

Alma Mater Studiorum Università di Bologna  
Archivio istituzionale della ricerca

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

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

*Published Version:*

Markus I., Constantini K., Hoffman J.R., Bartolomei S., Gepner Y. (2021). Exercise-induced muscle damage: mechanism, assessment and nutritional factors to accelerate recovery. EUROPEAN JOURNAL OF APPLIED PHYSIOLOGY, 121(4), 969-992 [10.1007/s00421-020-04566-4].

*Availability:*

This version is available at: <https://hdl.handle.net/11585/803132> since: 2024-05-21

*Published:*

DOI: <http://doi.org/10.1007/s00421-020-04566-4>

*Terms of use:*

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).  
When citing, please refer to the published version.

(Article begins on next page)

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

3 *Markus I<sup>1\*</sup>, Constantini K<sup>1\*</sup>, Hoffman JR<sup>2</sup>, Bartolomei S<sup>3</sup>, Gepner Y<sup>1</sup>*

4

5 *<sup>1</sup>Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler*  
6 *Faculty of Medicine, and Sylvan Adams Sports Institute, Tel-Aviv University, Tel-Aviv*

7 *<sup>2</sup>Department of Physical Therapy, Ariel University, Israel*

8 *<sup>3</sup>Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy*

9

10 *\* Equal contribution*

11

12 Correspondence to:

13 Yftach Gepner, Ph.D.

14 Department of Epidemiology and Preventive Medicine

15 School of Public Health, Sackler Faculty of Medicine, and Sylvan Adams Sports Institute

16 Tel-Aviv University

17 Tel-Aviv, Israel

18 Tel: +972 733804726

19 Fax: +972 73 3804427

20 E-mail: [gepner@tauex.tau.ac.il](mailto:gepner@tauex.tau.ac.il)

21

22

23 **Abstract**

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

37

38

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

40

41

42

43 **Author contribution:**

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

46

47

48 **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 <sub>2</sub> O <sub>2</sub>	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 <sub>2</sub> max	Maximal oxygen uptake

49

50

51

52 **Declarations:**

53 Funding

54 Non to declare

55

56 Conflict of interest:

57 Non to declare

58

59 Ethics approval

60 Not applicable

61

62 Consent to participate

63 Not applicable

64

65 Consent for publication

66 Not applicable

67

68 Availability of data & material

69 Not applicable

70

71 Code availability

72 Not applicable

73

74

75

76 **Introduction**

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

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



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

149 The effects of endurance exercise, especially training programs that involve a heavy  
150 emphasis on eccentric muscle contractions (e.g. downhill running) on EIMD have been  
151 previously studied (Malm et al. 2004; Smith et al. 2007; Chen et al. 2009; Hayashi et al. 2019).  
152 During eccentric muscle contractions, force is generated by muscle lengthening (Sudo et al.  
153 2015), which normally involves recruiting fewer motor units and requires less energy and  
154 oxygen compared to other forms of contraction such as concentric and isometric contractions  
155 (Abbott et al. 1952). A bout of eccentric exercise, performed at an intensity or volume that an  
156 individual is not accustomed to, can initiate a complex chain of events, resulting in myofibrillar  
157 damage, degradation of structural proteins, membrane damage and destruction of excitation  
158 contraction (E-C) coupling (**Figure 1**). This cascade leads to an accumulation of calcium ions  
159 within the cytoplasm, attraction of inflammatory markers to the site of tissue damage and a  
160 temporary disruption of muscle regeneration (Peake 2019).

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

### 166 **Exercise-Induced Muscle Damage Following Prolonged Endurance Exercise**

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



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

190

191 *[Place Table 1 and Figure 2 here]*

192

### 193 *Inflammatory and muscle protein responses: mechanisms & assessment*

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

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

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

216 The inflammatory response appears to have two phases, which include activation of  
217 both anti- and pro-inflammatory mediators, having antagonistic roles. Upon initial tissue insult  
218 from the exercise stimulus, pro-inflammatory cytokines are activated. This response then leads  
219 to an increase in anti-inflammatory cytokines. The anti-inflammatory markers inhibit the  
220 expression of pro-inflammatory cytokines, thus controlling the magnitude of the inflammatory  
221 process (Dinarello 2000). During the pro-inflammatory phase, cytokines such as interleukin  
222 (IL)-6, IL-8 and tumor necrosis factor (TNF)- $\alpha$  are activated (Ostrowski et al. 1998; Dinarello  
223 2000). TNF- $\alpha$  is involved in muscle regeneration and has a pro-inflammatory role at the site  
224 of cellular damage (Opal and Depalo 2000). IL-6 is a prominent cytokine that has been shown  
225 to increase during and following exercise (Ostrowski et al. 1998; Pedersen and Fischer 2007).  
226 It has both local (i.e. muscular) and systematic effects not only on mediating the local  
227 inflammatory response, but also on energy metabolism (Febbraio and Pedersen 2002; Pedersen  
228 and Fischer 2007). It has been demonstrated that during 2.5h of treadmill running at 75%  
229  $\text{VO}_2\text{max}$ , IL-6 concentrations begin to increase after 30 min of running and peaks immediately  
230 post-exercise (Ostrowski et al. 1998). IL-6 concentrations gradually decrease thereafter,  
231 returning to baseline between 6h to 5 days post-exercise (Ostrowski et al. 1998; Pedersen et al.  
232 2001; Peake et al. 2017).

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

236 damage and cellular necrosis. Both CK and Mb are normally found in skeletal muscle tissue,  
237 and when muscle integrity is disrupted, as occurs during EIMD, these molecules leak into the  
238 circulation (Pedersen and Fischer 2007). Yet, timing of appearance of these muscle damage  
239 markers in the circulation appears to differ. Since Mb is a smaller molecule, its elevation is  
240 generally seen immediately after repeated eccentric contractions, whereas CK is a larger  
241 molecule and therefore takes longer (24-48 hours) to leak out of the cell (Pedersen and Fischer  
242 2007). Despite the different timeline regarding peak appearance in the circulation, changes in  
243 both CK and Mb similarly reflect the extent of muscle damage and are positively correlated to  
244 each other (Febbraio and Pedersen 2002).

245 A variety of external factors, such as type of contraction (eccentric vs. concentric),  
246 duration and intensity of exercise and age can influence the magnitude of the inflammatory  
247 response and release of muscle proteins into the circulation following EIMD caused by aerobic  
248 exercise (Pedersen et al. 2001; Peake et al. 2005, 2017; Peake 2019) . Considering the type of  
249 muscle contraction, the prevalent belief is that eccentric lengthening contractions cause greater  
250 sarcomere damage that subsequently leads to a more severe inflammatory response than  
251 concentric or isometric contractions (Faulkner et al. 1993; Nosaka et al. 2001; Pokora et al.  
252 2014; Peake et al. 2017). For example, Pokora et al. (2014) compared the cytokine and CK  
253 response to 60-min of downhill (i.e. predominantly eccentric) vs. uphill (i.e. predominantly  
254 concentric) running in recreationally active men. The investigators indicated that CK  
255 concentrations were significantly increased immediately and 24h post-exercise only in the  
256 uphill/eccentric group (Pokora et al. 2014). Moreover, although the pro-inflammatory  
257 cytokines IL-1b and TNF- $\alpha$  demonstrated a similar response between groups, IL-6 was  
258 substantially elevated immediately and 24h post-downhill running while only a modest  
259 response was reported following uphill running (Pokora et al. 2014). With regard to exercise  
260 intensity, it has been shown that in men, concentrations of anti-inflammatory cytokines such  
261 as IL-receptor antagonist 1 (Ira) and IL-10 are greater following high intensity running  
262 compared to low intensity running, and these results have also been found after downhill  
263 running (Peake JM et al. 2005). The influence of exercise intensity on the primary  
264 inflammatory response was demonstrated in another study reporting that total circulating  
265 leukocytes and neutrophils were higher in trained runners who ran 60 min at a high intensity  
266 workload (85% maximal oxygen consumption; VO<sub>2</sub>max) in comparison to low intensity (60%  
267 VO<sub>2</sub>max) running immediately and one hour post-exercise (Peake et al. 2004).

268 Evidence examining differences in the inflammatory response following aerobically-  
269 based EIMD between sexes is limited. However, there do appear to be differences in the  
270 recovery response among women during different phases of the menstrual cycle as estrogen  
271 appears to enhance membrane stability, thus minimizing, or at least reducing the extent of  
272 muscle damage (Enns and Tiidus 2010). A study examining circulating cytokine and CK  
273 concentrations in female athletes running for 90 min at 70% VO<sub>2</sub>max reported that IL-6 and  
274 CK concentrations were greater during the mid-follicular phase of the menstrual cycle when  
275 sex hormones (e.g. estrogen and progesterone) are low compared to the mid-luteal phase  
276 (Hackney et al. 2019), however this finding was not specific to EIMD. Clearly, there is gap in  
277 the literature regarding sex differences in the inflammatory response associated with muscle  
278 damage induced by aerobic exercise. In the scant number of studies that assessed EIMD  
279 following aerobic exercise and included both men and women, the results of both sexes were  
280 combined either because the number of women was small (n=1-3; Kyrolainen et al. 2000;  
281 Malm et al. 2004) or because no significant differences were found between sexes (Hayashi et  
282 al. 2019). It should be mentioned that none of these studies (Kyrolainen et al. 2000; Malm et  
283 al. 2004; Hayashi et al. 2019) examined the expression of inflammatory markers. With regards  
284 to rate of recovery following EIMD caused by prolonged/aerobic exercise, future studies  
285 should directly compare the response between men and women, as it has been suggested that  
286 estrogen increases muscle permeability to leukocytes, which, in addition to blunting the extent  
287 of muscle damage, could accelerate muscle healing (Enns and Tiidus 2010).

288 Aging is accompanied by a decline in immune function that is associated with chronic  
289 low-grade inflammation and higher susceptibility for chronic disease, which could negatively  
290 influence the rate of recovery (Chung et al. 2009). Although it has been suggested that resting  
291 cytokine and TNF- $\alpha$  concentrations of elderly athletes are higher in comparison to young  
292 athletes (Tieland et al. 2018), a recent study by Lavin et al. (2020) demonstrated that lifelong  
293 aerobic exercise can negate these age-related effects by enhancing anti-inflammatory and  
294 reducing pro-inflammatory levels at rest and following acute exercise. It still remains to be  
295 determined whether the inflammatory (i.e. cytokine and white blood cell) response to muscle  
296 damage induced by *aerobic* exercise is age dependent. Interestingly, a recent study found that  
297 CK and Mb levels increased to a similar extent in both young and middle-aged trained  
298 individuals after 45 min of downhill running at 65% VO<sub>2</sub>max (Hayashi et al. 2019). However,  
299 this study did not assess inflammatory markers.

300 *Pain and Soreness*

301 EIMD is often associated with muscle soreness, reflected by pain or discomfort of  
302 activated muscles after a novel training stimulus or intense training session (Hody et al. 2019).  
303 Muscle soreness is often characterized by stiffness, muscle sensitivity and local pain (Lewis et  
304 al. 2012). It is thought to be a consequence of micro-trauma to the muscle caused by the strain  
305 and breakdown of the sarcomere (Lewis et al. 2012). The intracellular damage activates an  
306 inflammatory response that may heighten pain receptors, thus causing feelings of soreness,  
307 though the complete mechanism of muscle soreness remains unclear. Most of the research has  
308 focused on exercise in novice populations, which generally results in a heightened level of  
309 soreness, often referred to as delayed onset of muscle soreness or DOMS. This response likely  
310 differs from that seen following an intense exercise session in competitive athletes or even  
311 recreational individuals (Hotfiel et al. 2018). The scientific literature on the mechanisms  
312 associated with DOMS suggests two main pathways for this phenomenon. One mechanism  
313 involves activation of B2-bradykinin receptors, which are released during exercise resulting in  
314 mechanical hyperalgesia (Hody et al. 2019), while the second relates to cyclooxygenase  
315 (COX)-2 and glial cell line-derived neurotrophic factor (Paulsen et al. 2010). When COX-2  
316 inhibitors are provided orally after lengthening (i.e. eccentric) contractions, this treatment  
317 blunts the severity of muscle soreness, supporting the second hypothesis (Murase et al. 2013).  
318 Interestingly, the appearance and severity of DOMS appears to be independent of other markers  
319 of EIMD, including histological changes (Nosaka et al. 2002a). While strength studies  
320 commonly agree that perceived pain is greater after the first bout or resistance exercise versus  
321 a second bout, there is still lack of research regarding endurance/aerobic based EIMD and  
322 reduced muscle soreness in subsequent exercise bouts. In a study by Smith et al. (2007) it was  
323 shown that along with a blunted inflammatory response, participants experienced less severe  
324 soreness and that soreness peaked earlier following a repeated (i.e. second) exercise bout of 60  
325 min of downhill running at 75%  $\text{VO}_2\text{max}$  compared to the first bout. This is generally referred  
326 to as the “*repeated bout affect*” (Nosaka et al. 2001).

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

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

335

### 336 *EIMD following aerobic exercise & performance-related measures*

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

#### 341 *Strength loss*

342 In addition to histological and inflammatory markers, another reliable and valid  
343 approach for assessing muscle damage is the measurement of muscle *function* – i.e. the ability  
344 of the muscle to generate force – often assessed using maximal voluntary isometric or  
345 concentric contractions (Clarkson and Hubal 2002; Byrne et al. 2004; Paulsen et al. 2012)  
346 (**Table 1**). While an abundance of literature regarding muscle strength loss following single-  
347 joint and/or resistance exercise exists, data on strength loss following endurance exercise is  
348 limited (Clarkson et al. 1992). When considering whole-body aerobic-based exercise, strength  
349 loss following downhill running has been attributed to damage to the sarcoplasmic reticulum  
350 and disturbances in Ca<sup>2+</sup> homeostasis within the muscle fiber (Paulsen et al. 2012). This is in  
351 contrast to single-joint eccentric exercises where impairments in neuromuscular performance  
352 and thus strength were suggested to result from compromised conduction velocity of action  
353 potentials across the sarcolemma (Piitulainen et al. 2010), as well as alterations in central  
354 nervous system activity and motor unit recruitment (Prasartwuth et al. 2006; Dartnall et al.  
355 2008; Isner-Horobeti et al. 2013).

