier following a repeated (i.e. second) exercise bout of 60 min of downhill running at 75% VO_2max compared to the first bout. This is generally referred to as the "*repeated bout affect*" (Nosaka et al. 2001).

Whether DOMS and/or pain perception following a bout of muscle damaging aerobic exercise are different among men and women, or throughout different stages of the menstrual cycle, remains unknown. Comparing young trained, young untrained and older trained individuals, Hayashi et al. (2019) showed that following 45 min of downhill running, pain perception increased above baseline levels in all three groups up to 72h post exercise. Interestingly, although pain levels were similar between the young trained and untrained

groups, these subjects perceived their pain as more severe than the older trained subjects did, indicating that perhaps age has a greater influence on pain than training status.

EIMD following aerobic exercise & performance-related measures

For athletes, optimal recovery is vital for stimulating muscle regeneration, adaptation and ultimately improved endurance performance. Scientific understanding of how performance measures are affected by EIMD is important for optimizing recovery and enhancing subsequent endurance performance.

Strength loss

In addition to histological and inflammatory markers, another reliable and valid approach for assessing muscle damage is the measurement of muscle *function* – i.e. the ability of the muscle to generate force – often assessed using maximal voluntary isometric or concentric contractions (Clarkson and Hubal 2002; Byrne et al. 2004; Paulsen et al. 2012) (**Table 1**). While an abundance of literature regarding muscle strength loss following single-joint and/or resistance exercise exists, data on strength loss following endurance exercise is limited (Clarkson et al. 1992). When considering whole-body aerobic-based exercise, strength loss following downhill running has been attributed to damage to the sarcoplasmic reticulum and disturbances in Ca^{2+} homeostasis within the muscle fiber (Paulsen et al. 2012). This is in contrast to single-joint eccentric exercises where impairments in neuromuscular performance and thus strength were suggested to result from compromised conduction velocity of action potentials across the sarcolemma (Piitulainen et al. 2010), as well as alterations in central nervous system activity and motor unit recruitment (Prasartwuth et al. 2006; Dartnall et al. 2008; Isner-Horobeti et al. 2013).

The magnitude of strength loss after prolonged, whole-body endurance exercise appears to be lesser than that following more "purely" eccentric actions of maximal force of smaller muscle groups and/or single-joint movements (Eston et al. 1996). For example, activities such as prolonged (>30 min) downhill running or eccentric cycling have been shown to reduce muscle torque of the knee extensors by 15-30% (Eston et al. 1996; Malm et al. 2004) and maximal power during cycling by 15% (Féasson et al. 2002). Using a more "relevant" aerobic task causing EIMD, Sherman and colleagues (1984) reported a ~50% reduction in knee extensor torque in trained male runners following a marathon in addition to significant elevations in markers of muscle damage. This is in contrast to a high intensity

strength/resistance exercise bout where repeated movements of arm flexion or leg extension could reduce muscle strength by as much as 50-70% from baseline values, albeit these values were demonstrated in novice, and not trained, individuals (Newham et al. 1987; Clarkson and Dedrick 1988; Sayers and Clarkson 2001). Yet, the time course for strength loss following either resistance or aerobic exercise is relatively similar, with a return of strength to baseline values by ~7 days, at least when initial reduction was <50% (Paulsen et al. 2012).

In studies focusing on aerobically-based activities only, running – which includes both concentric and eccentric muscle contractions – is reported to cause a greater degree of muscle damage and strength loss compared to cycling (mainly concentric contractions) and cross-country skiing (Millet and Lepers 2004). In a recent study, Hayashi et al. (2019) assessed various markers of EIMD following 45 min of downhill running at 65% VO_2max, and examined the effect of sex, age and training status. While the authors did not find differences in muscle damage markers, including strength loss, between men and women, it was demonstrated that both training status and age affect the magnitude of strength loss associated with EIMD following downhill running (Hayashi et al. 2019). Specifically, the group of young untrained and old trained participants experienced greater reductions in strength 24h post-exercise compared to a group of young trained individuals (Hayashi et al. 2019). Furthermore, in terms of recovery of strength, the young trained participants recovered faster than the two other groups in the first 48h post-downhill running. To the best of our knowledge, no study has assessed strength loss following aerobic, muscle-damaging exercise in women only. Moreover, whether there are differences between sexes in strength losses and/or rate of recovery of strength post endurance-based EIMD is yet to be determined.

Running economy & gait mechanics

Running economy refers to the energetic cost (measured as oxygen consumption; VO_2) for a given intensity/speed and is considered to be one of the main determinants of running performance (Jones and Carter 2000; Joyner and Coyle 2008). A limited number of studies have investigated the relationship between EIMD following endurance activity and running economy. The results of these studies have generally been inconclusive (Hamill et al. 1991; Kyrolainen et al. 2000; Braun and Dutto 2003; Chen et al. 2007). For example, some investigations have reported a 3-7% increase in VO_2 for a given intensity for three days following endurance exercise (Braun and Dutto 2003; Chen et al. 2007), while others reported that downhill running impaired running economy only immediately post-exercise (Kyrolainen et al. 2000) or had no effect on running economy (Hamill et al. 1991). These discrepancies

could likely be due to differences in exercise mode (downhill vs. marathon running), study population (trained vs. untrained) and/or subjects' sex between studies. Interestingly, even when changes in running economy were observed following endurance exercise, these were not correlated with changes in blood markers of muscle damage such as CK and Mb. In fact, in both trained and untrained individuals changes in running economy appeared to follow a different time course than those of EIMD-related blood markers (Kyrolainen et al. 2000; Chen et al. 2007). Lastly, the presence of muscle soreness associated with EIMD was observed with and without changes in running economy in well-trained endurance athletes and recreational subjects (Hamill et al. 1991; Braun and Dutto 2003).

A number of potential mechanisms have been offered to explain EIMD-related impairments in running economy. Chen and colleagues (2007, 2008) indicated that changes in running economy were more pronounced with increasing intensity of exercise (i.e. greater impairment in running economy at 90% VO_2max compared to 80% VO_2max, and no change at 70% VO_2max). These investigators suggested that alterations in the running economy of untrained individuals may be related to greater recruitment of muscle fibers at higher intensities, likely changing the participant's running kinematics. Changes in running economy has also been proposed by Braun and Dutto (2003) who studied a group of highly trained endurance men and reported an association between changes in stride length and running economy 48h following downhill running. This finding is not surprising considering that VO_2 of experienced athletes has been shown to increase in a U-shape manner when stride length is either shorter or longer than preferred (Hunter and Smith 2007). Yet, this is not a universal finding and could be related to training status, as others observed changes in lower body kinematics without changes in running economy in recreational female runners after downhill running (Hamill et al. 1991). Taken together, it is possible that a combination of altered kinematics, impaired range of motion, and strength loss following prolonged exercise, especially that of a greater eccentric nature, leads to an increased recruitment of muscle fibers. This in turn will increase metabolic/energetic requirements and impair running economy (Braun and Dutto 2003; Chen et al. 2007; 2008). Given that sex, age and training status alter various aspects of EIMD, it appears reasonable to assume that these factors would also influence the magnitude of changes in recovery rate (i.e. return to baseline) of running economy and gait mechanics following aerobic-based EIMD. However, to the best of our knowledge, there is limited evidence providing a clear consensus.

