Title

Exercise-induced muscle damage: what is it, what causes it and what are the nutritional solutions?

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Abstract

Exercise-induced muscle damage (EIMD) is characterised by symptoms that present both immediately and for up to 14 days after the initial exercise bout. The main consequence of EIMD for the athlete is the loss of skeletal muscle function and soreness. As such, numerous nutrients and functional foods have been examined for their potential to ameliorate the effects of EIMD and accelerate recovery, which is the purpose of many nutritional strategies for the athlete. However, the trade-off between recovery and adaptation is rarely considered. For example, many nutritional interventions described in this review target oxidative stress and inflammation, both thought to contribute to EIMD but are also crucial for the recovery and adaptation process. This calls into question whether long term administration of supplements and functional foods used to target EIMD is indeed best practice. This rapidly growing area of sports nutrition will benefit from careful consideration of the potential hormetic effect of long term use of nutritional aids that ameliorate muscle damage. This review provides a concise overview of what EIMD is, its causes and consequences and critically evaluates potential nutritional strategies to ameliorate EIMD. We present a pragmatic practical summary that can be adopted by practitioners and direct future research, with the purpose of pushing the field to better consider the fine balance between recovery and adaptation and the potential that nutritional interventions have in modulating this balance.

Key words: Muscle, Nutrition, Exercise, Damage

1. Introduction

Exercise-induced muscle damage (EIMD) is characterised by symptoms that present both immediately and for up to ~14 days after the initial exercise bout. The consequences of EIMD for the athlete is the direct impact on functional capacity, muscle soreness (Byrne, Eston, & Edwards, 2001), exercise capacity (Marcora & Bosio, 2007; Twist & Eston, 2009) and disturbed sense of force production and limb position (Paschalis et al., 2010). The magnitude and time course of these symptoms and their subsequent impact on performance are variable and depend on the intensity and duration of the damaging exercise and the individual's susceptibility to the damaging stimulus (Reviewed by Douglas, Pearson, Ross, & McGuigan, 2017).

The EIMD associated losses in muscle function and increases in muscle soreness are important to athletes given their potential to impair performance. Accordingly, the focus of many sports nutrition strategies is to maximise the recovery from exercise and prepare for the next exercise bout. Numerous nutrients and functional foods have been examined for their potential to ameliorate EIMD. However, few studies have examined the balance between adequate exercise stress to stimulate adaptation and the need to intervene to avoid inadequate recovery or maladaptation (a phenomenon termed *hormesis*), creating difficulty when making assumptions about chronic exposure to nutritional compounds. In this review, we provide an overview of EIMD, its causes and consequences and then critically evaluate nutritional strategies that have the potential to ameliorate muscle damage. We conclude by presenting future research directions and recommendations for the management of EIMD.

2. Proposed mechanisms of EIMD

High force eccentric muscle actions typically produce ultrastructural muscular disruption (i.e. Z-line streaming and fibre degradation), delayed onset muscle soreness (DOMS), increases in specific intramuscular proteins in circulation, swelling of the affected limb, decreased range of motion and impaired muscle force producing capacity (Byrne, Twist, & Eston, 2004; Hyldahl & Hubal, 2014; Mackey & Kjaer, 2017). Modes of exercise that usually result in these symptoms include: resistance training (Burt, Lamb, Nicholas, & Twist, 2014), prolonged running (Millet et al., 2011), downhill running (Chen, Nosaka, Lin, Chen, & Wu, 2009), and intermittent, high intensity exercise (Leeder et al., 2014). The magnitude of damage resulting from eccentric

actions is exacerbated when performed at longer muscle length (Child, Saxton, & Donnelly, 1998; Nosaka & Sakamoto, 2001), with greater forces (Nosaka & Sakamoto, 2001) and at faster angular velocities (Chapman, Newton, Sacco, & Nosaka, 2006). A muscle's susceptibility to damage might also be reduced for subsequent bouts where prior exposure to eccentric exercise has occurred (Stupka, Tarnopolsky, Yardley, & Phillips, 2001). This protective adaptation is known as the repeated bout effect; RBE (Reviewed in detail by Hyldahl, Chen, & Nosaka, 2017).