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

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

371 In studies focusing on aerobically-based activities only, running – which includes both  
372 concentric and eccentric muscle contractions – is reported to cause a greater degree of muscle  
373 damage and strength loss compared to cycling (mainly concentric contractions) and cross-  
374 country skiing (Millet and Lepers 2004). In a recent study, Hayashi et al. (2019) assessed  
375 various markers of EIMD following 45 min of downhill running at 65%  $\text{VO}_2\text{max}$ , and  
376 examined the effect of sex, age and training status. While the authors did not find differences  
377 in muscle damage markers, including strength loss, between men and women, it was  
378 demonstrated that both training status and age affect the magnitude of strength loss associated  
379 with EIMD following downhill running (Hayashi et al. 2019). Specifically, the group of young  
380 untrained and old trained participants experienced greater reductions in strength 24h post-  
381 exercise compared to a group of young trained individuals (Hayashi et al. 2019). Furthermore,  
382 in terms of recovery of strength, the young trained participants recovered faster than the two  
383 other groups in the first 48h post-downhill running. To the best of our knowledge, no study  
384 has assessed strength loss following aerobic, muscle-damaging exercise in women only.  
385 Moreover, whether there are differences between sexes in strength losses and/or rate of  
386 recovery of strength post endurance-based EIMD is yet to be determined.

### 387 *Running economy & gait mechanics*

388 Running economy refers to the energetic cost (measured as oxygen consumption;  $\text{VO}_2$ )  
389 for a given intensity/speed and is considered to be one of the main determinants of running  
390 performance (Jones and Carter 2000; Joyner and Coyle 2008). A limited number of studies  
391 have investigated the relationship between EIMD following endurance activity and running  
392 economy. The results of these studies have generally been inconclusive (Hamill et al. 1991;  
393 Kyrolainen et al. 2000; Braun and Dutto 2003; Chen et al. 2007). For example, some  
394 investigations have reported a 3-7% increase in  $\text{VO}_2$  for a given intensity for three days  
395 following endurance exercise (Braun and Dutto 2003; Chen et al. 2007), while others reported  
396 that downhill running impaired running economy only immediately post-exercise (Kyrolainen  
397 et al. 2000) or had no effect on running economy (Hamill et al. 1991). These discrepancies

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

407 A number of potential mechanisms have been offered to explain EIMD-related  
408 impairments in running economy. Chen and colleagues (2007, 2008) indicated that changes  
409 in running economy were more pronounced with increasing intensity of exercise (i.e. greater  
410 impairment in running economy at 90%  $\text{VO}_2\text{max}$  compared to 80%  $\text{VO}_2\text{max}$ , and no change  
411 at 70%  $\text{VO}_2\text{max}$ ). These investigators suggested that alterations in the running economy of  
412 untrained individuals may be related to greater recruitment of muscle fibers at higher  
413 intensities, likely changing the participant's running kinematics. Changes in running economy  
414 has also been proposed by Braun and Dutto (2003) who studied a group of highly trained  
415 endurance men and reported an association between changes in stride length and running  
416 economy 48h following downhill running. This finding is not surprising considering that  $\text{VO}_2$   
417 of experienced athletes has been shown to increase in a U-shape manner when stride length is  
418 either shorter or longer than preferred (Hunter and Smith 2007). Yet, this is not a universal  
419 finding and could be related to training status, as others observed changes in lower body  
420 kinematics without changes in running economy in recreational female runners after downhill  
421 running (Hamill et al. 1991). Taken together, it is possible that a combination of altered  
422 kinematics, impaired range of motion, and strength loss following prolonged exercise,  
423 especially that of a greater eccentric nature, leads to an increased recruitment of muscle fibers.  
424 This in turn will increase metabolic/energetic requirements and impair running economy  
425 (Braun and Dutto 2003; Chen et al. 2007; 2008). Given that sex, age and training status alter  
426 various aspects of EIMD, it appears reasonable to assume that these factors would also  
427 influence the magnitude of changes in recovery rate (i.e. return to baseline) of running economy  
428 and gait mechanics following aerobic-based EIMD. However, to the best of our knowledge,  
429 there is limited evidence providing a clear consensus.

430 *Performance*



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

444

#### 445 **Exercise Induced Muscle Damage Following Resistance Exercise**

446 It has been well documented that resistance exercise (RE) may induce muscle damage  
447 resulting in inflammation, swelling and impairments in performance. Optimizing the recovery  
448 process following RE represents a crucial factor for strength and power athletes aimed at  
449 increasing their muscle mass and improving their performance. RE, including eccentric  
450 contractions, involve the active lengthening of sarcomeres and has been associated with greater  
451 disruption of contractile and structural elements (Newham et al. 1983; Enoka 1996) compared  
452 to concentric-only RE. Muscle damage resulting from eccentric RE, and in particular when  
453 the load applied to the muscle exceeds the force produced by the muscle itself, causes an  
454 induced overstretching of sarcomeres beyond filament overlap (Peake et al. 2017). This results  
455 in a disruption of Z lines causing sarcomere streaming (Friden et al. 1983). Damage also  
456 involves myofiber architecture, the sarcoplasmic reticulum and the sarcolemma (Clarkson  
457 1997).

458 Several experimental studies showed that eccentric muscle contractions activate a  
459 smaller number of motor units compared to concentric contractions, with the former also  
460 characterized by lower motor unit discharge rates (Nardone et al. 1989; Del Valle and Thomas  
461 2005; Douglas et al. 2017). A different pattern of motor unit activation in eccentric compared  
462 to concentric contractions induces a selective recruitment of high-threshold motor units

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

468 Muscle damage has also been reported following isometric RE (Allen et al. 2018).  
469 Muscle damage of elbow flexors and subsequent performance impairments were particularly  
470 evident when isometric exercise was performed by untrained individuals using a long muscle  
471 length obtained at an elbow angle of 155° compared to a shorter muscle length obtained at an  
472 elbow angle of 90° (Allen et al. 2018). Even if the muscle is only able to produce lower levels  
473 of force at a longer length, these isometric muscle contractions induce greater damage  
474 compared to stronger isometric contractions performed at a shorter muscle length (Allen et al.  
475 2018; Lieber and Friden 1993). Muscle damage induced by isometric contractions appears  
476 related more to muscle length than to muscle tension (Allen et al. 2018; Jones et al. 1989).  
477 Studies conducted on arm flexor muscles suggest that this phenomenon may be related to the  
478 non-uniform lengthening of sarcomeres during the isometric contraction (Allen et al. 2018).  
479 Muscle damage following isometric RE however, can be minimized by using muscle lengths  
480 below the optimum and submaximal force productions (Allen et al. 2018; Lieber and Friden  
481 1993).

482 Despite low levels of muscle damage being detected during concentric only RE  
483 (Lavender and Nosaka 2006), a higher metabolic stress has been associated with concentric-  
484 only compared to eccentric-only RE (Kraemer et al. 2004; Goto et al. 2009; Beaven et al. 2014;  
485 Paulus et al. 2019). Metabolic stress induced by RE is related to an exercise-induced  
486 accumulation of metabolites, particularly lactate, inorganic phosphate and H<sup>+</sup> (Suga et al.  
487 2009). This metabolic stress is maximized when anaerobic glycolysis is the predominant  
488 energy system and exercise lasts between 15-120 s (MacDougall et al. 1999).

489 Most RE programs performed by athletes and sport enthusiasts include both eccentric  
490 and concentric contractions. Metabolic stress, mainly induced by concentric contractions, may  
491 amplify muscle damage and inflammation produced by the eccentric contractions (Tee et al.  
492 2007). This combination may also provide the appropriate stimulus to enhance tissue repair  
493 and adaptation. The results of several investigations have supported the role of metabolite  
494 accumulation for muscle growth (Rooney et al. 1994; Schoenfeld 2010, 2013). Metabolic  
495 stress may promote muscle hypertrophy via influencing muscle fiber recruitment, hormonal

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

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

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

529 training status, it has been suggested that strength and power athletes demonstrate a greater  
530 recruitment of fast-twitch motor units and larger decreases in EMG activity during fatiguing  
531 high intensity resistance exercise compared to untrained individuals (Ahtiainen and Häkkinen  
532 2009). A long lasting depression of the excitation-contraction coupling were also registered up  
533 to 22 h following a high intensity resistance training protocol for the lower body in strength  
534 athletes (Raastad and Hallén 2000). It appears that during fatiguing exercise the trained  
535 strength/power athlete is able to recruit additional motor units to compensate for fatigued  
536 fibers, which is not observed in the untrained individuals. However, this compensation may  
537 reduce muscle contraction capability during the recovery period.

#### 538 *Influence of sex on the recovery phase following resistance exercise*

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

562 The exercise-induced inflammatory response may contribute to secondary muscle  
563 damage, caused by excessive macrophage accumulation and muscle swelling, and may slow  
564 down the recovery rate following eccentric exercise (Sayers and Clarkson 2001). The blunted  
565 inflammatory response observed in untrained women (Stupka et al. 2000; Clarkson and Hubal  
566 2001) and the antioxidant function of estrogens (Tiidus 1995; Komulainen et al. 1999), may be  
567 part of the physiological mechanism preventing the secondary muscle damage in women and  
568 accelerating the recovery process. The lower magnitude of inflammatory response and faster  
569 recovery in women following damaging protocols of RE may also be linked to sex differences  
570 in the distribution of muscle fiber-types (e.g., greater percent of type II fibers in men compared  
571 to women) (Fulco et al. 1999). Chronic exposure to RE, however, may drastically influence  
572 the individual's acute inflammatory response to single bouts of RE. The paucity of research  
573 involving highly resistance trained women make it difficult to draw conclusions about RE-  
574 induced inflammatory responses occurring in female strength and power athletes.

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

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

593 *Performance assessment during the recovery phase following resistance exercise*

594 A number of anthropometric, biochemical, physical performance and subjective  
595 markers have been used to monitor the recovery phase following RE (Clarkson and Hubal  
596 2002). Performance impairments following high intensity RE may be considered one of the  
597 most important indicators of muscle fatigue (Behm et al. 2004) and muscle damage (Warren et  
598 al. 1999). Isometric, isokinetic and dynamic strength and power measurements have been  
599 extensively used to assess the recovery process following various exercise stresses. Several  
600 investigations reported different time courses of recovery of different strength components  
601 following RE (Molina and Denadai 2012). In particular, ballistic muscle actions, such as  
602 countermovement jump (CMJ) and bench press throw, have shown a higher sensitivity for  
603 fatigue and muscle damage compared to both isometric (Raeder et al. 2016; Kennedy and  
604 Drake 2018; Aben et al. 2020) and isokinetic assessments (Bartolomei et al. 2019b).  
605 Significant reductions in CMJ power has been observed up to 48h following a HV squat  
606 protocol in resistance trained men (Bartolomei et al. 2017; Kennedy and Drake 2018).  
607 Interestingly, the drop in CMJ performance was correlated with plasma levels of IL-6 and with  
608 muscle swelling measured via ultrasound (Bartolomei et al. 2019b). CMJ represents a valid  
609 and reliable tool to assess lower-body recovery following both RE and other highly demanding  
610 activities such as soccer matches (Hoffman et al. 2003; Andersson et al. 2008). However,  
611 others have reported a greater sensitivity of squat jump (SJ) testing for assessing RE-induced  
612 muscle damage compared to both CMJ and drop jump (DJ) assessments (Byrne and Eston  
613 2002; Jakeman et al. 2010). The stretch-shortening cycle that characterizes both CMJ and DJ  
614 may attenuate the detrimental effect of HV RE on jump performance (Byrne and Eston 2002).  
615 Similarly, bench press throw power has been successfully used to monitor the recovery of the  
616 upper body (Bartolomei et al. 2019). This parameter was significantly reduced 24h following  
617 a HV bench press protocol in trained men and returned to baseline 48h following the exercise  
618 bout (Bartolomei et al. 2019b). Vertical jump and bench press throw assessments represent  
619 complex multi-joint assessments requiring a high level of neuromuscular activation and motor  
620 unit coordination. Both parameters may be affected by fatigue induced by RE.

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

627 has been detected in untrained individuals compared to highly trained men (Newton et al.  
628 2008). Trained individuals appear to be more resilient than novices regarding EIMD and  
629 appear to recover faster (Clarkson et al. 1992; McHugh 2003). In support, faster recovery rates  
630 of isometric force and power were noted following a single bout of HV RE in previously  
631 untrained individuals following a 7-week resistance training program compared to pre-training  
632 recovery rates (Izquierdo et al. 2009). Muscle damage may have different effects on  
633 performance depending on the speed of the movement during isokinetic assessments. Greater  
634 and more protracted reductions in torque have been noted when torque output was assessed at  
635 slow velocity speeds (60°/s) compared to high velocity speeds (180-270°/s) (Komulainen et al.  
636 1999; Molina and Denadai 2012). Isokinetic measurements, however, are highly velocity  
637 dependent, and should be performed as close as possible to the muscle contraction velocity  
638 used during training (Warren et al. 1999).

639 Recovery time may also vary between different muscle groups of the same individual.  
640 In one study, a similar decline in performance was noted immediately post-workout, but a faster  
641 recovery rate of initial peak torque was observed in the triceps compared to pectoral muscles  
642 following a HV bench press protocol consisting of 8 sets of 10 reps at 90% of the participant's  
643 10-RM (Ferreira et al. 2017b). Muscle mass and muscle architecture may also influence the  
644 recovery rate following resistance exercise. Large muscles such as the pectoralis major may  
645 be more prone to EIMD compared with pennate muscles such as triceps brachii, characterized  
646 by shorter fascicle lengths (Nosaka et al. 2002b). In addition, RE may elicit a more pronounced  
647 muscle damage, soreness and performance reductions in muscles with higher percentages of  
648 fast-twitch compared to slow twitch fibers (Jansson and Sylvén 1985; Anderson and Neuffer  
649 2006; Quindry et al. 2011).