Performance

Running economy is a key determinant of endurance performance, however it is not a true performance measure. Yet, any impairment in this component, especially in combination with other EIMD-related signs and symptoms, could affect performance outcomes in the hours/days following an activity inducing muscle damage. Although this hypothesis has been investigated following resistance and plyometric-based EIMD (Marcora and Bosio 2007; Burt and Twist 2011; Assumpção et al. 2013), there are limited data regarding the relationship between EIMD following endurance exercise, running economy and true performance outcomes. Whether this relationship exists has important implications for endurance athletes during intense training periods and multi-stage/day races such as cycling tours (~3 weeks), ultra-endurance running races, and even track competitions where athletes participate in multiple events over several days. Thus, further research is needed to assess the effects of muscle damage induced by aerobic/endurance exercise and its subsequent signs and symptoms on true performance measures.

Exercise Induced Muscle Damage Following Resistance Exercise

It has been well documented that resistance exercise (RE) may induce muscle damage resulting in inflammation, swelling and impairments in performance. Optimizing the recovery process following RE represents a crucial factor for strength and power athletes aimed at increasing their muscle mass and improving their performance. RE, including eccentric contractions, involve the active lengthening of sarcomeres and has been associated with greater disruption of contractile and structural elements (Newham et al. 1983; Enoka 1996) compared to concentric-only RE. Muscle damage resulting from eccentric RE, and in particular when the load applied to the muscle exceeds the force produced by the muscle itself, causes an induced overstretching of sarcomeres beyond filament overlap (Peake et al. 2017). This results in a disruption of Z lines causing sarcomere streaming (Friden et al. 1983). Damage also involves myofiber architecture, the sarcoplasmic reticulum and the sarcolemma (Clarkson 1997).

Several experimental studies showed that eccentric muscle contractions activate a smaller number of motor units compared to concentric contractions, with the former also characterized by lower motor unit discharge rates (Nardone et al. 1989; Del Valle and Thomas 2005; Douglas et al. 2017). A different pattern of motor unit activation in eccentric compared to concentric contractions induces a selective recruitment of high-threshold motor units

composed of type II muscle fibers (Gibala et al. 1995; Howell et al. 1995; Enoka 1996). During the eccentric contraction a smaller muscle cross-sectional area takes on the load that was lifted by a higher number of motor units during the concentric phase (Enoka 1996). High loads distributed to a fewer number of motor units during RE represents a key factor for the EIMD reported following eccentric contractions (Clarkson 1997).

Muscle damage has also been reported following isometric RE (Allen et al. 2018). Muscle damage of elbow flexors and subsequent performance impairments were particularly evident when isometric exercise was performed by untrained individuals using a long muscle length obtained at an elbow angle of 155° compared to a shorter muscle length obtained at an elbow angle of 90° (Allen et al. 2018). Even if the muscle is only able to produce lower levels of force at a longer length, these isometric muscle contractions induce greater damage compared to stronger isometric contractions performed at a shorter muscle length (Allen et al. 2018; Lieber and Friden 1993). Muscle damage induced by isometric contractions appears related more to muscle length than to muscle tension (Allen et al. 2018; Jones et al. 1989). Studies conducted on arm flexor muscles suggest that this phenomenon may be related to the non-uniform lengthening of sarcomeres during the isometric contraction (Allen et al. 2018). Muscle damage following isometric RE however, can be minimized by using muscle lengths below the optimum and submaximal force productions (Allen et al. 2018; Lieber and Friden 1993).

Despite low levels of muscle damage being detected during concentric only RE (Lavender and Nosaka 2006), a higher metabolic stress has been associated with concentric-only compared to eccentric-only RE (Kraemer et al. 2004; Goto et al. 2009; Beaven et al. 2014; Paulus et al. 2019). Metabolic stress induced by RE is related to an exercise-induced accumulation of metabolites, particularly lactate, inorganic phosphate and H^+ (Suga et al. 2009). This metabolic stress is maximized when anaerobic glycolysis is the predominant energy system and exercise lasts between 15-120 s (MacDougall et al. 1999).

Most RE programs performed by athletes and sport enthusiasts include both eccentric and concentric contractions. Metabolic stress, mainly induced by concentric contractions, may amplify muscle damage and inflammation produced by the eccentric contractions (Tee et al. 2007). This combination may also provide the appropriate stimulus to enhance tissue repair and adaptation. The results of several investigations have supported the role of metabolite accumulation for muscle growth (Rooney et al. 1994; Schoenfeld 2010, 2013). Metabolic stress may promote muscle hypertrophy via influencing muscle fiber recruitment, hormonal

concentrations, local myokine response and reactive oxygen species (Takarada et al. 2000; Nishimura et al. 2010). A problem with trying to define the relationship between mechanical tension and metabolic stress is that these phenomena occur in tandem, confounding the possibility of differentiating the specific role of each effect (Schoenfeld 2013). Investigations on low-intensity exercise using blood flow restriction, where inflated cuffs enhance the accumulation of exercise-induced metabolites, have provided important evidence supporting the role of metabolic stress in promoting muscle hypertrophy (Takarada et al. 2000; Pearson and Hussain 2015; Hill et al. 2018).

Microtrauma of myofibers and metabolic stress following RE have been shown to induce inflammation, DOMS, and changes in intra- and extracellular water balance in muscle cells, resulting in muscle swelling (Peake et al. 2017). In addition, RE may lead to significant changes in circulating concentrations of several biomarkers such as IL-1, myoglobin and CK. Inflammatory and immune responses following RE have been extensively reviewed elsewhere (Chazaud 2016; Gonzalez et al. 2016; Peake et al. 2017; Damas et al. 2018) and analyzed in relation to muscle adaptations. Some authors though have suggested that muscle damage and inflammation may not be essential for muscle hypertrophy (Flann et al. 2011). Muscle inflammation indeed, may be functional for muscle adaptation below a certain threshold, while higher levels of inflammation may not provide any further benefit (Schoenfeld 2012). Muscle damage and inflammation typically occur when unaccustomed exercises are performed by untrained individuals. On the contrary, resistance trained individuals are more protected against EIMD (McHugh et al. 1999) and may obtain further muscular adaptations with minimal inflammation.