The extent of muscle damage is typically assessed by measuring various indirect markers. Reduced muscle force after eccentric exercise is the most appropriate indirect marker (Damas, Nosaka, Libardi, Chen, & Ugrinowitsch, 2016; Paulsen, Mikkelsen, Raastad, & Peake, 2012; Warren, Lowe, & Armstrong, 1999). Depending on the factors described above, losses in force after exercise are between 15-60% of pre-damage values and can persist for ~2 weeks (Hyldahl, Olson, Welling, Groscost, & Parcell, 2014; Paulsen et al., 2012). The underlying mechanisms are complex and are attributed to physical damage to the sarcomere and sarcolemma from eccentric lengthening and excitation-contraction (E-C) coupling failure (see section 2.1). DOMS is the most commonly assessed marker (Warren et al., 1999), yet the underpinning mechanism for its appearance is unclear. Sensations of muscle soreness could result from a complex interaction of damage to the muscle structure, disrupted calcium (Ca^{2+}) homeostasis, and sensitization of nocioceptors from inflammatory cell infiltrates (Hyldahl & Hubal, 2014). However, studies reporting increased muscle soreness after eccentric exercise in the presence of limited inflammation in both animal (Hayashi et al., 2017) and human models (Yu, Liu, Carlsson, Thornell, & Stal, 2013) challenges the origins of DOMS. DOMS typically appears between 8 - 24 h after muscle-damaging exercise, peaks between 24 - 48 h and usually subsides within 96 h (Damas et al., 2016; Jones, Newham, & Clarkson, 1987). Finally, the appearance of muscle-specific proteins such as muscle-specific CK in plasma and myoglobin in serum, that peak 2-6 days after the initial insult are typically reported (Byrne et al., 2004; Hyldahl et al., 2014; Warren et al., 1999). Membrane damage caused by eccentric lengthening leads to increased membrane permeability and leaking of muscle proteins in to circulation (Sorichter, Puschendorf, & Mair, 1999), particularly in the immediate EIMD aftermath. Circulating muscle-specific proteins do, however, show a poor temporal relationship with muscle function (Friden & Lieber, 2001) and are probably best served as a marker that tissue damage has occurred rather than to assess its magnitude. The complex mechanisms associated with EIMD can be simplified into two phases: (i) the initial phase or primary damage that occurs as a consequence of the mechanical work

performed; and (ii) secondary damage that proliferates tissue damage through processes associated with the inflammatory response.

2.1 Primary muscle damage

Although several metabolic factors have been proposed as mechanisms of primary damage during eccentric exercise (Tee, Bosch, & Lambert, 2007), mechanical loading of the muscle during exercise is a more likely candidate (Proske & Morgan, 2001). Eccentric contractions have lower motor unit activation compared to isometric and concentric contractions for the same force (McHugh, Connolly, Eston, & Gleim, 2000), which places greater mechanical stress on a smaller number of muscle fibers during eccentric work (Enoka, 1996). It is also thought that faster motor units are preferentially recruited during lengthening contractions (Nardone, Romano, & Schieppati, 1989) and consequently, evidence suggests fast-twitch fibres are damaged (Friden, Sjostrom, & Ekblom, 1983). Sarcomeres lengthen heterogeneously under tension in a non-uniform manner (so-called inhomogeneity) until they are beyond myofilament overlap (Morgan & Allen, 1999; Proske & Morgan, 2001). At this point, some sarcomeres experience "popping" (See "popping sarcomere hypothesis"; Morgan & Allen, 1999; Proske & Morgan, 2001) and increase tension on passive structures that result in deformation of non-contractile proteins that has previously been evidenced by Z-line streaming (Friden et al., 1983). Subsequent repetition of non-uniform lengthening during eccentric contractions then leads to greater fibre disruption (Morgan & Allen, 1999; Proske & Allen, 2005).

Failure of the excitation-contraction (E-C) coupling process also contributes to the primary damage phase (Hyldahl & Hubal, 2014). Reduced force production immediately and in the days after eccentric exercise have been observed in animal models alongside reduced sarcoplasmic reticulum (SR) Ca^{2+} release (Balnave & Allen, 1996; Ingalls, Warren, Williams, Ward, & Armstrong, 1998; Warren, Hayes, Lowe, & Armstrong, 1993a). Treatment of damage isolated muscle fibers with caffeine, which acts to stimulate SR Ca^{2+} release, rescues force lending support to the E-C failure hypothesis (Warren et al., 1993b). Similarly, 'low-frequency fatigue' (LFF) after damaging exercise in humans is characterized by losses of force at low (10 - 20 Hz) compared to higher (50 – 100 Hz) surface electromyostimulation frequencies (Clarkson & Hubal, 2002; Jones, 1996) that suggest reduced SR Ca^{2+} release (Dundon, Cirillo, & Semmler, 2008). However, reduced force at low stimulation frequencies also occurs in over-extended sarcomeres (Allen, 2001), suggesting LFF might be attributable to structural damage to the myofibril rather than E-C coupling

failure (Allen, 2001; Clarkson & Hubal, 2002; Jones, 1996). Although there are competing theories to explain this phenomenon, it is generally acknowledged that the initial event after eccentric contraction disrupts the contractile and non-contractile apparatus, which is followed by membrane damage and subsequent E-C coupling dysfunction (Proske & Morgan, 2001).

2.2 Secondary muscle damage

After the primary phase, an uncontrolled movement of Ca^{2+} into the cytoplasm causes further damage (Armstrong, 1984; Ebbeling & Clarkson, 1989). High intracellular Ca^{2+} concentration activates Ca^{2+}-dependent proteolytic and phospholipase A2 pathways that result in the degradation of structural proteins (Gissel, 2005; Gissel & Clausen, 2001). Mitochondria maintain homeostasis by excess Ca^{2+} uptake (For a detailed review see Ebbeling & Clarkson, 1989; Gissel, 2005). However, mitochondrial Ca^{2+} overload can lead to inner mitochondrial membrane permeabilization and opening of the permeabilization transition pore, ultimately resulting in a large efflux of Ca^{2+} from the mitochondria, increasing intracellular Ca^{2+} and causing apoptosis or necrosis (Gissel, 2005). Increased intracellular Ca^{2+} could also cause uncontrolled muscle contraction that might be one explanation for increases in passive tension observed after EIMD (Allen, 2001; Morgan & Allen, 1999; Proske & Allen, 2005; Proske & Morgan, 2001).