## 650 **Nutritional Considerations for Enhancing the Recovery Response to Exercise**

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

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

### 662 *The Effect of Macronutrient Composition of Daily Diet on Recovery Indices of Exercise*

663 In a Position Stand emanating from the Academy of Nutrition and Dietetics, Dietitians  
664 of Canada (DC), and the American College of Sports Medicine (ACSM) no specific dietary  
665 recommendation for competitive athletes was provided (Thomas et al. 2016). Instead, the  
666 authors indicated that energy intake is dependent on the energy requirements of exercise and  
667 provided ranges for macronutrient intake. It was suggested that fat intakes typically range from  
668 20% - 35% of total energy consumption, while carbohydrate intake typically ranges from 3 to  
669 10 g·kg<sup>-1</sup> body mass per day (and up to 12 g·kg<sup>-1</sup> body mass per day for extreme and prolonged  
670 activities). It was further suggested that daily protein intake typically ranges from 1.2 to 2.0  
671 g·kg<sup>-1</sup> body mass per day. However, no specific recommendation or comparison was made in  
672 regard to the most appropriate macronutrient intake that can benefit exercise recovery. The  
673 dietary habits of competitive and recreational athletes appear to be quite variable, ranging from  
674 athletes that follow a traditional omnivore diet to those that prefer a more extreme diet such as  
675 vegetarian, ketogenic (high fat low carbohydrate) or carnivore (very high protein). The focus  
676 generally is on a specific macronutrient (e.g., fats or proteins) or a dietary restriction (e.g., no  
677 meat or animal products).

### 678 *Vegetarian and Omnivore Dietary Comparisons*

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



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

695 In one of the few studies comparing the oxidative stress response between omnivores,  
696 vegans and lacto-ovo (i.e. consume both milk and egg products) vegetarians, Nebl and  
697 colleagues (2019) reported significant increases from rest in malondialdehyde (MDA), a  
698 marker of lipid peroxidation and oxidative stress, in both lacto-ovo vegetarians (+24%) and  
699 vegans (+15%), while no significant change (+9%) was noted in omnivores. Although no  
700 differences were noted in antioxidant and vitamin content between these diets, there was still a  
701 difference in the oxidative stress response between these groups. The authors suggested that  
702 this was likely related to differences in creatine content of the three diets, with omnivores  
703 consuming a significantly greater amount of creatine from their meat consumption. In contrast,  
704 an animal study comparing a traditional Western diet to the Daniel fast, which is a strict vegan  
705 diet, reported that the diets combined with exercise resulted in significant improvements in  
706 time to exhaustion, but that the improvement in animals consuming the vegan diet was  
707 significantly greater (+81%) than animals consuming the Western diet (+36%) (Bloomer et al.  
708 2018). Although the oxidative stress response was significantly greater in animals consuming  
709 the Western diet, no differences were reported in any of the inflammatory cytokine levels.

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

725 bioavailability of antioxidant molecules such as polyphenols in the small intestine, and  
726 subsequently cause an increase in oxidative status and slower recovery following exercise. The  
727 results observed in both lacto-ovo-vegetarians and omnivores were consistent with previous  
728 research reporting similar FRAP values in individuals consuming these diets (Szeto et al.  
729 2004). In addition, lower resting C-reactive protein concentrations, an acute phase protein used  
730 as a marker of inflammation, were also noted in both lacto-ovo-vegetarians and omnivores  
731 compared to vegetarians (Vanacore et al. 2018).

732         There appears to be little to no support in the scientific literature regarding the benefits  
733 of a vegetarian diet in enhancing exercise recovery. Although there may be health benefits  
734 associated with this dietary model in various population groups, this is likely not the primary  
735 consideration for healthy competitive athletes. An additional concern for the vegetarian would  
736 be in the quality of the protein consumed (Hoffman and Falvo 2004). Without consuming  
737 animal protein, the quality of protein intake for a vegetarian may be substantially lower than  
738 an omnivore. Although the vegetarian athlete can compensate with a greater focus of soy  
739 protein, the diet would still be low in creatine and carnosine content, which may have important  
740 benefits in performance and recovery, especially for the strength/power athlete (Hoffman  
741 2016a).

#### 742 *Ketogenic and Omnivore Dietary Comparisons*

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

750         Volek and colleagues (2016) compared a low-carbohydrate diet to a high carbohydrate  
751 diet in elite male ultra-endurance athletes performing a maximal graded exercise test and a 180  
752 min submaximal run at 64%  $VO_2$ max. Participants had consumed their specific diets for at  
753 least 6-months prior to study enrollment. The results of the study indicated that peak fat  
754 oxidation was 2.3-fold higher in the low-carbohydrate group and it occurred at a higher  
755 percentage of  $VO_2$ max ( $70.3 \pm 6.3\%$  vs  $54.9 \pm 7.8\%$ ;  $p < 0.001$ ) than in the high-carbohydrate  
756 group. In addition, fat oxidation during submaximal exercise was 59% higher in the low-

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

762         The low-carbohydrate content of the ketogenic diet has been a major concern for many  
763 individuals, as the standard belief was that maximizing glycogen storage was critical for  
764 exercise performance. Traditional thought believes that for an athlete that competes or trains  
765 on a daily basis, glycogen replenishment would be a critical factor relating to exercise recovery.  
766 However, evidence does suggest that metabolic adaptations resulting from low-carbohydrate  
767 diets do compensate for low muscle glycogen content (Paoli et al. 2015). Low-carbohydrate,  
768 high-fat diets usually lead to ketosis when the liver oxidizes high concentrations of non-  
769 esterified fatty acids (NEFA) into ketone bodies (McPherson and McEneny 2012). This  
770 process of ketogenesis occurs primarily within the liver's mitochondrial matrix (Highton et al.  
771 2009). In general, when glycogen stores are depleted glucose levels are maintained through  
772 the process of gluconeogenesis resulting in the conversion of molecules with carbon skeletons  
773 such as amino acids and lactate to glucose (Fournier et al. 2002). In addition, glycerol derived  
774 from the metabolism of triglycerides can also be a source of glucose (Massicotte et al. 2006).  
775 These two sources appear to compensate for the low carbohydrate intake. Interestingly,  
776 compared with glucose, the energy produced from ketone bodies appears to be greater (Paoli  
777 et al. 2015).

778         An additional effect associated with the ketogenic diet is the increased production of  
779 low levels of reactive oxygen species molecules such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and 4-  
780 hydroxynonenal (4-HNE) (Milder and Patel 2012). This may provide a potential protective  
781 mechanism during high intensity training. Huang and colleagues (2018) compared the effect  
782 of an 8-week ketogenic diet and high-carbohydrate diet on the oxidative stress response to  
783 exhaustive exercise in rats. Animals in both groups experienced fatigue following the exercise  
784 protocol, however the animals that consumed the ketogenic diet appeared to recover faster (e.g.  
785 greater movement) than the control (high-carbohydrate fed) animals. In addition, markers of  
786 liver damage (i.e. aspartate transaminase and alanine transaminase) and skeletal muscle  
787 damage (i.e. creatine kinase) were significantly lower in the ketogenic group than the control  
788 group. No differences were noted in lipid peroxidation indicating no difference in the oxidative  
789 stress response to exhaustive exercise was observed between the two diets. However, hepatic

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

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

805

#### 806 *The Effect of Dietary Supplement Intervention on Recovery Indices of Exercise*

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

#### 813 Protein

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

822 2017). Several studies have reported a decrease in the extent of muscle damage, attenuation in  
823 force decrements, and enhanced recovery resulting from protein ingestion following resistance  
824 exercise (Kraemer et al. 2006; Hoffman et al. 2007; Hulmi et al. 2009; Cooke et al. 2010;  
825 Hoffman 2016b). When protein is consumed prior to, and immediately following a bout of  
826 resistance exercise an increase in messenger RNA (mRNA) expression is observed, preventing  
827 a post-exercise decrease in myogenin mRNA expression (Hulmi et al. 2009). This is thought  
828 to accelerate muscle adaptation and enhance muscle recovery from the workout.

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

851

852 β-Alanine

853  $\beta$ -alanine is a non-proteogenic amino acid. When ingested it combines with histidine  
854 within skeletal muscle and other organs to form carnosine.  $\beta$ -alanine is considered to be the  
855 rate-limiting step in muscle carnosine synthesis (Harris et al. 2006). Carnosine is a highly  
856 effective intracellular pH buffer that enables a greater tolerance of sustained anaerobic activity  
857 (Hoffman et al. 2018). Besides serving as an intracellular buffer, carnosine has also been  
858 suggested to act as an antioxidant (Kohen et al. 1988; Boldyrev et al. 2004; 2010). Carnosine  
859 has been demonstrated to scavenge reactive oxygen species and react directly with superoxide  
860 anions and peroxy radicals in vitro (Boldyrev et al. 2013). In addition, carnosine has been  
861 shown to behave as an ion-chelating agent, preventing ions such as copper and zinc from  
862 excessive accumulation, which may lead to lipid peroxidation and subsequent cellular damage  
863 (Trombley et al. 2000). Carnosine has also been reported to act as an anti-glycating agent,  
864 which also prevents the formation of advanced lipid oxidation end-products (Boldyrev et al.  
865 2013). Carnosine's physiological role clearly goes beyond those of muscle-buffering capacity  
866 and suggest that elevations in carnosine levels may enhance exercise recovery.

867 Unfortunately, investigations examining the role of  $\beta$ -alanine supplementation and  
868 oxidative stress have been limited. In one of the first human studies examining the effect of  $\beta$ -  
869 alanine supplementation on markers of oxidative stress, Smith and colleagues in a pair of  
870 studies (Smith et al. 2012; Smith-Ryan et al. 2014) investigated 28-days of  $\beta$ -alanine (4.8 g·day<sup>-1</sup>)  
871 during a 40-minute treadmill run in moderately trained college-aged men and women. No  
872 differences were noted in any of the antioxidant markers suggesting that  $\beta$ -alanine  
873 supplementation was unable to attenuate the oxidative stress response. However, a single 40-  
874 min treadmill run may not be the appropriate stressor to stimulate a large oxidative stress  
875 response. Interestingly, there have been several investigations, albeit in animal models,  
876 indicating that  $\beta$ -alanine may have a role as an antioxidant in the brain. Murakami and Furuse  
877 (2010) reported significant elevations of carnosine content in the cerebral cortex and  
878 hypothalamus of mice that supplemented with  $\beta$ -alanine for 5-weeks. Increases in brain  
879 carnosine were associated increases in brain derived neurotrophic factor (BDNF), and a  
880 decrease in 5-hydroxyindoleacetic acid concentrations, a metabolite of serotonin. These  
881 changes also corresponded to reduced anxiety. Subsequent investigations have shown that  
882 elevations in hippocampal carnosine content resulting from  $\beta$ -alanine ingestion can increase  
883 resiliency in rodents exposed to either a predator scent stress (PSS) (e.g., an animal model of  
884 post-traumatic stress disorder, PTSD) or a low-pressure blast wave (e.g., an animal model of  
885 mild traumatic brain injury, mTBI) (Hoffman et al. 2015, 2017a). Changes in brain carnosine

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

#### 898 Creatine

899 Creatine is a nitrogenous organic compound that is synthesized from the amino acids  
900 glycine, arginine and methionine primarily in the liver. It can also be synthesized in smaller  
901 amounts in both the kidneys and pancreas. Creatine can also be consumed in the diet with high  
902 concentrations found in both meat and fish, with approximately 525 mg of creatine found in  
903 100 g of uncooked red meat (Mateescu et al. 2012). Approximately 98% of creatine is stored  
904 within skeletal muscle in either its free form (40%) or in its phosphorylated form (60%)  
905 (Heymsfield et al. 1983). The efficacy of creatine supplementation in regards to strength and  
906 power performance has been well documented in numerous studies over the past 20-years  
907 (Hoffman 2016b; Kreider et al. 2017).

908 In addition to its ergogenic ability, creatine supplementation has also been suggested to  
909 enhance recovery from exercise (Kreider et al. 2017). Interestingly, creatine has been reported  
910 to enhance glycogen replenishment following exhaustive exercise (Nelson et al. 2001). It has  
911 been suggested that creatine induced increases in cell volume may be the mechanism  
912 responsible for augmenting glycogen synthesis. This was supported by Van Loon and  
913 colleagues (2004) who reported an association between an increase in muscle creatine (31%)  
914 and the change in glycogen storage (18 %) following 5-days of creatine supplementation. Later  
915 research confirmed these findings but also indicated that greater muscle glycogen accumulation  
916 (81%) occurred primarily within 24-hours of exhaustive exercise and was unrelated to changes  
917 in muscle creatine (Roberts et al. 2016).

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

937 Creatine supplementation has also been shown to reduce muscle damage and  
938 inflammatory markers following a 30-km road race in competitive marathoners (Santos et al.,  
939 2004). Similar to other investigations, participants were provided 20 g of creatine monohydrate  
940 per day for 5 days. Blood was obtained immediately prior to- and 24-hours following the race.  
941 Although differences in creatine kinase were not statistically different, there was still a 19.2%  
942 lower response in runners that supplemented with creatine compared to placebo. However,  
943 significantly lower lactate dehydrogenase (38%), prostaglandin E2 (66.5%) and TNF $\alpha$  (33.8%)  
944 concentrations were noted in the creatine group suggesting a reduction in muscle damage and  
945 inflammation resulting from creatine supplementation. These results were supported by others  
946 examining competitive soccer players performing repeated sprints (Deminice et al. 2013).  
947 Following 7-days of creatine supplementation (20 g per day) the soccer players performed two  
948 consecutive anaerobic sprint tests consisting of six 35-m sprint runs at maximum speed with  
949 10 sec rest between them. A 2-minute recovery period was provided between each sprint test.  
950 Blood markers of muscle damage, inflammation and oxidative stress were collected just prior



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

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

### 963 Polyphenols

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

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

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

993         Investigations examining the effect of polyphenol supplementation (1000 mg/day  
994 quercetin for 3 weeks) on high volume exercise (3 days of 2.5-hr per day at 65% VO<sub>2</sub>max)  
995 (Meeusen et al. 2013) and ultra-endurance racing (160 km) (Nieman et al. 2007) have reported  
996 no differences compared to placebo in the inflammatory and oxidative stress response to  
997 exercise. In contrast, Arent and colleagues (2010) examining 9-days of polyphenol  
998 supplementation (1760 mg of black tea extract) reported an improved recovery and a reduction  
999 in oxidative stress and muscle soreness to an acute high-intensity cycle ergometer interval  
1000 program compared to placebo. It appears that polyphenol supplementation may have a greater  
1001 effect on the recovery response during high intensity exercise compared to high volume  
1002 exercise.