EIMD has been associated with changes in muscle fiber recruitment during both submaximal and maximal muscle contractions. It has been hypothesized that changes in electromyography (EMG) activity may be more strongly associated with damage to type II muscle fibers, rather than type I fibers. EMG activity indeed is typically increased in submaximal muscle contractions following EIMD to compensate for muscle damage occurring in type II fibers with a more pronounced muscle fiber synchronization (Lamb 2009). Contrarily, EMG activity is reduced during maximal muscle contractions to protect muscle integrity from further damage (Plattner et al. 2011). Altered neural control strategies, especially those involving type II fibers, may occur during the entire recovery process following EIMD (Macgregor and Hunter 2018) and have been detected for up to 132h following RE in novice men (Plattner et al. 2011). While only a limited number of studies investigated the effects of

training status, it has been suggested that strength and power athletes demonstrate a greater recruitment of fast-twitch motor units and larger decreases in EMG activity during fatiguing high intensity resistance exercise compared to untrained individuals (Ahtiainen and Häkkinen 2009). A long lasting depression of the excitation-contraction coupling were also registered up to 22 h following a high intensity resistance training protocol for the lower body in strength athletes (Raastad and Hallén 2000). It appears that during fatiguing exercise the trained strength/power athlete is able to recruit additional motor units to compensate for fatigued fibers, which is not observed in the untrained individuals. However, this compensation may reduce muscle contraction capability during the recovery period.

Influence of sex on the recovery phase following resistance exercise

Muscle damage and inflammation are common in both men and women following damaging protocols of RE. However, there does appear to be a difference in the inflammatory response between sexes during the recovery phase following eccentric RE protocols (Schoenfeld 2010, 2013). Stupka and colleagues (2000) reported that muscle damage, as assessed by muscle tissue biopsy, was similar in both untrained men and women immediately following RE. The inflammatory response though was significantly greater in men than in women for up to 48h following the exercise bout. The authors hypothesized that estradiol provided an inhibitory effect of inflammation and enhanced the recovery process following muscle damage. Other experimental studies investigating the recovery rate following a single bout of RE in men and women, came to contrasting conclusions. Several authors, reported similar losses in strength in both untrained (Fulco et al. 1999; Rinard et al. 2000; Sayers and Clarkson 2001; Hatzikotoulas et al. 2004; Power et al. 2013) and trained (Hakkinen 1993) men and women immediately following different protocols of high intensity RE. However, these findings were in contrast with others who reported greater loss of strength in untrained women compared to untrained men immediately following both upper and lower body RE sessions (Sewright et al. 2008; Davies et al. 2018). Most studies support the notion that the rate of recovery following a single bout of RE is faster in women compared to men. Sayers and Clarkson (2001) reported faster rates of recovery in elbow flexor isometric strength in a large sample of untrained women compared to men following an eccentric RE session. Flores and colleagues (2011) also reported faster recovery rates in untrained women compared to men following a high volume (HV) elbow flexors exercises session. These results were consistent from earlier observations regarding a faster recovery rate of trained women compared to men following RE (Hakkinen 1993).

The exercise-induced inflammatory response may contribute to secondary muscle damage, caused by excessive macrophage accumulation and muscle swelling, and may slow down the recovery rate following eccentric exercise (Sayers and Clarkson 2001). The blunted inflammatory response observed in untrained women (Stupka et al. 2000; Clarkson and Hubal 2001) and the antioxidant function of estrogens (Tiidus 1995; Komulainen et al. 1999), may be part of the physiological mechanism preventing the secondary muscle damage in women and accelerating the recovery process. The lower magnitude of inflammatory response and faster recovery in women following damaging protocols of RE may also be linked to sex differences in the distribution of muscle fiber-types (e.g., greater percent of type II fibers in men compared to women) (Fulco et al. 1999). Chronic exposure to RE, however, may drastically influence the individual's acute inflammatory response to single bouts of RE. The paucity of research involving highly resistance trained women make it difficult to draw conclusions about RE-induced inflammatory responses occurring in female strength and power athletes.

Despite the vast majority of research finding no sex differences in muscle soreness following eccentric resistance exercises in untrained individuals (Sewright et al. 2008; Morawetz et al. 2020), several studies reported a tendency toward a higher level of soreness in untrained men compared to women (Dannecker et al. 2005, 2012). Results of several investigations comparing muscle soreness in men and women appeared to have been affected by methodological variations in soreness assessments (Morawetz et al. 2020) and by the potential influence of the menstrual phase on soreness perception in women (Fillingim and Maixner 1995).

Recently, some investigations reported that training adaptations to a RE program were influenced by the variability of training volume throughout the different phases of the menstrual cycle (Reis et al. 1995; Wikström-Frisén et al. 2017). These authors reported larger gains in lean body mass and strength following high frequency resistance training during the follicular stage of the menstrual cycle, compared to the luteal phase. Thus, the recovery rate following RE may also be influenced by hormonal fluctuations that characterize the different phases of the menstrual cycle. Additional research is warranted to further explore this hypothesis. In addition, most experimental studies have been conducted on untrained women. Training experience likely plays an important role in the recovery process following both metabolic and mechanical stress as a result of chronic exposure to high demanding RE.

Performance assessment during the recovery phase following resistance exercise

A number of anthropometric, biochemical, physical performance and subjective markers have been used to monitor the recovery phase following RE (Clarkson and Hubal 2002). Performance impairments following high intensity RE may be considered one of the most important indicators of muscle fatigue (Behm et al. 2004) and muscle damage (Warren et al. 1999). Isometric, isokinetic and dynamic strength and power measurements have been extensively used to assess the recovery process following various exercise stresses. Several investigations reported different time courses of recovery of different strength components following RE (Molina and Denadai 2012). In particular, ballistic muscle actions, such as countermovement jump (CMJ) and bench press throw, have shown a higher sensitivity for fatigue and muscle damage compared to both isometric (Raeder et al. 2016; Kennedy and Drake 2018; Aben et al. 2020) and isokinetic assessments (Bartolomei et al. 2019b). Significant reductions in CMJ power has been observed up to 48h following a HV squat protocol in resistance trained men (Bartolomei et al. 2017; Kennedy and Drake 2018). Interestingly, the drop in CMJ performance was correlated with plasma levels of IL-6 and with muscle swelling measured via ultrasound (Bartolomei et al. 2019b). CMJ represents a valid and reliable tool to assess lower-body recovery following both RE and other highly demanding activities such as soccer matches (Hoffman et al. 2003; Andersson et al. 2008). However, others have reported a greater sensitivity of squat jump (SJ) testing for assessing RE-induced muscle damage compared to both CMJ and drop jump (DJ) assessments (Byrne and Eston 2002; Jakeman et al. 2010). The stretch-shortening cycle that characterizes both CMJ and DJ may attenuate the detrimental effect of HV RE on jump performance (Byrne and Eston 2002). Similarly, bench press throw power has been successfully used to monitor the recovery of the upper body (Bartolomei et al. 2019). This parameter was significantly reduced 24h following a HV bench press protocol in trained men and returned to baseline 48h following the exercise bout (Bartolomei et al. 2019b). Vertical jump and bench press throw assessments represent complex multi-joint assessments requiring a high level of neuromuscular activation and motor unit coordination. Both parameters may be affected by fatigue induced by RE.