The subsequent inflammatory cascade is a vital process that clears damaged tissue, and initiates tissue repair and adaptation (Chazaud, 2016). A number of immune cell types infiltrate the damaged tissue, including mast cells, neutrophils, T regulatory lymphocytes, eosinophils and CD8 T lymphocytes (Burzyn et al., 2013; Castiglioni et al., 2015; Cote, Tremblay, Duchesne, & Lapoite, 2008; Heredia et al., 2013; Zhang et al., 2014) to carry out specific roles in a highly organised, temporal manner.

Neutrophils are probably the first group of immune cells to infiltrate muscle at the site of injury (Reviewed by Hyldahl & Hubal, 2014), activated by Ca^{2+}-stimulated proteolysis (Gissel & Clausen, 2001) and increased intracellular Ca^{2+} signaling pro-inflammatory cytokine release (Butterfield, Best, & Merrick, 2006). Neutrophils phagocytose necrotic myofibres and cellular debris (Pizza, Peterson, Baas, & Koh, 2005). However, neutrophils can also produce high concentrations of cytolytic and cytotoxic molecules through NADPH oxidase derived - superoxide anion dependent mechanisms that can aggravate existing damage and are, therefore, implicated in the

secondary damage process (Nguyen & Tidball, 2003).

Like neutrophils, macrophages are also capable of producing cytotoxic enzymes and reactive species (e.g. superoxide anion) that subsequently promote tissue degradation (Nguyen & Tidball, 2003). However, once engaged by damaged tissue, macrophages can convert into anti-inflammatory phenotypes responsible for releasing growth factors such as transforming growth factor β1 (Arnold et al., 2007). These observations suggest that macrophages do not contribute to membrane disruption during the inflammatory response, but instead have a role in facilitating tissue recovery and adaptation (Butterfield et al., 2006).

2.3 Satellite cell involvement in muscle repair

Myofibres lack intrinsic regenerative capacity, so muscle fibre regeneration relies on resident muscle stem cells, termed satellite cells. Satellite cells reside juxtaposed to the muscle fibre, between the sarcolemma and basal lamina (Mauro, 1961). Satellite cells remain quiescent until activated by appropriate cues ranging from intracellular signaling events to local interactions with the extracellular matrix and circulating systemic factors including inflammatory cells and nitric oxide (Reviewed in detail by Yin, Price, & Rudnicki, 2013).

The activation and expansion of satellite cells after strenuous muscle activity is well-documented in humans. Cermak et al. (2013) reported that 24 hours after 300 eccentric contractions, satellite cell content of type II fibres was increased. Similarly, single bouts of intense resistance exercise such as 45 cm drop jumps combined with maximal eccentric knee flexions on an isokinetic dynamometer (Crameri et al., 2004), high volume maximal unilateral eccentric dynamometry of the knee flexors (Dreyer, Blanco, Sattler, Schroeder, & Wiswell, 2006) and electrical stimulation (Mackey & Kjaer, 2017) all increase satellite cell activity. As these studies typically employ eccentric contractions, it has been suggested that it is exclusively eccentric contractions that lead to satellite cell activation. In a recent trial, a work-matched bout of repeated sets of eccentric or concentric contractions was employed (40 kJ work total per condition). The main finding was a 27% increase in satellite cell content at 24 hours after exercise in the eccentric but not the concentric exercise group, suggesting that satellite cells are differentially activated depending on contraction type (Hyldahl et al., 2014).

Collectively, satellite cells are necessary for the remodeling of untrained skeletal muscle, possibly to maintain an adequate DNA:protein ratio. Since only non-trained or sub-elite athletes have typically been recruited in existing studies, whether such observations apply to elite groups is unclear. Interestingly, during periods of unloading/detraining, the nuclei accumulated by myofibres as a result of satellite cell activation remain for up to 60 days in humans (Kadi et al., 2004) and mice (Bruusgaard, Johansen, Egner, Rana, & Gundersen, 2010). These findings indicate that sustained satellite cell activation provides the muscle with the potential capacity to mount an augmented response to a repeated challenge to myofibre homeostasis. Facilitating satellite cell activity in response to damaging exercise may be a route through which nutritional interventions can modulate recovery.