1003

1004

1005 **Conclusion**

1006           The study of exercise recovery is quite complex as a multitude of factors such as age,  
1007 sex, training experience, muscle fiber type and type of activity performed (i.e., endurance  
1008 versus resistance exercise) can influence interpretation. Thus, it is important to provide context  
1009 to such investigations. In addition, there is an extensive array of potential areas of investigation  
1010 that involve different degrees of sensitivity and complexity as it relates to exercise recovery.  
1011 Investigations of recovery have ranged from performance outcomes to molecular examination  
1012 of cellular signaling systems describing potential mechanisms of recovery. This broad array  
1013 of study creates a challenge in providing an encompassing review of the physiological question  
1014 of muscle damage and exercise recovery. As such, it was the primary focus of this review to  
1015 examine the effects of EIMD and subsequent recovery in recreational and competitive  
1016 athletes. In addition, mechanisms responsible for these effects were discussed, including  
1017 invasive and non-invasive techniques used to assess EIMD. Monitoring the recovery process  
1018 using validated tools for performance measurement may represent key factors in understanding  
1019 recovery of different components of performance.

1020           A focus of this review included discussion on the role of diet and nutritional  
1021 supplementation in accelerating recovery from exercise. There does not appear to be any  
1022 consensus on a specific diet being advantageous with regards to recovery compared to others.  
1023 However, there is evidence to suggest that the use of several of the dietary supplements  
1024 discussed in this review (e.g., protein, creatine and polyphenols) are efficacious in enhancing  
1025 recovery from both endurance and strength/power exercise. There is some interesting evidence  
1026 in animal studies regarding elevated carnosine levels resulting from  $\beta$ -alanine supplementation  
1027 and enhanced antioxidant status that has been reported to coincide with an attenuated  
1028 inflammatory response. However, further research still appears necessary regarding  $\beta$ -alanine  
1029 and its role in recovery from exercise.

1030

1031 **References:**

- 1032 Abbott BC, Bigland B, Ritchie JM (1952) The physiological cost of negative work. *J Physiol*  
1033 117:380–390. <https://doi.org/10.1113/jphysiol.1952.sp004755>
- 1034 Aben HGJ, Hills SP, Higgins D, et al (2020) The Reliability of Neuromuscular and  
1035 Perceptual Measures Used to Profile Recovery, and the Time-Course of Such Responses  
1036 Following Academy Rugby League Match-Play. *Sports* 8:73.  
1037 <https://doi.org/10.3390/sports8050073>
- 1038 Ahtiainen JP, Häkkinen K (2009) Strength athletes are capable to produce greater muscle  
1039 activation and neural fatigue during high-intensity resistance exercise than nonathletes. *J*  
1040 *Strength Cond Res* 23:1129–1134. <https://doi.org/10.1519/JSC.0b013e3181aa1b72>
- 1041 Allen J, Sun Y, Woods JA (2015) Exercise and the Regulation of Inflammatory Responses.  
1042 *Prog Mol Biol Transl Sci* 135:337–354. <https://doi.org/10.1016/bs.pmbts.2015.07.003>
- 1043 Allen TJ, Jones T, Tsay A, et al (2018) Muscle damage produced by isometric contractions in  
1044 human elbow flexors. *J Appl Physiol* 124:388–399.  
1045 <https://doi.org/10.1152/jappphysiol.00535.2017>
- 1046 Anderson EJ, Neuffer PD (2006) Type II skeletal myofibers possess unique properties that  
1047 potentiate mitochondrial H<sub>2</sub>O<sub>2</sub> generation. *Am J Physiol - Cell Physiol* 290:.  
1048 <https://doi.org/10.1152/ajpcell.00402.2005>
- 1049 Andersson H, Raastad T, Nilsson J, et al (2008) Neuromuscular fatigue and recovery in elite  
1050 female soccer: Effects of active recovery. *Med Sci Sports Exerc* 40:372–380.  
1051 <https://doi.org/10.1249/mss.0b013e31815b8497>
- 1052 Arent SM, Senso M, Golem DL, McKeever KH (2010) The effects of theaflavin-enriched  
1053 black tea extract on muscle soreness, oxidative stress, inflammation, and endocrine  
1054 responses to acute anaerobic interval training: A randomized, double-blind, crossover  
1055 study. *J Int Soc Sports Nutr* 7:.  
<https://doi.org/10.1186/1550-2783-7-11>
- 1056 Arnhold J, Flemmig J (2010) Human myeloperoxidase in innate and acquired immunity.  
1057 *Arch. Biochem. Biophys.* 500:92–106
- 1058 Arroyo E, Jajtner AR (2019) Vitamins and minerals. In: *Dietary Supplementation in Sport*  
1059 *and Exercise*. Routledge, Milton Park, Abingdon, Oxon ; New York, NY : Routledge,  
1060 2019. [Includes bibliographical references and index., pp 22–46
- 1061 Arroyo E, Wells AJ, Gordon JA, et al (2017) Tumor necrosis factor-alpha and soluble TNF-  
1062 alpha receptor responses in young vs. middle-aged males following eccentric exercise.  
1063 *Exp Gerontol* 100:28–35. <https://doi.org/10.1016/j.exger.2017.10.012>
- 1064 Assumpção C de O, Lima LCR, Oliveira FBD, et al (2013) Exercise-Induced Muscle  
1065 Damage and Running Economy in Humans. *ScientificWorldJournal*
- 1066 Baird MF, Graham SM, Baker JS, et al (2012) Creatine-Kinase-and Exercise-Related Muscle  
1067 Damage Implications for Muscle Performance and Recovery. *J Nutr Metab* 2012:13.  
1068 <https://doi.org/10.1155/2012/960363>

- 1069 Bartolomei S, Sadres E, Church DD, et al (2017) Comparison of the recovery response from  
1070 high-intensity and high-volume resistance exercise in trained men. *Eur J Appl Physiol*  
1071 117:1287–1298. <https://doi.org/10.1007/s00421-017-3598-9>
- 1072 Bartolomei S, Totti V, Griggio F, et al (2019a) Upper-Body Resistance Exercise Reduces  
1073 Time to Recover After a High-Volume Bench Press Protocol in Resistance-Trained  
1074 Men. *J Strength Cond Res*
- 1075 Bartolomei S, Totti V, Nigro F, et al (2019b) A comparison between the recovery responses  
1076 following an eccentrically loaded bench press protocol Vs. regular loading in highly  
1077 trained men. *J Hum Kinet* 68:59–67. <https://doi.org/10.2478/hukin-2019-0056>
- 1078 Baumert P, Lake MJ, Stewart CE, et al (2016) Genetic variation and exercise-induced muscle  
1079 damage: implications for athletic performance, injury and ageing. *Eur. J. Appl. Physiol.*  
1080 116:1595–1625
- 1081 Beaven CM, Willis SJ, Cook CJ, Holmberg H-C (2014) Physiological Comparison of  
1082 Concentric and Eccentric Arm Cycling in Males and Females. *PLoS One* 9:e112079.  
1083 <https://doi.org/10.1371/journal.pone.0112079>
- 1084 Behm DG, Button DC, Barbour G, et al (2004) Conflicting effects of fatigue and potentiation  
1085 on voluntary force. *J Strength Cond Res* 18:365–372. <https://doi.org/10.1519/R-12982.1>
- 1086 Berry DB, You S, Warner J, et al (2017) A 3D Tissue-Printing Approach for Validation of  
1087 Diffusion Tensor Imaging in Skeletal Muscle. *Tissue Eng Part A* 23:980–988.  
1088 <https://doi.org/10.1089/ten.tea.2016.0438>
- 1089 Bessa AL, Oliveira VN, G. Agostini G, et al (2016) Exercise Intensity and Recovery. *J*  
1090 *Strength Cond Res* 30:311–319. <https://doi.org/10.1519/JSC.0b013e31828f1ee9>
- 1091 Beyer KS, Stout JR, Fukuda DH, et al (2017) Impact of polyphenol supplementation on acute  
1092 and chronic response to resistance training. *J Strength Cond Res* 31:2945–2954.  
1093 <https://doi.org/10.1519/JSC.0000000000002104>
- 1094 Biglands JD, Grainger AJ, Robinson P, et al (2020) MRI in acute muscle tears in athletes: can  
1095 quantitative T2 and DTI predict return to play better than visual assessment? *Eur Radiol*  
1096 1–11. <https://doi.org/10.1007/s00330-020-06999-z>
- 1097 Black CD, Dobson RM (2013) Prior eccentric exercise augments muscle pain and perception  
1098 of effort during cycling exercise. *Clin J Pain* 29:443–449.  
1099 <https://doi.org/10.1097/AJP.0b013e318262ddfe>
- 1100 Bloomer R, Schriefer J, Gunnels T, et al (2018) Nutrient Intake and Physical Exercise  
1101 Significantly Impact Physical Performance, Body Composition, Blood Lipids, Oxidative  
1102 Stress, and Inflammation in Male Rats. *Nutrients* 10:1109.  
1103 <https://doi.org/10.3390/nu10081109>
- 1104 Bloomer RJ, Goldfarb AH, Wideman L, et al (2005) Effects of Acute Aerobic and Anaerobic  
1105 Exercise on Blood Markers of Oxidative Stress. *J Strength Cond Res* 19:276.  
1106 <https://doi.org/10.1519/14823.1>
- 1107 Boirie Y, Dangin M, Gachon P, et al (1997) Slow and fast dietary proteins differently

- 1108 modulate postprandial protein accretion. *Proc Natl Acad Sci U S A* 94:14930–14935.  
1109 <https://doi.org/10.1073/pnas.94.26.14930>
- 1110 Boldyrev A, Bulygina E, Leinsoo T, et al (2004) Protection of neuronal cells against reactive  
1111 oxygen species by carnosine and related compounds. *Comp Biochem Physiol - B*  
1112 *Biochem Mol Biol* 137:81–88. <https://doi.org/10.1016/j.cbpc.2003.10.008>
- 1113 Boldyrev AA, Aldini G, Derave W (2013) Physiology and pathophysiology of carnosine.  
1114 *Physiol Rev* 93:1803–1845. <https://doi.org/10.1152/physrev.00039.2012>
- 1115 Boldyrev AA, Stvolinsky SL, Fedorova TN, Suslina ZA (2010) Carnosine as a natural  
1116 antioxidant and geroprotector: From molecular mechanisms to clinical trials.  
1117 *Rejuvenation Res* 13:156–158. <https://doi.org/10.1089/rej.2009.0923>
- 1118 Bowtell JL, Sumners DP, Dyer A, et al (2011) Montmorency cherry juice reduces muscle  
1119 damage caused by intensive strength exercise. *Med. Sci. Sports Exerc.* 43:1544–1551
- 1120 Boychuk KE, Lanovaz JL, Krentz JR, et al (2016) Creatine supplementation does not alter  
1121 neuromuscular recovery after eccentric exercise. *Muscle and Nerve* 54:487–495.  
1122 <https://doi.org/10.1002/mus.25091>
- 1123 Braun WA, Dutto DJ (2003) The effects of a single bout of downhill running and ensuing  
1124 delayed onset of muscle soreness on running economy performed 48 h later. *Eur J Appl*  
1125 *Physiol* 90:29–34. <https://doi.org/10.1007/s00421-003-0857-8>
- 1126 Burd NA, Yang Y, Moore DR, et al (2012) Greater stimulation of myofibrillar protein  
1127 synthesis with ingestion of whey protein isolate v. micellar casein at rest and after  
1128 resistance exercise in elderly men. *Br J Nutr* 108:958–962.  
1129 <https://doi.org/10.1017/S0007114511006271>
- 1130 Burt DG, Twist C (2011) The effects of exercise-induced muscle damage on cycling time-  
1131 trial performance. *J Strength Cond Res* 25:2185–2192.  
1132 <https://doi.org/10.1519/JSC.0b013e3181e86148>
- 1133 Byrne C, Eston R (2002) The effect of exercise-induced muscle damage on isometric and  
1134 dynamic knee extensor strength and vertical jump performance. *J Sports Sci* 20:417–  
1135 425. <https://doi.org/10.1080/026404102317366672>
- 1136 Byrne C, Eston RG, Edwards RHT (2001) Characteristics of isometric and dynamic strength  
1137 loss following eccentric exercise-induced muscle damage. *Scand J Med Sci Sports*  
1138 11:134–140. <https://doi.org/10.1046/j.1524-4725.2001.110302.x>
- 1139 Byrne C, Twist C, Eston R (2004) Neuromuscular Function after Exercise-Induced Muscle  
1140 Damage: Theoretical and Applied Implications. *Sport. Med.* 34:49–69
- 1141 Castiglioni A, Corna G, Rigamonti E, et al (2015) FOXP3+ T cells recruited to sites of sterile  
1142 skeletal muscle injury regulate the fate of satellite cells and guide effective tissue  
1143 regeneration. *PLoS One* 10:. <https://doi.org/10.1371/journal.pone.0128094>
- 1144 Chazaud B (2016) Inflammation during skeletal muscle regeneration and tissue remodeling:  
1145 Application to exercise-induced muscle damage management. *Immunol. Cell Biol.*  
1146 94:140–145