Another common method to track muscle recovery is represented by the measurement of isokinetic peak force, performed using linear dynamometers (Bartolomei et al. 2019a, b) or peak torque performed using angular dynamometers (Ferreira et al. 2017a, 2017b; Gordon et al. 2017). Significant drops in isokinetic peak force have been reported following HV RE protocols or eccentric contractions in both advanced lifters (Bartolomei et al. 2019b) and untrained individuals (Byrne et al. 2001). A longer time course of recovery of isokinetic torque

has been detected in untrained individuals compared to highly trained men (Newton et al. 2008). Trained individuals appear to be more resilient than novices regarding EIMD and appear to recover faster (Clarkson et al. 1992; McHugh 2003). In support, faster recovery rates of isometric force and power were noted following a single bout of HV RE in previously untrained individuals following a 7-week resistance training program compared to pre-training recovery rates (Izquierdo et al. 2009). Muscle damage may have different effects on performance depending on the speed of the movement during isokinetic assessments. Greater and more protracted reductions in torque have been noted when torque output was assessed at slow velocity speeds (60°/s) compared to high velocity speeds (180-270°/s) (Komulainen et al. 1999; Molina and Denadai 2012). Isokinetic measurements, however, are highly velocity dependent, and should be performed as close as possible to the muscle contraction velocity used during training (Warren et al. 1999).

Recovery time may also vary between different muscle groups of the same individual. In one study, a similar decline in performance was noted immediately post-workout, but a faster recovery rate of initial peak torque was observed in the triceps compared to pectoral muscles following a HV bench press protocol consisting of 8 sets of 10 reps at 90% of the participant's 10-RM (Ferreira et al. 2017b). Muscle mass and muscle architecture may also influence the recovery rate following resistance exercise. Large muscles such as the pectoralis major may be more prone to EIMD compared with pennate muscles such as triceps brachii, characterized by shorter fascicle lengths (Nosaka et al. 2002b). In addition, RE may elicit a more pronounced muscle damage, soreness and performance reductions in muscles with higher percentages of fast-twitch compared to slow twitch fibers (Jansson and Sylvén 1985; Anderson and Neufer 2006; Quindry et al. 2011).

Nutritional Considerations for Enhancing the Recovery Response to Exercise

Nutritional considerations are an important component for accelerating recovery from exercise. For many nutritional organizations, recommendations have generally been focused on the athlete's meal plan but recently have acknowledged the importance that strategically timed nutritional supplements may provide for enhancing recovery. Nutritional supplements may provide the athlete with an ability to accumulate specific nutrients within skeletal muscle or other tissues in the body (i.e. the brain), to a greater magnitude than can be provided by regular meal consumption only, thus providing an advantage for enhancing recovery from exercise. This section will focus on the effect that diet and nutritional supplementation may have on the recovery period post-exercise. The nutritional supplementation section will focus

primarily on popular supplements, as the voluminous amount of published papers on various nutrients would be beyond the scope of this review.

The Effect of Macronutrient Composition of Daily Diet on Recovery Indices of Exercise

In a Position Stand emanating from the Academy of Nutrition and Dietetics, Dietitians of Canada (DC), and the American College of Sports Medicine (ACSM) no specific dietary recommendation for competitive athletes was provided (Thomas et al. 2016). Instead, the authors indicated that energy intake is dependent on the energy requirements of exercise and provided ranges for macronutrient intake. It was suggested that fat intakes typically range from 20% - 35% of total energy consumption, while carbohydrate intake typically ranges from 3 to 10 $g \cdot kg^{-1}$ body mass per day (and up to 12 $g \cdot kg^{-1}$ body mass per day for extreme and prolonged activities). It was further suggested that daily protein intake typically ranges from 1.2 to 2.0 $g \cdot kg^{-1}$ body mass per day. However, no specific recommendation or comparison was made in regard to the most appropriate macronutrient intake that can benefit exercise recovery. The dietary habits of competitive and recreational athletes appear to be quite variable, ranging from athletes that follow a traditional omnivore diet to those that prefer a more extreme diet such as vegetarian, ketogenic (high fat low carbohydrate) or carnivore (very high protein). The focus generally is on a specific macronutrient (e.g., fats or proteins) or a dietary restriction (e.g., no meat or animal products).

Vegetarian and Omnivore Dietary Comparisons

There have been only limited attempts to examine the effect of a specific diet on recovery aspects of performance, and even less has been published on dietary comparisons and recovery from exercise. Exercise is known to cause an increase in oxidative stress that causes an increase in the production of free radicals and lipid peroxidation, resulting in cell damage and a potential cascade of events that impacts the health and well-being of the athlete (Bloomer et al. 2005). At rest, the body's antioxidant system is sufficient to remove these harmful oxidants; however, during exercise, this system can be overwhelmed, and an imbalance can occur resulting in the accumulation of antioxidants that can negatively affect recovery. It is thought that a diet rich in antioxidants such as vitamins C and E, polyphenols and β-carotene can enhance one's ability to combat oxidative stress (Craddock et al. 2020). Polyphenols may have the richest concentration of antioxidants, and they are abundant in plant-based foods. Kim and colleagues (2012) reported that people who maintained a vegetarian diet for more than 20 years had a lower degree of oxidative stress compared to omnivores. Whether this provides

vegetarians an advantage in term of recovery from EIMD is not clear, especially considering that meat contains specific nutrients that are also considered to be antioxidants, such as carnosine and creatine.