3. Dietary Solutions for Exercise-Induced Muscle Damage

3.1 Protein and Amino Acids

Dietary protein intake is undoubtedly a crucial factor in the regulation of muscle protein turnover, particularly in response to exercise. Adaptive processes to both resistance and endurance type exercise are enhanced when protein is fed around the exercise bout (Reviewed in detail by Phillips & Van Loon, 2011). Whether protein intake around intense/damaging exercise can alleviate aspects of muscle damage is less clear (Tipton, 2015). Evidence suggests protein or free amino acids fed around exercise can alleviate markers of muscle damage and accelerate recovery of force (Buckley et al., 2010; Cockburn, Stevenson, Hayes, Robson-Ansley, & Howatson, 2010; Nosaka, Sacco, & Mawatari, 2006). However, others have not found comparable effects (Blacker, Williams, Fallowfield, Bilzon, & Willems, 2010; Wojcik, Walber-Rankin, Smith, & Gwazdauskas, 2001). A recent systematic review concluded that when protein supplements are provided, acute increases in post-exercise protein synthesis and anabolic intracellular signalling have not resulted in measureable reductions in muscle damage and enhanced recovery of muscle function. This is logical as adaptations in muscle protein turnover are slow (Tipton, Borsheim, Wolf, Sanford, & Wolfe, 2003) and do not parallel the acute changes in muscle damage associated with protein supplementation, that typically occur within hours after damage. However, heterogeneity in study design and markers selected to monitor muscle damage and recovery of function may account for the lack of a clear consensus. So, whilst protein is undoubtedly important for adaptive remodelling of skeletal muscle after any form of exercise, and should never be compromised in the

diet, it is unclear whether supplementing with protein after EIMD *accelerates* recovery.

3.2 Functional Foods

So-called 'functional foods' have the potential to exert a positive physiological effect that is related to improved or preserved human health and disease prevention (Bell, McHugh, Stevenson, & Howatson, 2014). Exercise scientists, practitioners and athletes have identified these foods as potential synergistic solutions to manage the negative effects associated with strenuous physical activity. This is of particular interest for sports where muscle damage can impact upon subsequent training and competition. This section of the review will focus on the evidence derived from selected, contemporary and emerging functional foods applied in exercise recovery paradigms, with particular reference to foods (or their analogues) that contain dietary polyphenols and n3 fatty acids.

3.2.1 Dietary polyphenols

Dietary polyphenols are present in numerous fruits and vegetables that are consumed as part of a balanced diet and have been shown to possess antioxidant properties, *in vitro* (Seeram et al., 2008; Traustadottir et al., 2009; Wang, Cao, & Prior, 1997) and anti-inflammatory properties (Seeram, Momin, Nair, & Bourquin, 2001; Tall et al., 2004; Wang et al., 1999). In addition, many possess the ability to attenuate the arachadonic acid pathways by inhibiting cyclo-oxygenase (COX) 1 and 2 production (Seeram et al., 2001) to a similar magnitude to over-the-counter non-steroidal anti-inflammatory drugs or NSAIDs (Bondesen, Mills, Kegley, & Pavlath, 2004). Polyphenol enriched nutrients include tea, coffee, grapes, cocoa, nuts, blueberries, cherries, and pomegranates. Here, we will review whether polyphenol supplementation influences EIMD before considering potential mechanisms.

From an EIMD perspective, a dietary intervention is unlikely to interact with the primary phase of the mechanical stress during the exercise bout (Bell et al., 2014; Howatson & van Someren, 2008). What is more likely is an interaction with the secondary cascade, which results in inflammation and the production of reactive oxygen species (ROS) after the damaging exercise; consequently, further exacerbation of damage may be modulated and aid the subsequent recovery process. Quercetin is a polyphenol in the group of flavonol compounds present in berries, grapes, tomatoes and teas. Quercetin has good bioavailability in plasma after consumption (Egert et al., 2008) and could therefore exert positive effects *in vivo*.

However, limited evidence supports its use in managing EIMD. After three days of high intensity cycling for 3 hours per day, increases in exercise-induced inflammation and oxidative stress were reported (McAnulty et al., 2008). Despite 6 weeks of supplementation, quercetin performed no better than the placebo. Although cycling could be considered non-damaging, these data concur with previous work examining quercetin in an EIMD setting (Nieman et al., 2007a; Nieman et al., 2007b; O'Fallon et al., 2012). Despite some evidence of attenuated pro-inflammatory cytokine mRNA expression (Nieman et al., 2007b), quercetin failed to improve muscle function or reduce inflammation, oxidative stress and muscle soreness (Nieman et al., 2007a; Nieman et al., 2007b; O'Fallon et al., 2012).

Catechins and their derivatives are commonly found in tea and have the potential to enhance recovery from damaging exercise, although the literature on this flavonoid is scarce. One study has shown a modest change in post-exercise muscle soreness, but all other indices of muscle function or muscle damage remained unaltered compared with a control (Kerksick, Kreider, & Willoughby, 2010). Catechins and quercetin warrant greater research efforts to elucidate their potential, but at present their application in managing EIMD is unsupported.