- 1147 Chen TC, Nosaka K, Lin M-J, et al (2009) Changes in running economy at different  
1148 intensities following downhill running. *J Sports Sci* 27:1137–44.  
1149 <https://doi.org/10.1080/02640410903062027>
- 1150 Chen TC, Nosaka K, Tu JH (2007) Changes in running economy following downhill running.  
1151 *J Sports Sci* 25:55–63. <https://doi.org/10.1080/02640410600718228>
- 1152 Chen TC, Nosaka K, Wu CC (2008) Effects of a 30-min running performed daily after  
1153 downhill running on recovery of muscle function and running economy. *J Sci Med Sport*  
1154 11:271–279. <https://doi.org/10.1016/j.jsams.2007.02.015>
- 1155 Chung HY, Cesari M, Anton S, et al (2009) Molecular inflammation: Underpinnings of aging  
1156 and age-related diseases. *Ageing Res. Rev.* 8:18–30
- 1157 Clarkson P, Dedrick M (1988) Exercise-induced muscle damage, repair, and adaptation in old  
1158 and young subjects. *J Gerontol* 43:M91–M96.  
1159 <https://doi.org/10.1093/GERONJ/43.4.M91>
- 1160 Clarkson PM (1997) Eccentric exercise and muscle damage. *Int J Sport Med Suppl* 18:.  
1161 <https://doi.org/10.1055/s-2007-972741>
- 1162 Clarkson PM, Hubal MJ (2002) Exercise-induced muscle damage in humans. In: *American*  
1163 *Journal of Physical Medicine and Rehabilitation*. *Am J Phys Med Rehabil*, pp S52–S69
- 1164 Clarkson PM, Hubal MJ (2001) Are women less susceptible to exercise-induced muscle  
1165 damage? *Curr. Opin. Clin. Nutr. Metab. Care* 4:527–531
- 1166 Clarkson PM, Nosaka K, Braun B (1992) Muscle function after exercise-induced muscle  
1167 damage and rapid adaptation. *Med Sci Sports Exerc* 24:512–520.  
1168 <https://doi.org/10.1249/00005768-199205000-00004>
- 1169 Cooke MB, Rybalka E, Stathis CG, et al (2010) Whey protein isolate attenuates strength  
1170 decline after eccentrically-induced muscle damage in healthy individuals. *J Int Soc*  
1171 *Sports Nutr* 7:30. <https://doi.org/10.1186/1550-2783-7-30>
- 1172 Cooke MB, Rybalka E, Williams AD, et al (2009) Creatine supplementation enhances muscle  
1173 force recovery after eccentrically-induced muscle damage in healthy individuals. *J Int*  
1174 *Soc Sports Nutr* 6:13. <https://doi.org/10.1186/1550-2783-6-13>
- 1175 Craddock JC, Neale EP, Peoples GE, Probst YC (2020) Plant-based eating patterns and  
1176 endurance performance: A focus on inflammation, oxidative stress and immune  
1177 responses. *Nutr Bull* 45:123–132. <https://doi.org/10.1111/nbu.12427>
- 1178 Cribb PJ, Hayes A (2006) Effects of supplement timing and resistance exercise on skeletal  
1179 muscle hypertrophy. *Med Sci Sports Exerc* 38:1918–1925.  
1180 <https://doi.org/10.1249/01.mss.0000233790.08788.3e>
- 1181 Damas F, Libardi CA, Ugrinowitsch C (2018) The development of skeletal muscle  
1182 hypertrophy through resistance training: the role of muscle damage and muscle protein  
1183 synthesis. *Eur J Appl Physiol* 118:485–500. <https://doi.org/10.1007/s00421-017-3792-9>
- 1184 Dannecker EA, Hausenblas HA, Kaminski TW, Robinson ME (2005) Sex Differences in

- 1185 Delayed Onset Muscle Pain. *Clin J Pain* 21:
- 1186 Dannecker EA, Liu Y, Rector RS, et al (2012) Sex differences in exercise-induced muscle  
1187 pain and muscle damage. *J Pain* 13:1242–1249.  
1188 <https://doi.org/10.1016/j.jpain.2012.09.014>
- 1189 Dartnall TJ, Nordstrom MA, Semmler JG (2008) Motor unit synchronization is increased in  
1190 biceps brachii after exercise-induced damage to elbow flexor muscles. *J Neurophysiol*  
1191 99:1008–1019. <https://doi.org/10.1152/jn.00686.2007>
- 1192 Davies RW, Carson BP, Jakeman PM (2018) Sex differences in the temporal recovery of  
1193 neuromuscular function following resistance training in resistance trained men and  
1194 women 18 to 35 years. *Front Physiol* 9:. <https://doi.org/10.3389/fphys.2018.01480>
- 1195 Del Valle A, Thomas CK (2005) Firing rates of motor units during strong dynamic  
1196 contractions. *Muscle and Nerve* 32:316–325. <https://doi.org/10.1002/mus.20371>
- 1197 Deminice R, Rosa FT, Franco GS, et al (2013) Effects of creatine supplementation on  
1198 oxidative stress and inflammatory markers after repeated-sprint exercise in humans.  
1199 *Nutrition* 29:1127–1132. <https://doi.org/10.1016/j.nut.2013.03.003>
- 1200 Dinarello CA (2000) Proinflammatory cytokines. *Chest* 118:503–508.  
1201 <https://doi.org/10.1378/chest.118.2.503>
- 1202 Douglas J, Pearson S, Ross A, McGuigan M (2017) Eccentric Exercise: Physiological  
1203 Characteristics and Acute Responses. *Sport. Med.* 47:663–675
- 1204 Enns DL, Tiidus PM (2010) The Influence of Estrogen on Skeletal Muscle Sex Matters. *Sport*  
1205 *Med* 40:41–58
- 1206 Enoka RM (1996) Eccentric contractions require unique activation strategies by the nervous  
1207 system. *J. Appl. Physiol.* 81:2339–2346
- 1208 Eston RG, Finney S, Baker S, Baltzopoulos V (1996) Muscle tenderness and peak torque  
1209 changes after downhill running following a prior bout of isokinetic eccentric exercise. *J*  
1210 *Sports Sci* 14:291–299. <https://doi.org/10.1080/02640419608727714>
- 1211 Fatouros IG, Jamurtas AZ (2016) Insights into the molecular etiology of exercise-induced  
1212 inflammation: Opportunities for optimizing performance. *J. Inflamm. Res.* 9:175–186
- 1213 Faulkner J, Brooks S, Opiteck J (1993) Injury to skeletal muscle fibers during contractions:  
1214 conditions of occurrence and prevention. *Phys Ther* 73:911–921
- 1215 Féasson L, Stockholm D, Freyssenet D, et al (2002) Molecular adaptations of neuromuscular  
1216 disease-associated proteins in response to eccentric exercise in human skeletal muscle. *J.*  
1217 *Physiol.* 543:297–306
- 1218 Febbraio MA, Pedersen BK (2002) Muscle-derived interleukin-6: mechanisms for activation  
1219 and possible biological roles. *FASEB J* 16:1335–131. <https://doi.org/10.1096/fj.01-0876rev>
- 1220
- 1221 Fehrenbach E, Schneider ME (2006) Trauma-induced systemic inflammatory response versus



- 1222 exercise-induced immunomodulatory effects. *Sport Med* 36:373–384.  
1223 <https://doi.org/10.2165/00007256-200636050-00001>
- 1224 Ferreira D V., Gentil P, Ferreira-Junior JB, et al (2017a) Dissociated time course between  
1225 peak torque and total work recovery following bench press training in resistance trained  
1226 men. *Physiol Behav* 179:143–147. <https://doi.org/10.1016/j.physbeh.2017.06.001>
- 1227 Ferreira D V., Gentil P, Soares SRS, Bottaro M (2017b) Recovery of pectoralis major and  
1228 triceps brachii after bench press exercise. *Muscle and Nerve* 56:963–967.  
1229 <https://doi.org/10.1002/mus.25541>
- 1230 Fillingim RB, Maixner W (1995) Gender differences in the responses to noxious stimuli. *Pain*  
1231 *Forum* 4:209–221. [https://doi.org/10.1016/s1082-3174\(11\)80022-x](https://doi.org/10.1016/s1082-3174(11)80022-x)
- 1232 Flann KL, LaStayo PC, McClain DA, et al (2011) Muscle damage and muscle remodeling:  
1233 no pain, no gain? *J Exp Biol* 214:674 LP – 679. <https://doi.org/10.1242/jeb.050112>
- 1234 Flores DF, Gentil P, Brown LE, et al (2011) Dissociated time course of recovery between  
1235 genders after resistance exercise. *J Strength Cond Res* 25:3039–3044.  
1236 <https://doi.org/10.1519/JSC.0b013e318212dea4>
- 1237 Fournier PA, Bräu L, Ferreira LB, et al (2002) Glycogen resynthesis in the absence of food  
1238 ingestion during recovery from moderate or high intensity physical activity: Novel  
1239 insights from rat and human studies. *Comp Biochem Physiol - A Mol Integr Physiol*  
1240 133:755–763. [https://doi.org/10.1016/S1095-6433\(02\)00254-4](https://doi.org/10.1016/S1095-6433(02)00254-4)
- 1241 Friden J, Sjoström M, Ekblom B (1983) Myofibrillar damage following intense eccentric  
1242 exercise in man. *Int J Sports Med* 4:170–176. <https://doi.org/10.1055/s-2008-1026030>
- 1243 Froeling M, Oudeman J, Strijkers GJ, et al (2015) Muscle changes detected with diffusion-  
1244 tensor imaging after long-distance running. *Radiology* 274:548–562.  
1245 <https://doi.org/10.1148/radiol.14140702>
- 1246 Fulco CS, Rock PB, Muza SR, et al (1999) Slower fatigue and faster recovery of the adductor  
1247 pollicis muscle in women matched for strength with men. *Acta Physiol Scand* 167:233–  
1248 239. <https://doi.org/10.1046/j.1365-201X.1999.00613.x>
- 1249 Gepner Y, Hoffman JR, Shemesh E, et al (2017) Combined effect of *Bacillus coagulans* GBI-  
1250 30, 6086 and HMB supplementation on muscle integrity and cytokine response during  
1251 intense military training. *J Appl Physiol* 123:11–18.  
1252 <https://doi.org/10.1152/jappphysiol.01116.2016>
- 1253 Gibala MJ, MacDougall JD, Tarnopolsky MA, et al (1995) Changes in human skeletal  
1254 muscle ultrastructure and force production after acute resistance exercise. *J Appl Physiol*  
1255 78:702–708. <https://doi.org/10.1152/jappl.1995.78.2.702>
- 1256 Gonzalez AM, Hoffman JR, Stout JR, et al (2016) Intramuscular Anabolic Signaling and  
1257 Endocrine Response Following Resistance Exercise: Implications for Muscle  
1258 Hypertrophy. *Sport. Med.* 46:671–685
- 1259 Gonzalez AM, Stout JR, Jajtner AR, et al (2014) Effects of  $\beta$ -hydroxy- $\beta$ -methylbutyrate free  
1260 acid and cold water immersion on post-exercise markers of muscle damage. *Amino*

- 1261 Acids 46:1501–1511. <https://doi.org/10.1007/s00726-014-1722-2>
- 1262 Gordon JA, Hoffman JR, Arroyo E, et al (2017) Comparisons in the recovery response from  
1263 resistance exercise between young and middle-aged men. *J Strength Cond Res* 31:3454–  
1264 3462. <https://doi.org/10.1519/JSC.0000000000002219>
- 1265 Goto K, Ishii N, Kizuka T, et al (2009) Hormonal and metabolic responses to slow movement  
1266 resistance exercise with different durations of concentric and eccentric actions. *Eur J*  
1267 *Appl Physiol* 106:731–739. <https://doi.org/10.1007/s00421-009-1075-9>
- 1268 Hackney AC, Kallman AL, Aġgön E (2019) Female sex hormones and the recovery from  
1269 exercise: Menstrual cycle phase affects responses. *Biomed Hum Kinet* 11:87–89.  
1270 <https://doi.org/10.2478/bhk-2019-0011>
- 1271 Hakkinen K (1993) Neuromuscular fatigue and recovery in male and female athletes during  
1272 heavy resistance exercise. *Int J Sports Med* 14:53–59. <https://doi.org/10.1055/s-2007-1021146>
- 1274 Hamill J, Freedson PS, Clarkson PM, Braun B (1991) Muscle Soreness during Running:  
1275 Biomechanical and Physiological Considerations, *International Journal of Sport*  
1276 *Biomechanics*. *Int J Sport Biomech* 7:125–137
- 1277 Harris RC, Tallon MJ, Dunnett M, et al (2006) The absorption of orally supplied  $\beta$ -alanine  
1278 and its effect on muscle carnosine synthesis in human vastus lateralis. *Amino Acids*  
1279 30:279–289. <https://doi.org/10.1007/s00726-006-0299-9>
- 1280 Harvey KL, Holcomb LE, Kolwicz SC (2019) Ketogenic Diets and Exercise Performance.  
1281 *Nutrients* 11
- 1282 Hatzikotoulas K, Siatras T, Spyropoulou E, et al (2004) Muscle fatigue and  
1283 electromyographic changes are not different in women and men matched for strength.  
1284 *Eur J Appl Physiol* 92:298–304. <https://doi.org/10.1007/s00421-004-1095-4>
- 1285 Hayashi K, Leary ME, Roy SJ, et al (2019) Recovery from Strenuous Downhill Running in  
1286 Young and Older Physically Active Adults. *Int J Sports Med* 40:696–703.  
1287 <https://doi.org/10.1055/a-0951-0017>
- 1288 Heymsfield SB, Arteaga C, McManus CM, et al (1983) Measurement of muscle mass in  
1289 humans: Validity of the 24-hour urinary creatinine method. *Am J Clin Nutr* 37:478–494.  
1290 <https://doi.org/10.1093/ajcn/37.3.478>
- 1291 Highton JM, Twist C, Eston RG (2009) The effects of exercise-induced muscle damage on  
1292 agility and sprint running performance. *J Exerc Sci Fit* 7:24–30.  
1293 [https://doi.org/10.1016/S1728-869X\(09\)60004-6](https://doi.org/10.1016/S1728-869X(09)60004-6)
- 1294 Hill EC, Housh TJ, Keller JL, et al (2018) Early phase adaptations in muscle strength and  
1295 hypertrophy as a result of low-intensity blood flow restriction resistance training. *Eur J*  
1296 *Appl Physiol* 118:1831–1843. <https://doi.org/10.1007/s00421-018-3918-8>
- 1297 Hody S, Croisier J-L, Bury T, et al (2019) Eccentric Muscle Contractions: Risks and  
1298 Benefits. *Front Physiol* 10:536. <https://doi.org/10.3389/fphys.2019.00536>