In one of the few studies comparing the oxidative stress response between omnivores, vegans and lacto-ovo (i.e. consume both milk and egg products) vegetarians, Nebl and colleagues (2019) reported significant increases from rest in malondialdehyde (MDA), a marker of lipid peroxidation and oxidative stress, in both lacto-ovo vegetarians (+24%) and vegans (+15%), while no significant change (+9%) was noted in omnivores. Although no differences were noted in antioxidant and vitamin content between these diets, there was still a difference in the oxidative stress response between these groups. The authors suggested that this was likely related to differences in creatine content of the three diets, with omnivores consuming a significantly greater amount of creatine from their meat consumption. In contrast, an animal study comparing a traditional Western diet to the Daniel fast, which is a strict vegan diet, reported that the diets combined with exercise resulted in significant improvements in time to exhaustion, but that the improvement in animals consuming the vegan diet was significantly greater (+81%) than animals consuming the Western diet (+36%) (Bloomer et al. 2018). Although the oxidative stress response was significantly greater in animals consuming the Western diet, no differences were reported in any of the inflammatory cytokine levels.

A recent comparison on resting oxidative stress markers was performed on individuals who followed a specific diet of either being a vegetarian, lacto-ovo-vegetarian or omnivore for at least two years (Vanacore et al. 2018). The diets of both omnivores and lacto-ovo-vegetarians included foods with high leucine content (e.g. cheese, soybeans, beef, chicken, pork, nuts, seeds, fish) compared to the strict vegetarian diet. Although differences in leucine content likely contributed to the significantly lower lean body mass observed in the vegetarians compared to the other two groups, this specific diet also appeared to effect markers of oxidative stress. Although antioxidant compounds, found in fruits and vegetables, should maintain low levels of oxidative stress in both lacto-ovo-vegetarians and vegetarians compared to omnivores, the investigators indicated that FRAP value (total antioxidant status of plasma) was significantly lower in vegetarians compared to lacto-ovo-vegetarians and omnivores. In addition, lipid peroxidation levels evaluated by Thiobarbituric acid-reactive species (TBARS) increased only in vegetarians compared to lacto-ovo-vegetarians and omnivorous. The authors suggested that these results may have been related to the higher presence of indigestible dietary fibers in the vegetarian. A diet high in dietary fiber may result in lower bioaccessibility and

bioavailability of antioxidant molecules such as polyphenols in the small intestine, and subsequently cause an increase in oxidative status and slower recovery following exercise. The results observed in both lacto-ovo-vegetarians and omnivores were consistent with previous research reporting similar FRAP values in individuals consuming these diets (Szeto et al. 2004). In addition, lower resting C-reactive protein concentrations, an acute phase protein used as a marker of inflammation, were also noted in both lacto-ovo-vegetarians and omnivores compared to vegetarians (Vanacore et al. 2018).

There appears to be little to no support in the scientific literature regarding the benefits of a vegetarian diet in enhancing exercise recovery. Although there may be health benefits associated with this dietary model in various population groups, this is likely not the primary consideration for healthy competitive athletes. An additional concern for the vegetarian would be in the quality of the protein consumed (Hoffman and Falvo 2004). Without consuming animal protein, the quality of protein intake for a vegetarian may be substantially lower than an omnivore. Although the vegetarian athlete can compensate with a greater focus of soy protein, the diet would still be low in creatine and carnosine content, which may have important benefits in performance and recovery, especially for the strength/power athlete (Hoffman 2016a).

Ketogenic and Omnivore Dietary Comparisons

A diet that has gained tremendous popularity in recent years is the ketogenic diet, which is defined by its low carbohydrate, high fat intake. The basis of this diet is to provide a dietary treatment plan to treat obesity and diabetes, but is also used by athletes to enhance their metabolic system for competition (Harvey et al. 2019). Generally, the macronutrient caloric composition of the ketogenic diet is 80% fat, 15% protein, and 5% carbohydrates (Veech 2004). The increase in ketone bodies from a high consumption of fat is thought to provide a more energy efficient substrate than glucose or fatty acids (Veech 2004; Harvey et al. 2019).

Volek and colleagues (2016) compared a low-carbohydrate diet to a high carbohydrate diet in elite male ultra-endurance athletes performing a maximal graded exercise test and a 180 min submaximal run at 64% VO_2max. Participants had consumed their specific diets for at least 6-months prior to study enrollment. The results of the study indicated that peak fat oxidation was 2.3-fold higher in the low-carbohydrate group and it occurred at a higher percentage of VO_2max ($70.3 \pm 6.3\%$ vs $54.9 \pm 7.8\%$; $p < 0.001$) than in the high-carbohydrate group. In addition, fat oxidation during submaximal exercise was 59% higher in the low-

carbohydrate group than in the high-carbohydrate group. Despite these differences in fuel use between the groups, no significant differences were noted in resting muscle glycogen and the level of glycogen depletion after 180 min of running. Interestingly, subsequent research has confirmed these findings, and have indicated that the metabolic adaptations occur quite quickly as an athlete changes from a high-carbohydrate to a low-carbohydrate diet (Prins et al. 2019).

The low-carbohydrate content of the ketogenic diet has been a major concern for many individuals, as the standard belief was that maximizing glycogen storage was critical for exercise performance. Traditional thought believes that for an athlete that competes or trains on a daily basis, glycogen replenishment would be a critical factor relating to exercise recovery. However, evidence does suggest that metabolic adaptations resulting from low-carbohydrate diets do compensate for low muscle glycogen content (Paoli et al. 2015). Low-carbohydrate, high-fat diets usually lead to ketosis when the liver oxidizes high concentrations of non-esterified fatty acids (NEFA) into ketone bodies (McPherson and McEneny 2012). This process of ketogenesis occurs primarily within the liver's mitochondrial matrix (Highton et al. 2009). In general, when glycogen stores are depleted glucose levels are maintained through the process of gluconeogenesis resulting in the conversion of molecules with carbon skeletons such as amino acids and lactate to glucose (Fournier et al. 2002). In addition, glycerol derived from the metabolism of triglycerides can also be a source of glucose (Massicotte et al. 2006). These two sources appear to compensate for the low carbohydrate intake. Interestingly, compared with glucose, the energy produced from ketone bodies appears to be greater (Paoli et al. 2015).