An emerging food of interest for managing EIMD is tart Montmorency cherries (*Prunus cerasus*). The first study to investigate the efficacy of tart cherries in exercise recovery used heavy eccentric contractions to induce unilateral muscle damage to the elbow flexors in a placebo-controlled, randomized, cross-over design with a two-week washout, whereby the contralateral limb was used as the placebo control (Connolly, McHugh, Padilla-Zakour, Carlson, & Sayers, 2006). Participants consumed two servings per day of a cherry juice blend (fresh pressed Montmorency cherries and proprietary apple juice) for a total of eight days (four days before the damaging bout and for the duration of recovery period). An accelerated rate of muscle function recovery and reduced soreness post EIMD was observed. The investigators speculated that the positive effects were attributable to modulating the secondary damage phase. However, the influence of the proprietary apple juice in the blend cannot be excluded as a contributing factor for these positive observations. In addition, an important, but nonetheless often-overlooked limitation in this study (and many other damage studies) was the use of a crossover design in a damaging paradigm, which has been shown to confer a contralateral RBE and hence influence the damage in the contralateral limb (Howatson & van Someren, 2007; Newton, Sacco, Chapman, & Nosaka, 2013; Starbuck & Eston, 2012; Xin, Hyldahl, Chipkin, & Clarkson, 2014). In a

subsequent study, the same Montmorency cherry juice blend was investigated in a similar supplementation regimen, but used an independent group design and recorded measures of oxidative stress and inflammation before and after a marathon (Howatson et al., 2010). Like Connolly et al. (2006), this study showed an accelerated recovery of muscle function in the days after the marathon, but importantly indices of inflammation (interleukin-6; IL-6 and C-reactive protein; CRP) and lipid peroxidation (thiobarbituric acid; TBARS) were attenuated and hence concluded that the phytochemicals were modulating EIMD; with the caveat that TBARS is now considered an assay with marked limitations (Cobley, Close, Bailey, & Davison, 2017; Margaritelis et al., 2016a). The positive effects of tart cherries on recovery from strenuous damaging exercise have subsequently been demonstrated with Montmorency cherry juice blends (Kuehl, Perrier, Elliot, & Chesnutt, 2010), a Montmorency cherry concentrate (Bell et al., 2014; Bell, Walshe, Davison, Stevenson, & Howatson, 2015; Bowtell, Sumners, Dyer, Fox, & Mileva, 2011) and other Montmorency cherry analogues (Kastello et al., 2014) after different exercise paradigms. At the time of this review all published studies data examining Montmorency cherries as an intervention showed some positive effects. How these compounds exert beneficial effects is, however, unclear.

Pomegranate and its extracts are a polyphenol-rich fruit that principally contain ellagitannins (Medjakovic & Jungbauer, 2013). To our knowledge only two studies, from the same laboratory have examined the application of pomegranate on EIMD (Trombold, Barnes, Critchley, & Coyle, 2010; Trombold, Reinfeld, Casler, & Coyle, 2011). The first of these studies used elbow flexion eccentric contractions to induce damage in recreationally active males. In a placebo controlled trial, the authors showed that the consumption of a pomegranate extract, in the days before and after the damaging exercise bout, improved recovery of muscle function; however, no other index of damage or inflammation was different between groups. The second study damaged both the elbow flexors and the knee extensors in resistance-trained males. In support of their initial work, an accelerated recovery elbow flexor function, that was accompanied by less muscle soreness in the pomegranate group. Finally, both studies used a cross-over design which has previously been highlighted as a potential limitation owing to the contralateral RBE. Notwithstanding, the positive results with pomegranate suggest it could be an effective intervention for recreational and well-trained individuals to promote recovery from EIMD.

From a mechanistic perspective, how polyphenols exert their effects is unclear. Polyphenols react with free radicals (e.g. superoxide anion, peroxyl radical, aloxyl

radical and hydroxyl radical) *in vitro* to yield polyphenol radicals. While polyphenols generally have favorable kinetics, whether they accumulate in sufficient amounts to scavenge free radicals is debatable (not to mention whether scavenging free radicals is even desirable). For example, copper zinc superoxide dismutase (CuZnSOD) reacts rapidly with superoxide anion and is present at ~20 µM (Halliwell & Gutteridge, 2015). Plasma concentrations of "free" polyphenols rarely exceed 1 µM, even assuming a tissue concentration of 1 µM CuZnSOD still outcompetes polyphenols, which questions the plausibility of scavenging mechanisms (Schaffer & Halliwell, 2012). Note tissue polyphenol concentrations above the nanomolar range are unlikely (Forman, Davies, & Ursini, 2014; Schaffer & Halliwell, 2012). A situation abetted by the fact that polyphenol metabolism via methylation, sulphation and glucoronidation abrogates their activity towards free radicals (Goszcz, Duthie, Stewart, Leslie, & Megson, 2017; Halliwell & Gutteridge, 2015). Further, it is unlikely that polyphenols accumulate at the sites of free radical generation in an EIMD setting because inflammatory cell infiltrates release superoxide anion and other reactive species into the phagosome (Winterbourn et al, 2016), which imposes a spatial restriction. For these reasons, we disfavor scavenging mechanisms. Instead, we favor the hypothesis that small amounts of polyphenols are metabolized to electrophiles (e.g. quinones), that then activate the cyto-protective endogenous antioxidant response via Nrf-2 signaling (Forman et al., 2014; Goszcz, Deakin, Duthie, Stewart, & Megson, 2017). As reviewed in Forman et al, 2014, electrophiles can activate Nrf-2 signaling by conjugating reactive cysteine residues within KEAP-1—an inhibitory protein responsible for sequestering Nrf-2 in the cytoplasm —via Michael addition. For investigators wanting to disambiguate the mechanism, limited mechanistic insight can be derived from evaluating oxidized macromolecule adduct levels at the circulating level (Cobley et al., 2015a; Cobley, Moult, Burniston, Morton, & Close, 2015c; Cobley et al., 2014; Margaritelis et al., 2016a, b).