- 1299 Hoffman JR (2016a) Creatine and beta-alanine supplementation in strength / power athletes.  
1300 Curr Top Nutraceutical Res
- 1301 Hoffman JR (2019) Dietary Supplementation in Sport and Exercise Evidence, Safety and  
1302 Ergogenic Benefits
- 1303 Hoffman JR (2016b) Creatine and  $\beta$ -alanine supplementation in strength/power athletes.  
1304 8:19–32
- 1305 Hoffman JR, Falvo MJ (2004) Protein - Which is best? J Sport Sci Med 3:118–130
- 1306 Hoffman JR, Gepner Y, Stout JR, et al (2016)  $\beta$ -Hydroxy- $\beta$ -methylbutyrate attenuates  
1307 cytokine response during sustained military training. Nutr Res 36:553–63.  
1308 <https://doi.org/10.1016/j.nutres.2016.02.006>
- 1309 Hoffman JR, Nusse V, Kang J (2003) The Effect of an Intercollegiate Soccer Game on  
1310 Maximal Power Performance. Can J Appl Physiol 28:807–817.  
1311 <https://doi.org/10.1139/h03-060>
- 1312 Hoffman JR, Ostfeld I, Stout JR, et al (2015)  $\beta$ -alanine supplemented diets enhance  
1313 behavioral resilience to stress exposure in an animal model of PTSD. Amino Acids  
1314 47:1247–1257. <https://doi.org/10.1007/s00726-015-1952-y>
- 1315 Hoffman JR, Ratamess NA, Kang J, et al (2007) Effects of protein supplementation on  
1316 muscular performance and resting hormonal changes in college football players. J Sport  
1317 Sci Med 6:85–92
- 1318 Hoffman JR, Ratamess NA, Tranchina CP, et al (2010) Effect of a proprietary protein  
1319 supplement on recovery indices following resistance exercise in strength/power athletes.  
1320 Amino Acids 38:771–778. <https://doi.org/10.1007/s00726-009-0283-2>
- 1321 Hoffman JR, Varanoske A, Stout JR (2018) Effects of  $\beta$ -Alanine Supplementation on  
1322 Carnosine Elevation and Physiological Performance. In: Advances in Food and  
1323 Nutrition Research. Academic Press Inc., pp 183–206
- 1324 Hoffman JR, Zuckerman A, Ram O, et al (2017a) Behavioral and inflammatory response in  
1325 animals exposed to a low-pressure blast wave and supplemented with  $\beta$ -alanine. Amino  
1326 Acids 49:871–886. <https://doi.org/10.1007/s00726-017-2383-8>
- 1327 Hoffman JR, Zuckerman A, Ram O, et al (2017b) Behavioral and inflammatory response in  
1328 animals exposed to a low-pressure blast wave and supplemented with  $\beta$ -alanine. Amino  
1329 Acids 49:871–886. <https://doi.org/10.1007/s00726-017-2383-8>
- 1330 Hotfiel T, Freiwald J, Hoppe MW, et al (2018) Advances in Delayed-Onset Muscle Soreness  
1331 (DOMS): Part I: Pathogenesis and Diagnostics. Sportverletzung-Sportschaden 32:243–  
1332 250. <https://doi.org/10.1055/a-0753-1884>
- 1333 Howell JN, Fuglevand AJ, Walsh ML, Bigland-Ritchie B (1995) Motor unit activity during  
1334 isometric and concentric-eccentric contractions of the human first dorsal interosseus  
1335 muscle. J Neurophysiol 74:901–904. <https://doi.org/10.1152/jn.1995.74.2.901>
- 1336 Hulmi JJ, Kovanen V, Selänne H, et al (2009) Acute and long-term effects of resistance

- 1337 exercise with or without protein ingestion on muscle hypertrophy and gene expression.  
1338 *Amino Acids* 37:297–308. <https://doi.org/10.1007/s00726-008-0150-6>
- 1339 Hunter I, Smith GA (2007) Preferred and optimal stride frequency, stiffness and economy:  
1340 Changes with fatigue during a 1-h high-intensity run. *Eur J Appl Physiol* 100:653–661.  
1341 <https://doi.org/10.1007/s00421-007-0456-1>
- 1342 Isner-Horobeti ME, Dufour SP, Vautravers P, et al (2013) Eccentric Exercise Training:  
1343 Modalities, Applications and Perspectives. *Sport. Med.* 43:483–512
- 1344 Izquierdo M, Ibañez J, Calbet JAL, et al (2009) Neuromuscular fatigue after resistance  
1345 training. *Int J Sports Med* 30:614–623. <https://doi.org/10.1055/s-0029-1214379>
- 1346 Jäger R, Kerksick CM, Campbell BI, et al (2017) International Society of Sports Nutrition  
1347 Position Stand: Protein and exercise. *J Int Soc Sports Nutr* 14:20.  
1348 <https://doi.org/10.1186/s12970-017-0177-8>
- 1349 Jajtner AR, Hoffman JR, Townsend JR, et al (2016) The effect of polyphenols on cytokine  
1350 and granulocyte response to resistance exercise. *Physiol Rep* 4:  
1351 <https://doi.org/10.14814/phy2.13058>
- 1352 Jajtner AR, Townsend JR, Beyer KS, et al (2018) Resistance Exercise Selectively Mobilizes  
1353 Monocyte Subsets. *Med Sci Sport Exerc* 50:2231–2241.  
1354 <https://doi.org/10.1249/MSS.0000000000001703>
- 1355 Jakeman JR, Byrne C, Eston RG (2010) Lower limb compression garment improves recovery  
1356 from exercise-induced muscle damage in young, active females. *Eur J Appl Physiol*  
1357 109:1137–1144. <https://doi.org/10.1007/s00421-010-1464-0>
- 1358 Jansson E, Sylvén C (1985) Creatine kinase MB and citrate synthase in type I and type II  
1359 muscle fibres in trained and untrained men. *Eur J Appl Physiol Occup Physiol* 54:207–  
1360 209. <https://doi.org/10.1007/BF02335931>
- 1361 Jones AM, Carter H (2000) The effect of endurance training on parameters of aerobic fitness.  
1362 *Sport Med* 29:373–386. <https://doi.org/10.2165/00007256-200029060-00001>
- 1363 Jones DA, Newham DJ, Torgan C (1989) Mechanical influences on long-lasting human  
1364 muscle fatigue and delayed-onset pain. *J Physiol* 412:415–427.  
1365 <https://doi.org/10.1113/jphysiol.1989.sp017624>
- 1366 Jówko E, Sacharuk J, Balasinska B, et al (2012) Effect of a single dose of green tea  
1367 polyphenols on the blood markers of exercise-induced oxidative stress in soccer players.  
1368 *Int J Sport Nutr Exerc Metab* 22:486–496. <https://doi.org/10.1123/ijnsnem.22.6.486>
- 1369 Joyner MJ, Coyle EF (2008) Endurance exercise performance: the physiology of champions.  
1370 *J Physiol* 586:35–44. <https://doi.org/10.1113/jphysiol.2007.143834>
- 1371 Kayani AC, Morton JP, McArdle A (2008) The exercise-induced stress response in skeletal  
1372 muscle: failure during aging. *Appl Physiol Nutr Metab* 33:1033–1041.  
1373 <https://doi.org/10.1139/h08-089>
- 1374 Kennedy RA, Drake D (2018) Dissociated time course of recovery between strength and

- 1375 power after isoinertial resistance loading in rugby union players. *J Strength Cond Res*  
1376 32:748–755. <https://doi.org/10.1519/jsc.0000000000001821>
- 1377 Kerksick CM, Kreider RB, Willoughby DS (2010) Intramuscular adaptations to eccentric  
1378 exercise and antioxidant supplementation. *Amino Acids* 39:219–232.  
1379 <https://doi.org/10.1007/s00726-009-0432-7>
- 1380 Kim MK, Cho SW, Park YK (2012) Long-term vegetarians have low oxidative stress, body  
1381 fat, and cholesterol levels. *Nutr Res Pract* 6:155–161.  
1382 <https://doi.org/10.4162/nrp.2012.6.2.155>
- 1383 Klemm C, Simeone FJ, Melnic CM, et al (2020) MARS MRI assessment of fatty degeneration  
1384 of the gluteal muscles in patients with THA: reliability and accuracy of commonly used  
1385 classification systems. *Skeletal Radiol*. <https://doi.org/10.1007/s00256-020-03611-9>
- 1386 Kohen R, Yamamoto Y, Cundy KC, Ames BN (1988) Antioxidant activity of carnosine,  
1387 homocarnosine, and anserine present in muscle and brain. *Proc Natl Acad Sci U S A*  
1388 85:3175–3179. <https://doi.org/10.1073/pnas.85.9.3175>
- 1389 Komulainen J, Koskinen SOA, Kalliokoski R, et al (1999) Gender differences in skeletal  
1390 muscle fibre damage after eccentrically biased downhill running in rats. *Acta Physiol*  
1391 *Scand* 165:57–63. <https://doi.org/10.1046/j.1365-201x.1999.00481.x>
- 1392 Koutnik AP, D’Agostino DP, Egan B (2019) Anticatabolic Effects of Ketone Bodies in  
1393 Skeletal Muscle. *Trends Endocrinol. Metab.* 30:227–229
- 1394 Kraemer RR, Durand RJ, Hollander DB, et al (2004) Ghrelin and other glucoregulatory  
1395 hormone responses to eccentric and concentric muscle contractions. *Endocrine* 24:93–  
1396 98. <https://doi.org/10.1385/endo:24:1:093>
- 1397 Kraemer WJ, Ratamess NA, Volek JS, et al (2006) The effects of amino acid  
1398 supplementation on hormonal responses to resistance training overreaching. *Metabolism*  
1399 55:282–291. <https://doi.org/10.1016/j.metabol.2005.08.023>
- 1400 Kreider RB, Kalman DS, Antonio J, et al (2017) International Society of Sports Nutrition  
1401 position stand: Safety and efficacy of creatine supplementation in exercise, sport, and  
1402 medicine. *J. Int. Soc. Sports Nutr.* 14
- 1403 Krisanda J, Moreland T, Kushmerick M (1988) ATP supply and demand during exercise. In:  
1404 Horton ES, Terjung RL, editors. *Exerc Nutr energy Metab* 27–44
- 1405 Kyrolainen H, Pullinen T, Candau R, et al (2000) Effects of marathon running on running  
1406 economy and kinematics. *Eur J Appl Physiol* 82:297–304.  
1407 <https://doi.org/10.1007/s004210000219>
- 1408 Lamb G (2009) Mechanisms of excitation–contraction coupling relevant to activity-induced  
1409 muscle fatigue. *Appl Physiol Nutr Metab* 34:368–372. <https://doi.org/10.1139/H09-032>
- 1410 Lavender AP, Nosaka K (2006) Changes in fluctuation of isometric force following eccentric  
1411 and concentric exercise of the elbow flexors. *Eur J Appl Physiol* 96:235–240.  
1412 <https://doi.org/10.1007/s00421-005-0069-5>

- 1413 Lavin KM, Perkins RK, Jemiolo B, et al (2020) Effects of aging and lifelong aerobic exercise  
1414 on basal and exercise-induced inflammation. *J Appl Physiol* 128:87–99.  
1415 <https://doi.org/10.1152/jappphysiol.00495.2019>
- 1416 Lewis PB, Ruby D, Bush-Joseph CA (2012) Muscle Soreness and Delayed-Onset Muscle  
1417 Soreness. *Clin Sports Med* 31:255–262. <https://doi.org/10.1016/j.csm.2011.09.009>
- 1418 Lieber RL, Friden J (1993) Muscle damage is not a function of muscle force but active  
1419 muscle strain. *J Appl Physiol* 74:520–526. <https://doi.org/10.1152/jappl.1993.74.2.520>
- 1420 Ma S, Huang Q, Yada K, et al (2018) An 8-week ketogenic low carbohydrate, high fat diet  
1421 enhanced exhaustive exercise capacity in mice. *Nutrients* 10:.  
1422 <https://doi.org/10.3390/nu10060673>
- 1423 MacDougall JD, Ray S, Sale DG, et al (1999) Muscle substrate utilization and lactate  
1424 production during weightlifting. *Can J Appl Physiol* 24:209–215.  
1425 <https://doi.org/10.1139/h99-017>
- 1426 Macgregor LJ, Hunter AM (2018) High-threshold motor unit firing reflects force recovery  
1427 following a bout of damaging eccentric exercise. *PLoS One* 13:e0195051–e0195051.  
1428 <https://doi.org/10.1371/journal.pone.0195051>
- 1429 Malm C, Sjödin B, Sjöberg B, et al (2004) Leukocytes, cytokines, growth factors and  
1430 hormones in human skeletal muscle and blood after uphill or downhill running. *J Physiol*  
1431 556:983–1000. <https://doi.org/10.1113/jphysiol.2003.056598>
- 1432 Manach C, Scalbert A, Morand C, et al (2004) Polyphenols: Food sources and bioavailability.  
1433 *Am. J. Clin. Nutr.* 79:727–747
- 1434 Marcora SM, Bosio A (2007) Effect of exercise-induced muscle damage on endurance  
1435 running performance in humans. *Scand J Med Sci Sport* 17:662–671.  
1436 <https://doi.org/10.1111/j.1600-0838.2006.00627.x>
- 1437 Marqueste T, Giannesini B, Fur Y Le, et al (2008) Comparative MRI analysis of T2 changes  
1438 associated with single and repeated bouts of downhill running leading to eccentric-  
1439 induced muscle damage. *J Appl Physiol* 105:299–307.  
1440 <https://doi.org/10.1152/jappphysiol.00738.2007>
- 1441 Massicotte D, Scotto A, Péronnet F, et al (2006) Metabolic fate of a large amount of 13C-  
1442 glycerol ingested during prolonged exercise. *Eur J Appl Physiol* 96:322–329.  
1443 <https://doi.org/10.1007/s00421-005-0058-8>
- 1444 Mateescu RG, Garmyn AJ, O’Neil MA, et al (2012) Genetic parameters for carnitine,  
1445 creatine, creatinine, carnosine, and anserine concentration in longissimus muscle and  
1446 their association with palatability traits in angus cattle. *J Anim Sci* 90:4248–4255.  
1447 <https://doi.org/10.2527/jas.2011-5077>
- 1448 McHugh MP (2003) Recent advances in the understanding of the repeated bout effect: The  
1449 protective effect against muscle damage from a single bout of eccentric exercise. *Scand*  
1450 *J Med Sci Sport* 13:88–97. <https://doi.org/10.1034/j.1600-0838.2003.02477.x>
- 1451 McHugh MP, Connolly DAJ, Eston RG, Gleim GW (1999) Exercise-induced muscle damage