An additional effect associated with the ketogenic diet is the increased production of low levels of reactive oxygen species molecules such as hydrogen peroxide (H_2O_2) and 4-hydroxynonenal (4-HNE) (Milder and Patel 2012).This may provide a potential protective mechanism during high intensity training. Huang and colleagues (2018) compared the effect of an 8-week ketogenic diet and high-carbohydrate diet on the oxidative stress response to exhaustive exercise in rats. Animals in both groups experienced fatigue following the exercise protocol, however the animals that consumed the ketogenic diet appeared to recover faster (e.g. greater movement) than the control (high-carbohydrate fed) animals. In addition, markers of liver damage (i.e. aspartate transaminase and alanine transaminase) and skeletal muscle damage (i.e. creatine kinase) were significantly lower in the ketogenic group than the control group. No differences were noted in lipid peroxidation indicating no difference in the oxidative stress response to exhaustive exercise was observed between the two diets. However, hepatic

protein carbonyl group, a product of specific protein side chains, was attenuated in animals consuming the ketogenic diet suggesting a protection of exercise-induced liver damage. Although a greater recovery appeared to be experienced by the animals consuming the ketogenic diet, the mechanisms behind this benefit were not clear, and may be somewhat related to the low protein content of this diet that may have attenuated antioxidant production.

Studies examining the effects of a ketogenic diet on the oxidative response in competitive athletes are very limited. It has been hypothesized that an increase in ketone bodies can attenuate the inflammatory response and result in an anti-catabolic response in muscle (Koutnik et al. 2019), however this has yet to be established in human studies of competitive athletes. In one study examining taekwondo athletes, 3-weeks of a ketogenic diet during high intensity training resulted in a significant reduction in MDA concentrations suggestive of an improved oxidative stress response (Rhyu et al. 2014). Thus, further research on the role of the ketogenic diet on exercise recovery is clearly warranted. Further, there are no studies comparing dietary extremes (e.g., vegetarian compared to ketogenic) to determine which diet presents the greatest benefit for exercise recovery.

The Effect of Dietary Supplement Intervention on Recovery Indices of Exercise

There are numerous dietary supplements that have been suggested to enhance exercise recovery (Hoffman 2019). To discuss each supplement is beyond the scope of this review. Thus, the focus will be on the more popular dietary supplements used by competitive athletes such as protein, creatine, β-alanine and polyphenols. Discussion will be focused on their potential role in enhancing recovery from exercise, and not their potential role in enhancing exercise performance.

Protein

Protein can be consumed from a variety of dietary sources that can be from animal and/or plant origin. Protein can also be ingested as a supplement, which can provide protein from the same variety of sources. Which type of protein should be consumed is based on its quality and digestibility. Quality refers to the availability of amino acids that it supplies, and digestibility considers how the protein is best utilized (Hoffman and Falvo 2004). Thus, if the focus is on which protein provides the maximum benefit for enhancing exercise recovery these factors need to be considered. It is well-accepted that protein consumption following an intense workout can enhance the recovery and remodeling processes within skeletal tissue (Jäger et al.

2017). Several studies have reported a decrease in the extent of muscle damage, attenuation in force decrements, and enhanced recovery resulting from protein ingestion following resistance exercise (Kraemer et al. 2006; Hoffman et al. 2007; Hulmi et al. 2009; Cooke et al. 2010; Hoffman 2016b). When protein is consumed prior to, and immediately following a bout of resistance exercise an increase in messenger RNA (mRNA) expression is observed, preventing a post-exercise decrease in myogenin mRNA expression (Hulmi et al. 2009). This is thought to accelerate muscle adaptation and enhance muscle recovery from the workout.

The two most common whole proteins used in dietary supplements are casein and whey. The differences in these proteins are primarily related to their differences in digestive properties and amino acid composition. When casein is ingested it forms a gel or clot in the stomach which slows down absorption. As a result, casein provides a sustained but slow release of amino acids into the bloodstream, sometimes lasting for several hours (Boirie et al. 1997). Whey protein is the translucent liquid part of milk and contains higher amounts of the essential and branched chain amino acids (Hoffman and Falvo 2004). In addition, whey protein has been shown to have a faster absorption capability than casein, which may have important implications for increasing the rate of protein synthesis following a training session (Boirie et al. 1997). Whey protein's fast rate of absorption and high concentrations of leucine may provide a great benefit when consumed immediately following a training session. In one study, whey and casein protein were provided before and after resistance exercise in older adults (Burd et al. 2012). Results indicated that the whey protein supplement stimulated a significantly greater increase in muscle protein synthesis than casein. Considering that there may be a heightened sensitivity in skeletal tissue following a workout (Cribb and Hayes 2006; Hoffman 2016b), ingestion of whey protein immediately following a training session may be the most beneficial protein to enhance muscle remodeling and recovery. Interestingly, whey protein has also been demonstrated to enhance glycogen synthesis in both liver and skeletal muscle more than casein, which appears to be related to its capacity to upregulate glycogen synthase activity (Morifuji et al. 2005). Therefore, ingestion of a whey protein supplement post-exercise may not only augment recovery and improve protein balance, but it also appears to speed glycogen replenishment.

β-Alanine

β-alanine is a non-proteogenic amino acid. When ingested it combines with histidine within skeletal muscle and other organs to form carnosine. β-alanine is considered to be the rate-limiting step in muscle carnosine synthesis (Harris et al. 2006). Carnosine is a highly effective intracellular pH buffer that enables a greater tolerance of sustained anaerobic activity (Hoffman et al. 2018). Besides serving as an intracellular buffer, carnosine has also been suggested to act as an antioxidant (Kohen et al. 1988; Boldyrev et al. 2004; 2010). Carnosine has been demonstrated to scavenge reactive oxygen species and react directly with superoxide anions and peroxyl radicals in vitro (Boldyrev et al. 2013). In addition, carnosine has been shown to behave as an ion-chelating agent, preventing ions such as copper and zinc from excessive accumulation, which may lead to lipid peroxidation and subsequent cellular damage (Trombley et al. 2000). Carnosine has also been reported to act as an anti-glycating agent, which also prevents the formation of advanced lipid oxidation end-products (Boldyrev et al. 2013). Carnosine's physiological role clearly goes beyond those of muscle-buffering capacity and suggest that elevations in carnosine levels may enhance exercise recovery.