Pharmacological interventions are often consumed in doses that are well in excess of the recommended daily allowance that could result in unwanted side-effects, and importantly for athletic populations, increases the risk of consuming contaminated supplements. The use of polyphenolic-rich foods is growing in interest and represents a realistic alternative for numerous areas of sport and exercise nutrition, not least in managing muscle damage and exercise recovery. Other polyphenol-rich foods (for example, chokeberry, beetroot, acai, Concord grapes and blackcurrants) that have not been explored could provide effective interventions to manage signs and symptoms associated with EIMD. A caveat to the polyphenol literature discussed here is that

many of the studies have removed polyphenols from the diet in order to control the study and observe whether potential effects are due to the polyphenol supplement. Whether these effects would persist as a supplement to a polyphenol rich diet is unknown. At worst, these foods provide vital nutrients; at best, exercise recovery could be augmented. Pragmatically, a diet rich in polyphenols (fruit and vegetables) may be the best strategy to augment recovery from damaging exercise.

3.2.2 Omega-3 Polyunsaturated fatty acids

Omega-3 polyunsaturated fatty acids (n-3 PUFA), specifically n-3 PUFA eicosapentaenoic acid (EPA) and docasahexaenoic acid (DHA) are a group of nutrients that possess anti-inflammatory properties (Mickleborough, 2013). n-3 PUFA occur in natural abundance in nuts and oily fish like salmon, mackerel and tuna (Sousa et al., 2014). Multiple investigations have examined the effects of n-3 PUFA on muscle function, inflammation and oxidative stress induced by damaging exercise. For the most part, these have shown a positive effect (DiLorenzo, Drager, & Rankin, 2014; Gray, Chappell, Jenkinson, Thies, & Gray, 2014; Jouris, McDaniel, & Weiss, 2011; Marques et al., 2015; Phillips, Childs, Dreon, Phinney, & Leeuwenburgh, 2003; Tartibian, Maleki, & Abbasi, 2009, 2011) on one or more variables associated with EIMD. All of these studies tend to use a loading phase of several days that can extend up to a month, which might go some way to explaining the discrepancies in meaningful findings. The most comprehensive study to assess loading demonstrated that a minimum of 2 weeks supplementation with 5 g/day of fish oil capsules (providing 3500 mg EPA and 900 mg DHA) is necessary to permit detectable increases in muscle n-3 PUFA lipid composition (McGlory et al., 2014). Only one study (Lenn et al., 2002) showed n-3 PUFA to have no effect on muscle function, inflammation or oxidative stress after damaging eccentric contractions. Taken collectively these studies support the efficacy of n-3 PUFA as a promising intervention to manage EIMD.

3.3 Vitamin D

Vitamin D is a seco-steroid hormone predominantly obtained in humans by exposure to ultraviolet B radiation (UVB; sunlight) . Lack of sunlight exposure and predominantly indoor life styles have led to a large number of vitamin D deficiency cases worldwide (defined as <30 nmol/L 25[OH]D) (reviewed recently in Palacios & Gonzalez, 2014). Professional athletes also exhibit low 25[OH]D concentrations (Close et al., 2013; Hamilton, Grantham, Racinais, & Chalabi, 2010; Morton et al., 2012). The canonical role for vitamin D is its role in Ca^{2+} homeostasis and thus bone mineralization (Holick, 2004). It is now understood that the biological effects of the seco-steroid are much wider than Ca^{2+} homeostasis. Of particular relevance to this review are the emerging data that imply a role in muscle regeneration and remodeling as vitamin D exerts potent effects on the innate and acquired immune system, as well as, directly within skeletal muscle.

Few data exist to couple vitamin D's potential role in modulating the immune response to EIMD, despite a plethora of data that show vitamin D is a robust regulator of the immune system (Hewison, 2012). In one trial, the anti-inflammatory cytokine response after intense exercise correlated with individual's serum 25[OH]D (Barker et al., 2014). Although serum IL-10 and IL-13 responses to muscle damage were increased in the vitamin D sufficient group, the immediate and persistent peak isometric force and peak power output deficits caused by the intense single leg exercise protocol remained, despite vitamin D sufficiency. In another observational study, the inflammatory cytokine TNF-α was increased in runners with low serum 25[OH]D (Willis, 2012), which could be detrimental for cellular homeostasis in muscle. But this remains speculative in the absence of functional measures.