- 1452 and potential mechanisms for the repeated bout effect. *Sport. Med.* 27:157–170
- 1453 Mckinnon NB, Graham MT, Tiidus PM (2012) Effect of creatine supplementation on muscle  
1454 damage and repair following eccentrically-induced damage to the elbow flexor muscles.  
1455 *J Sport Sci Med* 11:653–659
- 1456 McPherson PAC, McEneny J (2012) The biochemistry of ketogenesis and its role in weight  
1457 management, neurological disease and oxidative stress. *J. Physiol. Biochem.* 68:141–  
1458 151
- 1459 Meeusen R, Duclos M, Foster C, et al (2013) Prevention, diagnosis, and treatment of the  
1460 overtraining syndrome: Joint consensus statement of the european college of sport  
1461 science and the American College of Sports Medicine. *Med Sci Sports Exerc* 45:186–  
1462 205. <https://doi.org/10.1249/MSS.0b013e318279a10a>
- 1463 Milder J, Patel M (2012) Modulation of oxidative stress and mitochondrial function by the  
1464 ketogenic diet. *Epilepsy Res* 100:295–303.  
1465 <https://doi.org/10.1016/j.epilepsyres.2011.09.021>
- 1466 Millet GY, Lepers R (2004) Alterations of Neuromuscular Function after Prolonged Running,  
1467 Cycling and Skiing Exercises. *Sport. Med.* 34:105–116
- 1468 Millet GY, Tomazin K, Verges S, et al (2011) Neuromuscular consequences of an extreme  
1469 mountain ultra-marathon. *PLoS One* 6:. <https://doi.org/10.1371/journal.pone.0017059>
- 1470 Molina R, Denadai BS (2012) Dissociated time course recovery between rate of force  
1471 development and peak torque after eccentric exercise. *Clin Physiol Funct Imaging*  
1472 32:179–184. <https://doi.org/10.1111/j.1475-097X.2011.01074.x>
- 1473 Morawetz D, Blank C, Koller A, et al (2020) Sex-Related Differences After a Single Bout of  
1474 Maximal Eccentric Exercise in Response to Acute Effects: A Systematic Review and  
1475 Meta-analysis. *J Strength Cond Res* 34:.  
1476 <https://doi.org/doi:10.1519/JSC.0000000000002867>
- 1477 Morifuji M, Sakai K, Sanbongi C, Sugiura K (2005) Dietary whey protein increases liver and  
1478 skeletal muscle glycogen levels in exercise-trained rats. *Br J Nutr* 93:439–445.  
1479 <https://doi.org/10.1079/bjn20051373>
- 1480 Murakami T, Furuse M (2010) The impact of taurine-and beta-alanine-supplemented diets on  
1481 behavioral and neurochemical parameters in mice: Antidepressant versus anxiolytic-like  
1482 effects. *Amino Acids* 39:427–434. <https://doi.org/10.1007/s00726-009-0458-x>
- 1483 Murase S, Terazawa E, Hirate K, et al (2013) Upregulated glial cell line-derived neurotrophic  
1484 factor through cyclooxygenase-2 activation in the muscle is required for mechanical  
1485 hyperalgesia after exercise in rats. *J Physiol* 591:3035–3048.  
1486 <https://doi.org/10.1113/jphysiol.2012.249235>
- 1487 Nardone A, Romanò C, Schieppati M (1989) Selective recruitment of high-threshold human  
1488 motor units during voluntary isotonic lengthening of active muscles. *J Physiol* 409:451–  
1489 471. <https://doi.org/10.1113/jphysiol.1989.sp017507>
- 1490 Nebl J, Drabert K, Haufe S, et al (2019) Exercise-induced oxidative stress, nitric oxide and

- 1491 plasma amino acid profile in recreational runners with vegetarian and non-vegetarian  
1492 dietary patterns. *Nutrients* 11:. <https://doi.org/10.3390/nu11081875>
- 1493 Nelson A, Arnall D, Kokkonen J, et al (2001) Muscle glycogen supercompensation is  
1494 enhanced by prior creatine supplementation. *Med Sci Sport Exerc* 33:1096–1100.  
1495 <https://doi.org/10.1097/00005768-200107000-00005>
- 1496 Neubauer O, Sabapathy S, Lazarus R, et al (2013) Transcriptome analysis of neutrophils after  
1497 endurance exercise reveals novel signaling mechanisms in the immune response to  
1498 physiological stress. *J Appl Physiol* 114:1677–1688.  
1499 <https://doi.org/10.1152/jappphysiol.00143.2013>
- 1500 Newham DJ, Jones DA, Clarkson PM (1987) Repeated high-force eccentric exercise: Effects  
1501 on muscle pain and damage. *J Appl Physiol* 63:1381–1386.  
1502 <https://doi.org/10.1152/jappl.1987.63.4.1381>
- 1503 Newham DJ, McPhail G, Mills KR, Edwards RHT (1983) Ultrastructural changes after  
1504 concentric and eccentric contractions of human muscle. *J Neurol Sci* 61:109–122.  
1505 [https://doi.org/10.1016/0022-510X\(83\)90058-8](https://doi.org/10.1016/0022-510X(83)90058-8)
- 1506 Newton MJ, Morgan GT, Sacco P, et al (2008) Comparison of responses to strenuous  
1507 eccentric exercise of the elbow flexors between resistance-trained and untrained men. *J*  
1508 *Strength Cond Res* 22:597–607. <https://doi.org/10.1519/JSC.0b013e3181660003>
- 1509 Nieman DC, Henson DA, Davis JM, et al (2007) Quercetin ingestion does not alter cytokine  
1510 changes in athletes competing in the Western States endurance run. *J Interf Cytokine*  
1511 *Res* 27:1003–1011. <https://doi.org/10.1089/jir.2007.0050>
- 1512 Nishimura A, Sugita M, Kato K, et al (2010) Hypoxia increases muscle hypertrophy induced  
1513 by resistance training. *Int J Sports Physiol Perform* 5:497–508.  
1514 <https://doi.org/10.1123/ijsp.5.4.497>
- 1515 Nosaka K, Newton M, Sacco P (2002a) Delayed-onset muscle soreness does not reflect the  
1516 magnitude of eccentric exercise-induced muscle damage. *Scand J Med Sci Sports*  
1517 12:337–346. <https://doi.org/10.1034/j.1600-0838.2002.10178.x>
- 1518 Nosaka K, Newton M, Sacco P (2002b) Muscle damage and soreness after endurance  
1519 exercise of the elbow flexors. *Med Sci Sports Exerc* 34:920–927.  
1520 <https://doi.org/10.1097/00005768-200206000-00003>
- 1521 Nosaka K, Sakamoto K, Newton M, Sacco P (2001) How long does the protective effect on  
1522 eccentric exercise-induced muscle damage last? *Med Sci Sports Exerc* 33:1490–1495.  
1523 <https://doi.org/10.1097/00005768-200109000-00011>
- 1524 Opal SM, Depalo VA (2000) Anti-Inflammatory Cytokines. *Chest* 117:1162–1172
- 1525 Ostrowski K, Hermann C, Bangash A, et al (1998) A trauma-like elevation of plasma  
1526 cytokines in humans in response to treadmill running. *J Physiol* 513:889–894.  
1527 <https://doi.org/10.1111/j.1469-7793.1998.889ba.x>
- 1528 Oudeman J, Nederveen AJ, Strijkers GJ, et al (2016) Techniques and applications of skeletal  
1529 muscle diffusion tensor imaging: A review. *J Magn Reson Imaging* 43:773–788.



1530 <https://doi.org/10.1002/jmri.25016>

1531 Owens DJ, Twist C, Cobley JN, et al (2018) What is it, what causes it and what are the  
1532 nutritional solutions? *Eur J Sport Sci* 19:71–85.  
1533 <https://doi.org/10.1080/17461391.2018.1505957>

1534 Panza VSP, Wazlawik E, Ricardo Schütz G, et al (2008) Consumption of green tea favorably  
1535 affects oxidative stress markers in weight-trained men. *Nutrition* 24:433–442.  
1536 <https://doi.org/10.1016/j.nut.2008.01.009>

1537 Paoli A, Bianco A, Grimaldi KA (2015) The Ketogenic Diet and Sport: A Possible Marriage?  
1538 *Exerc Sport Sci Rev* 43:153–162. <https://doi.org/10.1249/JES.0000000000000050>

1539 Paulsen G, Egner IM, Drange M, et al (2010) A COX-2 inhibitor reduces muscle soreness,  
1540 but does not influence recovery and adaptation after eccentric exercise. *Scand J Med Sci*  
1541 *Sports* 20:e195–e207. <https://doi.org/10.1111/j.1600-0838.2009.00947.x>

1542 Paulsen G, Mikkelsen UR, Raastad T, Peake JM (2012) Leucocytes, cytokines and satellite  
1543 cells: What role do they play in muscle damage and regeneration following eccentric  
1544 exercise? *Exerc Immunol Rev* 18:42–97

1545 Paulus J, Croisier J-L, Kaux J-F, Bury T (2019) Eccentric versus Concentric — Which Is the  
1546 Most Stressful Cardiovascularly and Metabolically? *Curr Sports Med Rep* 18:477–489.  
1547 <https://doi.org/10.1249/JSR.0000000000000666>

1548 Peake J, Wilson G, Hordern M, et al (2004) Changes in neutrophil surface receptor  
1549 expression, degranulation, and respiratory burst activity after moderate- and high-  
1550 intensity exercise. *J Appl Physiol* 97:612–618.  
1551 <https://doi.org/10.1152/jappphysiol.01331.2003>

1552 Peake JM (2019) Recovery after exercise: what is the current state of play? *Curr Opin*  
1553 *Physiol* 10:17–26. <https://doi.org/10.1016/j.cophys.2019.03.007>

1554 Peake JM, K S, M H, et al (2005) Plasma cytokine changes in relation to exercise intensity  
1555 and muscle damage. *Eur J Appl Physiol* 95:514–521. <https://doi.org/10.1007/s00421-005-0035-2>  
1556

1557 Peake JM, Neubauer O, Gatta DP, Nosaka K (2017) Muscle damage and inflammation during  
1558 recovery from exercise. *J. Appl. Physiol.* 122:559–570

1559 Peake JM, Suzuki K, Hordern M, et al (2005) Plasma cytokine changes in relation to exercise  
1560 intensity and muscle damage. *Eur J Appl Physiol* 95:514–521.  
1561 <https://doi.org/10.1007/s00421-005-0035-2>

1562 Pearson SJ, Hussain SR (2015) A Review on the Mechanisms of Blood-Flow Restriction  
1563 Resistance Training-Induced Muscle Hypertrophy. *Sport. Med.* 45:187–200

1564 Pedersen BK, Fischer CP (2007) Physiological roles of muscle-derived interleukin-6 in  
1565 response to exercise. *Curr. Opin. Clin. Nutr. Metab. Care* 10:265–271

1566 Pedersen BK, Steensberg A, Schjerling P (2001) Exercise and interleukin-6. *Curr. Opin.*  
1567 *Hematol.* 8:137–141