Unfortunately, investigations examining the role of β-alanine supplementation and oxidative stress have been limited. In one of the first human studies examining the effect of β-alanine supplementation on markers of oxidative stress, Smith and colleagues in a pair of studies (Smith et al. 2012; Smith-Ryan et al. 2014) investigated 28-days of β-alanine (4.8 $g \cdot day^{-1}$) during a 40-minute treadmill run in moderately trained college-aged men and women. No differences were noted in any of the antioxidant markers suggesting that β-alanine supplementation was unable to attenuate the oxidative stress response. However, a single 40-min treadmill run may not be the appropriate stressor to stimulate a large oxidative stress response. Interestingly, there have been several investigations, albeit in animal models, indicating that β-alanine may have a role as an antioxidant in the brain. Murakami and Furuse (2010) reported significant elevations of carnosine content in the cerebral cortex and hypothalamus of mice that supplemented with β-alanine for 5-weeks. Increases in brain carnosine were associated increases in brain derived neurotrophic factor (BDNF), and a decrease in 5-hydroxyindoleacetic acid concentrations, a metabolite of serotonin. These changes also corresponded to reduced anxiety. Subsequent investigations have shown that elevations in hippocampal carnosine content resulting from β-alanine ingestion can increase resiliency in rodents exposed to either a predator scent stress (PSS) (e.g., an animal model of post-traumatic stress disorder, PTSD) or a low-pressure blast wave (e.g., an animal model of mild traumatic brain injury, mTBI) (Hoffman et al. 2015, 2017a). Changes in brain carnosine

in the different regions of the hippocampus were inversely associated with anxiety index. The protective effects associated with elevations in brain carnosine appeared to be related to a protection of BDNF expression in the hippocampus, which was maintained in animals that supplemented with β-alanine. In addition, glial fibrillary acidic protein (GFAP), a marker of brain inflammation was significantly attenuated in the animals supplemented with β-alanine and exposed to the blast wave compared to rats that were exposed but fed a normal diet (Hoffman et al. 2017b). These results support the potential role that carnosine may have as an antioxidant. These results also suggest a potential role of β-alanine for increasing resiliency and/or recovery from concussive events in competitive contact sports. However, whether β-alanine supplementation can provide any anti-inflammatory or antioxidant protection to enhance recovery following intense exercise in competitive athletes requires additional examination.

Creatine

Creatine is a nitrogenous organic compound that is synthesized from the amino acids glycine, arginine and methionine primarily in the liver. It can also be synthesized in smaller amounts in both the kidneys and pancreas. Creatine can also be consumed in the diet with high concentrations found in both meat and fish, with approximately 525 mg of creatine found in 100 g of uncooked red meat (Mateescu et al. 2012). Approximately 98% of creatine is stored within skeletal muscle in either its free form (40%) or in its phosphorylated form (60%) (Heymsfield et al. 1983). The efficacy of creatine supplementation in regards to strength and power performance has been well documented in numerous studies over the past 20-years (Hoffman 2016b; Kreider et al. 2017).

In addition to its ergogenic ability, creatine supplementation has also been suggested to enhance recovery from exercise (Kreider et al. 2017). Interestingly, creatine has been reported to enhance glycogen replenishment following exhaustive exercise (Nelson et al. 2001). It has been suggested that creatine induced increases in cell volume may be the mechanism responsible for augmenting glycogen synthesis. This was supported by Van Loon and colleagues (2004) who reported an association between an increase in muscle creatine (31%) and the change in glycogen storage (18 %) following 5-days of creatine supplementation. Later research confirmed these findings but also indicated that greater muscle glycogen accumulation (81%) occurred primarily within 24-hours of exhaustive exercise and was unrelated to changes in muscle creatine (Roberts et al. 2016).

One of the first studies to examining creatine supplementation and muscle damage following resistance exercise did not provide any support for the ability of creatine supplementation (5-days of 20 g per day) to attenuate muscle damage and soreness (Rawson et al. 2001). However, this investigation used previously untrained individuals performing eccentric contractions recruiting a small muscle mass (forearm flexors). Subsequent examinations using similar exercise protocols and untrained participants, also reported no benefit associated with creatine supplementation and exercise recovery (Mckinnon et al. 2012; Boychuk et al. 2016). When creatine supplementation was provided to experienced, resistance-trained individuals performing an overreaching exercise protocol using dynamic compound movements (e.g., squat, bench press exercises), significant reductions in uric acid (marker of exercise stress) and a greater maintenance of performance was noted in the creatine supplemented group (Volek et al. 2004). These findings were supported by Cooke and colleagues (2009), who examined previously untrained men and required them to perform 4 sets of 10 eccentric-only repetitions at 120% of their maximum concentric 1-RM on the leg press, leg extension and leg flexion exercise machine. Creatine supplementation significantly increased both isokinetic (10%) and isometric (21%) knee extension strength in the creatine supplemented group of participants during the recovery period compared to the placebo group. In addition, markers of muscle damage were significantly lower (-84%) in the creatine supplemented versus placebo groups during the week following the muscle damaging protocol.

Creatine supplementation has also been shown to reduce muscle damage and inflammatory markers following a 30-km road race in competitive marathoners (Santos et al., 2004). Similar to other investigations, participants were provided 20 g of creatine monohydrate per day for 5 days. Blood was obtained immediately prior to- and 24-hours following the race. Although differences in creatine kinase were not statistically different, there was still a 19.2% lower response in runners that supplemented with creatine compared to placebo. However, significantly lower lactate dehydrogenase (38%), prostaglandin E2 (66.5%) and TNFα (33.8%) concentrations were noted in the creatine group suggesting a reduction in muscle damage and inflammation resulting from creatine supplementation. These results were supported by others examining competitive soccer players performing repeated sprints (Deminice et al. 2013). Following 7-days of creatine supplementation (20 g per day) the soccer players performed two consecutive anaerobic sprint tests consisting of six 35-m sprint runs at maximum speed with 10 sec rest between them. A 2-minute recovery period was provided between each sprint test. Blood markers of muscle damage, inflammation and oxidative stress were collected just prior

to the start, immediately following and 1-hour following completion of the sprint protocol. Creatine supplementation resulted in significant reductions in inflammatory markers (TNFα and C-reactive protein), but no significant differences were noted in markers of muscle damage (CK and lactate dehydrogenase) or oxidative stress (MDA, glutathione or FRAP). These results appeared to be more focused on the acute response rather than the actual recovery question. This is especially relevant for blood markers of muscle damage and oxidative stress, as these measures were still elevating during the period of study. Recovery should be focused more on the rate of attenuation, especially during the 24 – 48 hours post-exercise.

Results from these investigations do support the benefits of creatine supplementation on enhancing recovery from exercise. The precise mechanism though is still not clear, which is likely contributing to lack of consistency seen among studies. Further research examining the potential recovery benefits of creatine in an athletic population is still warranted.

Polyphenols

Polyphenols are the most plentiful antioxidant in the diet and are common in many plant-based foods and beverages, such as fruits, tea and coffee (Arroyo and Jajtner 2019). There are four main polyphenols, which differ in their structure: phenolic acids, flavonoids, stilbenes, and lignans (Manach et al. 2004). Flavonoids are the most common polyphenol supplement that has been investigated (Manach et al. 2004; Arroyo and Jajtner 2019). Polyphenols are considered antioxidants whose major function is to maintain oxidative balance within the body. Several studies have demonstrated that acute supplementation can attenuate strength deficits following exercise that elicits muscle damage (Panza et al. 2008; Bowtell et al. 2011; Jówko et al. 2012; Jajtner et al. 2016, 2018; Beyer et al. 2017; Townsend et al. 2018).