Data suggest vitamin D may be important in the intrinsic repair process after muscle damage. Initial insights were provided in a randomized controlled study that assessed the potential relationship between vitamin D and functional recovery of muscle after strenuous exercise. After 10 sets of 10 repetitive eccentric-concentric jumps on a custom horizontal plyo-press at 75% of body mass with a 20 second rest between sets, individuals with higher circulating 25[OH]D, the main marker of vitamin D status, demonstrated a faster recovery of maximal force in the recovery phase after exercise (Barker, Schneider, Dixon, Henriksen, & Weaver, 2013). Using a systems approach in young, recreationally active vitamin D insufficient males, we later confirmed that supplemental vitamin D (4,000 IU/day) could augment the recovery of maximal force after eccentric unilateral exercise compared to a placebo control group (Owens et al., 2015). Moreover, skeletal myoblasts were obtained via a muscle biopsy from the vitamin D insufficient participants and demonstrated improved migration, fusion and hypertrophic capacity of skeletal myoblasts in the presence of 1α,25-dihydroxyvitamin D3 (the

active vitamin D metabolite). These data provided good evidence for a role of vitamin D in muscle repair at the whole muscle and cellular level. With regards to muscle soreness, nociceptors also express the vitamin D receptor (VDR) making them a potential vitamin D target. Indeed, vitamin D deficiency may lead to selective alterations in target innervation, resulting in possible nociceptor hyper-innervation of skeletal muscle, which in turn is likely to contribute to muscular hypersensitivity and pain (Tague et al., 2011).

It appears that a daily as opposed to weekly or monthly vitamin D supplementation strategy is more effective and doses up to 4,000 IU/day vitamin D_3 during the winter months are adequate (Owens et al., 2017). Higher doses and mega bolus supplementation protocols often implemented are likely to produce unwanted effects due to negative feedback in the vitamin D metabolic pathway (Owens et al., 2017).

3.4. Vitamin C and Vitamin E

Vitamin C (i.e. ascorbic acid, AA) and vitamin E (α-tocopherol, α-TOC) are two essential nutrients, with pleiotropic redox-dependent and independent biochemical functionality (reviewed in Cobley, McHardy, Morton, Nikolaidis, & Close, 2015b; Niki, 2014). Several studies have investigated whether AA and α-TOC supplementation in combination or isolation ameliorates EIMD in humans, on the theoretical premise that they prevent cell damage inflicted by inflammatory cell infiltrates by scavenging free radicals. With few exceptions, the general consensus is that AA and α-TOC have limited ability to offset EIMD induced decrements in muscle function (reviewed in McGinley, Shafat, & Donnelly, 2009). For example, AA supplementation fails to improve muscle function, as assessed by isokinetic dynamometry (IKD), post EIMD (Thompson et al., 2004; Thompson et al., 2003; Thompson et al., 2001). The literature is mixed with regards to muscle soreness, some studies report no effect and others positive effects (reviewed in Close, Ashton, McArdle, & Maclaren, 2005). Whether potentially improving muscle soreness justifies their use to improve EIMD against a background of negligible effects on muscle function is debatable; especially when AA supplementation can delay recovery from EIMD (Close et al., 2006).

From a mechanistic perspective, use of AA and α-TOC is primarily based on their ability to “scavenge” free radicals—both nutrients have limited reactivity with non-radicals to generate a less reactive AA and α-TOC radical owing to electron delocalisation (Halliwell & Gutteridge, 2015). With a few exceptions (e.g. rapid reaction of α-TOC with lipid peroxyl radicals in the cell membrane Niki, 2014) whether they react with biologically meaningful free radicals near their site of generation and with a sufficient rate constant to outcompete endogenous reactants is unclear (Cobley et al., 2015b). In an EIMD setting, spatial constraints are particularly important. For example, α-TOC would have to accumulate at phagosome

membranes. If it did, it would likely protect the invading inflammatory cell infiltrate from oxidative damage, which may promote superoxide anion generation. Likewise, AA may potentiate superoxide anion generation by reducing Fe^{3+} to Fe^{2+} in NADPH oxidase (NOX) thereby enabling NOX to bind and reduce oxygen. Resolving the influence of AA and α-TOC is complicated by the difficulties associated with measuring free radical and non-radical species (Cobley et al., 2017; Halliwell & Whiteman, 2004). Notwithstanding, we suggest that AA and α-TOC are unlikely to directly scavenge free radicals in the phagosome to significantly interfere with the inflammatory responses.

Overall, no evidence based rationale exists to justify their use in an adaptive setting in AA and α-TOC sufficient athletes (Close & Jackson, 2014). It has been suggested that vitamin C and E could be considered for their use to offset muscle soreness during competitive situations when maximising adaption is inconsequential (Cobley, McGlory, Morton, & Close, 2011). However, a recent Cochrane review suggests only moderate to low quality evidence supports the use of 'antioxidant' supplements in reducing DOMS (Ranchordas, Rogerson, Soltani, & Costello, 2017). The use of vitamin C and E supplements in an EIMD setting therefore appears to lack support, especially when AA and α-TOC may interfere with certain exercise adaptations to non-damaging exercise (Gomez-Cabrera et al., 2008; Paulsen et al., 2014a; Paulsen et al., 2014b; Ristow et al., 2009). A graphical representation of the muscle damage-repair process and nutritional interventions that may interact with one or more of these events to augment recovery can be found in Figure 1.