- 1568 Piitulainen H, Bottas R, Komi P, et al (2010) Impaired action potential conduction at high  
 1569 force levels after eccentric exercise. *J Electromyogr Kinesiol* 20:879–887.  
 1570 <https://doi.org/10.1016/j.jelekin.2009.10.001>
- 1571 Pillon NJ, Bilan PJ, Fink LN, Klip A (2013) Cross-talk between skeletal muscle and immune  
 1572 cells: Muscle-derived mediators and metabolic implications. *Am J Physiol - Endocrinol*  
 1573 *Metab* 304:. <https://doi.org/10.1152/ajpendo.00553.2012>
- 1574 Plattner K, Baumeister J, Lamberts R, Lambert M (2011) Dissociation changes in emg  
 1575 activation during maximal isometric and submaximal low force dynamic contractions  
 1576 after exercise induced muscle damage. *J Electromyogr Kinesiol* 21:542–550
- 1577 Pokora I, Kempa K, Chrapusta SJ, Langfort J (2014) Effects of downhill and uphill exercises  
 1578 of equivalent submaximal intensities on selected blood cytokine levels and blood  
 1579 creatine kinase activity. *Biol Sport* 31:173–178.  
 1580 <https://doi.org/10.5604/20831862.1111434>
- 1581 Power GA, Dalton BH, Rice CL, Vandervoort AA (2013) Peak power is reduced following  
 1582 lengthening contractions despite a maintenance of shortening velocity. *Appl Physiol*  
 1583 *Nutr Metab* 38:1196–1205. <https://doi.org/10.1139/apnm-2013-0092>
- 1584 Prasartwuth O, Allen TJ, Butler JE, et al (2006) Length-dependent changes in voluntary  
 1585 activation, maximum voluntary torque and twitch responses after eccentric damage in  
 1586 humans. *J Physiol* 571:243–252. <https://doi.org/10.1113/jphysiol.2005.101600>
- 1587 Prins PJ, Noakes TD, Welton GL, et al (2019) High rates of fat oxidation induced by a low-  
 1588 carbohydrate, high-fat diet, do not impair 5-km running performance in competitive  
 1589 recreational athletes. *J Sport Sci Med* 18:738–750
- 1590 Quindry J, Miller L, McGinnis G, et al (2011) Muscle-fiber type and blood oxidative stress  
 1591 after eccentric exercise. *Int J Sport Nutr Exerc Metab* 21:462–470.  
 1592 <https://doi.org/10.1123/ijsnem.21.6.462>
- 1593 Raastad T, Hallén J (2000) Recovery of skeletal muscle contractility after high- and  
 1594 moderate-intensity strength exercise. *Eur J Appl Physiol* 82:206–214.  
 1595 <https://doi.org/10.1007/s004210050673>
- 1596 Radak Z, Chung H, Koltai E, et al (2008) Exercise, oxidative stress and hormesis. *Ageing*  
 1597 *Res Rev* 7:34–42. <https://doi.org/10.1016/j.arr.2007.04.004>
- 1598 Radunsky D, Blumenfeld-Katzir T, Volovyk O, et al (2019) Analysis of magnetization  
 1599 transfer (MT) influence on quantitative mapping of T2 relaxation time. *Magn Reson*  
 1600 *Med* 82:145–158. <https://doi.org/10.1002/mrm.27704>
- 1601 Raeder C, Wiewelhove T, Westphal-Martinez MP, et al (2016) Neuromuscular Fatigue and  
 1602 Physiological Responses After Five Dynamic Squat Exercise Protocols. *J Strength Cond*  
 1603 *Res* 30:953–965. <https://doi.org/10.1519/JSC.0000000000001181>
- 1604 Rawson ES, Gunn B, Clarkson PM (2001) The Effects of Creatine Supplementation on  
 1605 Exercise-Induced Muscle Damage. *J Strength Cond Res* 15:178–184
- 1606 Reis E, Frick U, Schmidtbleicher D (1995) Frequency variations of strength training sessions

- 1607 triggered by the phases of the menstrual cycle. *Int J Sports Med* 16:545–550.  
1608 <https://doi.org/10.1055/s-2007-973052>
- 1609 Rhyu H, Cho S-Y, Roh H-T (2014) The effects of ketogenic diet on oxidative stress and  
1610 antioxidative capacity markers of Taekwondo athletes. *J Exerc Rehabil* 10:362–366.  
1611 <https://doi.org/10.12965/jer.140178>
- 1612 Rinard J, Clarkson PM, Smith LL, Grossman M (2000) Response of males and females to  
1613 high-force eccentric exercise. *J Sports Sci* 18:229–236.  
1614 <https://doi.org/10.1080/026404100364965>
- 1615 Roberts PA, Fox J, Peirce N, et al (2016) Creatine ingestion augments dietary carbohydrate  
1616 mediated muscle glycogen supercompensation during the initial 24 h of recovery  
1617 following prolonged exhaustive exercise in humans. *Amino Acids* 48:1831–1842.  
1618 <https://doi.org/10.1007/s00726-016-2252-x>
- 1619 Roig M, O'Brien K, Kirk G, et al (2009) The effects of eccentric versus concentric resistance  
1620 training on muscle strength and mass in healthy adults: a systematic review with meta-  
1621 analysis. <https://doi.org/10.1136/bjsm.2008.051417>
- 1622 Rooney KJ, Herbert RD, Balnave RJ (1994) Fatigue contributes to the strength training  
1623 stimulus. *Med Sci Sports Exerc* 26:1160–1164. [https://doi.org/10.1249/00005768-  
1624 199409000-00014](https://doi.org/10.1249/00005768-199409000-00014)
- 1625 Sayers SP, Clarkson PM (2001) Force recovery after eccentric exercise in males and females.  
1626 *Eur J Appl Physiol* 84:122–126. <https://doi.org/10.1007/s004210000346>
- 1627 Schoenfeld BJ (2010) The mechanisms of muscle hypertrophy and their application to  
1628 resistance training. *J. Strength Cond. Res.* 24:2857–2872
- 1629 Schoenfeld BJ (2013) Potential mechanisms for a role of metabolic stress in hypertrophic  
1630 adaptations to resistance training. *Sport. Med.* 43:179–194
- 1631 Schoenfeld BJ (2012) Does Exercise-Induced Muscle Damage Play a Role in Skeletal Muscle  
1632 Hypertrophy? *J Strength Cond Res* 26:
- 1633 Sewright KA, Hubal MJ, Kearns A, et al (2008) Sex Differences in Response to Maximal  
1634 Eccentric Exercise. *Med Sci Sport Exerc* 40:242–251.  
1635 <https://doi.org/10.1249/mss.0b013e31815aedda>
- 1636 Sherman WM, Armstrong LE, Murray TM, et al (1984) Effect of a 42.2-km footrace and  
1637 subsequent rest or exercise on muscular strength and work capacity. *J Appl Physiol*  
1638 *Respir Environ Exerc Physiol* 57:1668–1673.  
1639 <https://doi.org/10.1152/jappl.1984.57.6.1668>
- 1640 Smith-Ryan AE, Fukuda DH, Stout JR, Kendall KL (2014) The influence of  $\beta$ -alanine  
1641 supplementation on markers of exercise-induced oxidative stress. *Appl Physiol Nutr*  
1642 *Metab* 39:101–104. <https://doi.org/10.1139/apnm-2013-0229>
- 1643 Smith AE, Stout JR, Kendall KL, et al (2012) Exercise-induced oxidative stress: The effects  
1644 of  $\beta$ -alanine supplementation in women. *Amino Acids* 43:77–90.  
1645 <https://doi.org/10.1007/s00726-011-1158-x>

- 1646 Smith LL, McKune AJ, Semple SJ, et al (2007) Changes in serum cytokines after repeated  
1647 bouts of downhill running. *Appl Physiol Nutr Metab* 32:233–240.  
1648 <https://doi.org/10.1139/H06-106>
- 1649 Stupka N, Lowther S, Chorneyko K, et al (2000) Gender differences in muscle inflammation  
1650 after eccentric exercise. *J Appl Physiol* 89:2325–2332.  
1651 <https://doi.org/10.1152/jappl.2000.89.6.2325>
- 1652 Sudo M, Ando S, Poole DC, Kano Y (2015) Blood flow restriction prevents muscle damage  
1653 but not protein synthesis signaling following eccentric contractions. *Physiol Rep*  
1654 3:e12449. <https://doi.org/10.14814/phy2.12449>
- 1655 Suga T, Okita K, Morita N, et al (2009) Intramuscular metabolism during low-intensity  
1656 resistance exercise with blood flow restriction. *J Appl Physiol* 106:1119–1124.  
1657 <https://doi.org/10.1152/jappphysiol.90368.2008>
- 1658 Suzuki K, Tominaga T, Ruhee RT, Ma S (2020) Characterization and modulation of systemic  
1659 inflammatory response to exhaustive exercise in relation to oxidative stress.  
1660 *Antioxidants* 9:. <https://doi.org/10.3390/antiox9050401>
- 1661 Suzuki K, Totsuka M, Nakaji S, et al (1999) Endurance exercise causes interaction among  
1662 stress hormones, cytokines, neutrophil dynamics, and muscle damage. *J Appl Physiol*  
1663 87:1360–1367. <https://doi.org/10.1152/jappl.1999.87.4.1360>
- 1664 Szeto YT, Kwok TCY, Benzie IFF (2004) Effects of a long-term vegetarian diet on  
1665 biomarkers of antioxidant status and cardiovascular disease risk. *Nutrition* 20:863–866.  
1666 <https://doi.org/10.1016/j.nut.2004.06.006>
- 1667 Takarada Y, Nakamura Y, Aruga S, et al (2000) Rapid increase in plasma growth hormone  
1668 after low-intensity resistance exercise with vascular occlusion. *J Appl Physiol* 88:61–65.  
1669 <https://doi.org/10.1152/jappl.2000.88.1.61>
- 1670 Tee JC, Bosch AN, Lambert MI (2007) Metabolic consequences of exercise-induced muscle  
1671 damage. *Sport. Med.* 37:827–836
- 1672 Thomas DT, Erdman KA, Burke LM (2016) Position of the Academy of Nutrition and  
1673 Dietetics, Dietitians of Canada, and the American College of Sports Medicine: Nutrition  
1674 and Athletic Performance. *J Acad Nutr Diet* 116:501–528.  
1675 <https://doi.org/10.1016/j.jand.2015.12.006>
- 1676 Tieland M, Trouwborst I, Clark BC (2018) Skeletal muscle performance and ageing. *J*  
1677 *Cachexia Sarcopenia Muscle* 9:3–19. <https://doi.org/10.1002/jcsm.12238>
- 1678 Tiidus PM (1995) Can estrogens diminished exercise induced muscle damage? *Can J Appl*  
1679 *Physiol* 20:26–38. <https://doi.org/10.1139/h95-002>
- 1680 Townsend JR, Stout JR, Jajtner AR, et al (2018) Polyphenol supplementation alters  
1681 intramuscular apoptotic signaling following acute resistance exercise. *Physiol Rep* 6:.  
1682 <https://doi.org/10.14814/phy2.13552>
- 1683 Trombly PQ, Horning MS, Blakemore LJ (2000) Interactions between Carnosine and Zinc  
1684 and Copper: Implications for Neuromodulation and Neuroprotection. *Biochem* 65:807–

1685 816

1686 Urhausen A, Gabriel H, Kindermann W (1995) Blood Hormones as Markers of Training  
1687 Stress and Overtraining. *Sports Med* 20:251–276. [https://doi.org/10.2165/00007256-](https://doi.org/10.2165/00007256-199520040-00004)  
1688 [199520040-00004](https://doi.org/10.2165/00007256-199520040-00004)

1689 Van Loon LJC, Murphy R, Oosterlaar AM, et al (2004) Creatine supplementation increases  
1690 glycogen storage but not GLUT-4 expression in human skeletal muscle. *Clin Sci*  
1691 106:99–106. <https://doi.org/10.1042/CS20030116>

1692 Vanacore D, Messina G, Lama S, et al (2018) Effect of restriction vegan diet's on muscle  
1693 mass, oxidative status, and myocytes differentiation: A pilot study. *J Cell Physiol*  
1694 233:9345–9353. <https://doi.org/10.1002/jcp.26427>

1695 Veech RL (2004) The therapeutic implications of ketone bodies: The effects of ketone bodies  
1696 in pathological conditions: Ketosis, ketogenic diet, redox states, insulin resistance, and  
1697 mitochondrial metabolism. *Prostaglandins Leukot Essent Fat Acids* 70:309–319.  
1698 <https://doi.org/10.1016/j.plefa.2003.09.007>

1699 Volek JS, Freidenreich DJ, Saenz C, et al (2016) Metabolic characteristics of keto-adapted  
1700 ultra-endurance runners. *Metabolism* 65:100–110.  
1701 <https://doi.org/10.1016/j.metabol.2015.10.028>

1702 Volek JS, Ratamess NA, Rubin MR, et al (2004) The effects of creatine supplementation on  
1703 muscular performance and body composition responses to short-term resistance training  
1704 overreaching. *Eur J Appl Physiol* 91:628–637. [https://doi.org/10.1007/s00421-003-](https://doi.org/10.1007/s00421-003-1031-z)  
1705 [1031-z](https://doi.org/10.1007/s00421-003-1031-z)

1706 Warren GL, Lowe DA, Armstrong RB (1999) Measurement tools used in the study of  
1707 eccentric contraction-induced injury. *Sport Med* 27:43–59.  
1708 <https://doi.org/10.2165/00007256-199927010-00004>

1709 Webb R, Hughes MG, Thomas AW, Morris K (2017) The Ability of Exercise-Associated  
1710 Oxidative Stress to Trigger Redox-Sensitive Signalling Responses. *Antioxidants* (Basel,  
1711 Switzerland) 6:63. <https://doi.org/10.3390/antiox6030063>

1712 Wikström-Frisén L, Boraxbekk CJ, Henriksson-Larsén K (2017) Effects on power, strength  
1713 and lean body mass of menstrual/oral contraceptive cycle based resistance training. *J*  
1714 *Sports Med Phys Fitness* 57:43–52. <https://doi.org/10.23736/S0022-4707.16.05848-5>

1715

1716

1717 **Figure Legends**

1718 **Figure 1. Schematic representation of the causes, physiological processes, and**  
1719 **consequences of exercise-induced muscle damage (EIMD).** Unaccustomed exercise, with  
1720 or without excessive overload, is associated with disruption of muscle tissue homeostasis and  
1721 mechanical damage to the muscle tissue. This, in turn, leads to a complex chain of  
1722 physiological events, both locally within the muscle and systematically, with a tight  
1723 connection between the outlined responses. As a result, inflammation is present, delayed  
1724 onset of muscle soreness (DOMS) occurs, range of motion (ROM) is compromised and,  
1725 subsequently, athletic performance is impaired. As outlined on the left, various factors can  
1726 affect the response to and degree of EIMD signs and symptoms. E-C: excitation-contraction

1727  
1728 **Figure 2. MRI-DTI of skeletal muscle.** Image showing a posterior view of the thigh muscle  
1729 fibers using 3-Tesla magnetic resonance imaging (MRI) scan with the color-coded measure  
1730 of mean diffusivity (MD). Diffusion-tensor imaging (DTI) assessment is dependent on cell  
1731 membranes and other structures constraining water diffusion. Water movement can be  
1732 evaluated by determining the three orthogonal directions of water diffusion, called  
1733 eigenvectors, and their intensities - eigenvalues. From the three eigenvalues ( $\lambda_1$ ,  $\lambda_2$ , and  $\lambda_3$ ),  
1734 parameters such as fractional anisotropy (FA) and mean diffusivity (MD) can be calculated to  
1735 evaluate the character of water diffusion in a voxel. These measures have been shown to  
1736 provide information about the integrity of skeletal muscle. FA and direction map with per-  
1737 voxel color-coded vector values.

1738

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

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