Kerksick and colleagues (2010) examined the effect of 2-weeks of polyphenol supplementation on the inflammatory and oxidative response to 100 eccentric contractions of the leg extensors. Study participants were randomized into one of three groups: 1800 mg N-acetyl-cysteine, 1800 mg epigallocatechin gallate or placebo. The investigators reported that an eccentric bout of strength exercise resulted in significant increases in muscle damage, markers of mitochondrial apoptosis, apoptotic enzyme activity, and whole-blood cell markers of inflammation with no differences noted between groups. However, soreness ratings were blunted in the two polyphenol supplementation groups 24 h after exercise when compared to placebo. Jajtner and colleagues (2018) examined the effect of 28-days of polyphenol supplementation in recreationally trained college students. Participants completed three

different leg exercises at 70% of the participant's maximal strength levels, with 90 sec of rest between sets. The results of the investigation revealed that resistance exercise-initiated monocyte recruitment and mobilization was enhanced following polyphenol supplementation, thus possibly enhancing expression on nonclassical monocytes after exercise. Others, using the same exercise and supplementation protocol reported significant attenuation in the inflammatory response (Jajtner et al. 2016) and a reduction in apoptotic markers (Townsend et al. 2018) during the recovery period following resistance exercise. Furthermore, Beyer and colleagues (2017) reported that a 4-week supplementation period with polyphenols and resistance exercise resulted in an increase in total antioxidant capacity compared to placebo, which may have important implications for exercise recovery.

Investigations examining the effect of polyphenol supplementation (1000 mg/day quercetin for 3 weeks) on high volume exercise (3 days of 2.5-hr per day at 65% VO_2max) (Meeusen et al. 2013) and ultra-endurance racing (160 km) (Nieman et al. 2007) have reported no differences compared to placebo in the inflammatory and oxidative stress response to exercise. In contrast, Arent and colleagues (2010) examining 9-days of polyphenol supplementation (1760 mg of black tea extract) reported an improved recovery and a reduction in oxidative stress and muscle soreness to an acute high-intensity cycle ergometer interval program compared to placebo. It appears that polyphenol supplementation may have a greater effect on the recovery response during high intensity exercise compared to high volume exercise.

Conclusion

The study of exercise recovery is quite complex as a multitude of factors such as age, sex, training experience, muscle fiber type and type of activity performed (i.e., endurance versus resistance exercise) can influence interpretation. Thus, it is important to provide context to such investigations. In addition, there is an extensive array of potential areas of investigation that involve different degrees of sensitivity and complexity as it relates to exercise recovery. Investigations of recovery have ranged from performance outcomes to molecular examination of cellular signaling systems describing potential mechanisms of recovery. This broad array of study creates a challenge in providing an encompassing review of the physiological question of muscle damage and exercise recovery. As such, it was the primary focus of this review to examine the effects of EIMD and subsequent recovery in recreational and competitive athletes. In addition, mechanisms responsible for these effects were discussed, including invasive and non-invasive techniques used to assess EIMD. Monitoring the recovery process using validated tools for performance measurement may represent key factors in understanding recovery of different components of performance.

A focus of this review included discussion on the role of diet and nutritional supplementation in accelerating recovery from exercise. There does not appear to be any consensus on a specific diet being advantageous with regards to recovery compared to others. However, there is evidence to suggest that the use of several of the dietary supplements discussed in this review (e.g., protein, creatine and polyphenols) are efficacious in enhancing recovery from both endurance and strength/power exercise. There is some interesting evidence in animal studies regarding elevated carnosine levels resulting from β-alanine supplementation and enhanced antioxidant status that has been reported to coincide with an attenuated inflammatory response. However, further research still appears necessary regarding β-alanine and its role in recovery from exercise.

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Figure Legends

Figure 1. Schematic representation of the causes, physiological processes, and consequences of exercise-induced muscle damage (EIMD). Unaccustomed exercise, with or without excessive overload, is associated with disruption of muscle tissue homeostasis and mechanical damage to the muscle tissue. This, in turn, leads to a complex chain of physiological events, both locally within the muscle and systematically, with a tight connection between the outlined responses. As a result, inflammation is present, delayed onset of muscle soreness (DOMS) occurs, range of motion (ROM) is compromised and, subsequently, athletic performance is impaired. As outlined on the left, various factors can affect the response to and degree of EIMD signs and symptoms. E-C: excitation-contraction

Figure 2. MRI-DTI of skeletal muscle. Image showing a posterior view of the thigh muscle fibers using 3-Tesla magnetic resonance imaging (MRI) scan with the color-coded measure of mean diffusivity (MD). Diffusion-tensor imaging (DTI) assessment is dependent on cell membranes and other structures constraining water diffusion. Water movement can be evaluated by determining the three orthogonal directions of water diffusion, called eigenvectors, and their intensities - eigenvalues. From the three eigenvalues ($\lambda 1$, $\lambda 2$, and $\lambda 3$), parameters such as fractional anisotropy (FA) and mean diffusivity (MD) can be calculated to evaluate the character of water diffusion in a voxel. These measures have been shown to provide information about the integrity of skeletal muscle. FA and direction map with per-voxel color-coded vector values.

1739 **Table 1. Methods for assessing exercise-induced muscle damage**

Parameter	Invasive	Non-invasive
Mechanical muscle damage	Muscle biopsy	- MRI (T1, T2), MRI-DTI - Ultrasound - Electromyography
Inflammation	- Muscle proteins (creatine kinase & myoglobin) - Muscle biopsy - Pro- & anti-inflammatory cytokines (e.g. IL-6, IL-8, TNF-α) - White blood cells (e.g. neutrophils, macrophages) - C-creative protein - Lactate dehydrogenase	- Edema - Swelling
Muscle soreness		- VAS - Borg RPE scale - McGill Pain Questionnaire - Stretching protocol
Performance & related measures		- Vertical jump - Muscle strength using maximal voluntary contraction and/or 1-Repetition maximum - Economy/efficiency
Range of motion		- Goniometer - Joint movement
Muscle regeneration	Muscle biopsy	- MRI (T1, T2), MRI-DTI - Ultrasound

MRI: magnetic resonance imaging; DTI: Diffusion tensor imaging; IL: interleukin; TNF: tumor necrosis factor; VAS: visual analog scale; RPE: rating of perceived exertion

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