3.4 Creatine Monohydrate

Creatine monohydrate supplementation shows positive effects on satellite cell number and myonuclear content in response to heavy resistance exercise. When administered at a dose of 24 g (4 x 6 g servings) per day for 7 days followed by 6 g per day for the following 15 weeks, satellite cell number and myonuclear content were increased above that of a 20 g whey protein supplement or a no training/no supplement control (Olsen et al., 2006). The signaling mechanism by which this occurs is still elusive; however, the data are supported by *in vitro* insights that show creatine monohydrate induces differentiation (myotube formation) of skeletal myoblasts (Vierck, Icenoggle, Bucci, & Dodson, 2003).

<<< FIGURE 1 HERE >>>

4. Practical nutritional considerations to modulate exercise-induced muscle damage

The long-term use of recovery strategies on adaptation to training and athletic development is an area of interest, and perhaps concern. The basis for this is predominantly concerned with interventions reducing the exercise-induced stress response, which may reduce adaptive potential—assuming the two are related. Many of the nutritional interventions highlighted here may modulate oxidative stress and inflammation, which are known to be important in the adaptive response to an exercise stimulus. As an example, blunting the pro-inflammatory phase of the repair process may be problematic as a decrease in the number of immune cell infiltrates leads to a decrease in the diameter of new myofibers and to the development of fibrosis (Bondesen et al., 2004; Shen, Li, Tang, Cummins, & Huard, 2005). This calls in to question whether long-term supplementation might bring about a maladaptive response and affect long-term athletic development.

With pragmatism in mind, a balanced diet that is rich in fruits and vegetables is always necessary. However, when training and competition stress is high and recovery is unlikely to be achieved before the next competition or high intensity training session, there is certainly rationale to supplement with additional foods that could help manage the negative effects of the exercise stressor. If the primary aim is to maximize the training stimulus, then a degree of caution is needed, whereby athletes and practitioners need to consider a periodised approach to nutrition to adequately support training and competition to maximize the potential for adaptation (see Figure 2). This notion can be conceptualized with the idea of hormesis, which was first applied to exercise paradigms by (Radak, Chung, & Goto, 2005). This idea suggests that biological systems respond in a bell-shaped fashion, where a positive adaptive response is experienced when exposed to a stimulus. However, when the exposure becomes too great (i.e. when EIMD impairs function for an extended period) a need to intervene to negate potential negative effects exists. Given that EIMD can shape our fundamental understanding of skeletal muscle adaptation (Hyldahl et al., 2017), ascertaining how nutritional strategies might impact differently on adaptation to damaging resistance and endurance training is important.

<<< FIGURE 2 HERE >>>

5. Future directions

The field of sports nutrition is rapidly growing, and we are gaining greater insights into how nutrition interacts with physiological phenomena that are important for athletic development and performance. However, there is still much to be unveiled regarding nutrition as it relates to muscle damage and repair. Particularly lacking is our understanding of the underpinning

mechanisms of how functional foods and their derivatives exert their effects. Understanding these mechanisms will allow researchers and practitioners to better identify how nutritional interventions may be applied to maximize recovery and avoid performance impairments.

It is also important to understand whether foods with anti-inflammatory properties negatively interfere with the pro-inflammatory phase of muscle repair and consequently blunt the repair process. The same can be said for foods with “antioxidant” properties, as recent research highlights the fundamental importance of oxidative stress in exercise adaptations (Margaritelis et al., 2017). A major challenge to the field will be in defining how nutritional interventions targeted to alleviate muscle damage and accelerate repair should be translated to the real-world setting, in which the aim of nutrition interventions is highly dependent upon the goal of the session and whether it is more important to recover quickly or adapt.

Future studies must employ appropriate test measures when investigating functional foods and muscle function. We have highlighted how important the selection of laboratory assays can be for redox exercise biology studies (Cobley et al., 2017). Given many of the nutritional strategies described here are purported to have an impact on redox processes, particular attention should be paid to assay/method selection.

6. Conclusion

This review sought to provide a concise overview of what EIMD is, its causes and consequences and to critically evaluate potential nutritional strategies to ameliorate muscle damage. It is clear that the aetiology of EIMD is complex and some of the contributing factors are a double-edged sword. On the one hand, oxidative stress and inflammation may amplify tissue damage, but on the other hand both processes play important roles in the resolution of function and in adaptation. With this in mind, the majority of nutritional strategies presented here should be adopted with pragmatism. It is crucial to find the balance between recovery and adaptation and for this reason, a periodised approach to nutrition should yield the greatest benefit for the athlete.

Figure Legends

Figure 1. A) Time course of events following a bout of muscle damaging exercise and B) nutritional interventions that may interact with one or more of these events to augment recovery. Coloured spheres in figure 1B related to figure 1A to denote where the interventions may target. The strength of evidence for these interventions is expressed with stars on a scale of 0-3 depending on the depth and consistency of evidence.

Figure 2. Theoretical framework for the hormesis theory in the context of nutritional interventions for the management of EIMD. This framework suggests that the adaptive response to EIMD presents as a bell-shaped curve; A positive effect of the exercise stress exists to a point when the exposure becomes too great, thereafter there is an impaired adaptive response. Using this theory, we suggest a conceptual region for intervention (yellow text box) where the exercise stress impairs timely return to training & competition or is detrimental to adaptation.

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