

# Exercise-Induced Muscle Damage: Is it detrimental or beneficial?

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Exercise-induced muscle damage (EIMD) is a well-known phenomenon that happens after performing lengthening contractions or unaccustomed exercise. Many studies have tried to reduce this muscle damage yet muscle damage is also known to produce a protective effect against future damaging exercise bouts.

**Objectives:** The purpose of this paper was to briefly discuss how EIMD can result in negative consequences and examine evidence for or against potential benefits of EIMD.

**Design and Methods:** Non-systematic review

**Results:** EIMD is detrimental in that it produces prolonged decreases in force and decreased exercise performance. If muscle damage is severe it may result in exercise-induced rhabdomyolysis and when it occurs in combination with dehydration or heat stress, it may potentially lead to life threatening issues such as acute kidney failure. Despite its detrimental effects, some have suggested possible benefits from EIMD. The potential benefits of EIMD include the repeated bout effect and muscle hypertrophy but these benefits can be produced without inducing EIMD.

**Conclusion:** After examining the detrimental and beneficial effects of EIMD, it seems that the detrimental effects outweigh any possible benefits of EIMD and many of the proposed benefits (repeated bout effect and hypertrophy) can be produced without EIMD.

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**Key words:** Eccentric ■ resistance training ■ repeated bout effect

In the early 1900's Dr. Theodore Hough noted a long lasting decline in force and increased soreness following exercise of the finger flexors<sup>1</sup>. In the early 1980's research on this exercise-induced muscle damage (EIMD) noted by Dr. Hough began to considerably increase. Newham et al.<sup>2</sup> investigated EIMD using electron microscopy and found significant changes in muscle structure immediately after exercise, and the number of damaged fibers continued to increase after 30 hours. Furthermore, cases of extreme muscle damage, such as rhabdomyolysis, following exercise could potentially lead to life-threatening problems such as acute kidney failure and hypokalemia<sup>3</sup>. Deciphering the mechanisms behind EIMD has been perplexing and is still not completely understood despite the many years of research. Because of the negative effects of EIMD many researchers have sought to decrease the amount of muscle damage after a damaging bout of exercise but few prophylactic interventions have proven effective<sup>4</sup>. Interestingly, one of the most powerful protections against muscle damage is a preceding damaging exercise bout<sup>4</sup> which raises the question, is muscle damage detrimental or beneficial? This is a pertinent question to many people who train recreationally or who train for exercise competitions. Some may have the idea that muscle damage is necessary for maximal gains or others may feel that it should be avoided altogether. Thus, the purpose of this brief review will be to discuss some of the detrimental effects of muscle damage and to examine if muscle damage is needed to provide beneficial adaptations such as the repeated bout effect or muscle hypertrophy.

## Muscle damage mechanisms

Before discussing possible detrimental effects of muscle damage, it is important for the athlete and recreationally active individual to understand the mechanisms initiating EIMD. This review will briefly discuss some potential mechanisms producing EIMD and recommends the reader to see other reviews for more detailed information<sup>5-7</sup>. Figure 1 outlines a simple diagram of the possible mechanisms of muscle damage. Several events happen to induce muscle damage. Specifically, the type of exercise producing the damage is important. Lengthening contractions tend to produce the greatest amount of muscle damage. It was noted by Newham et al.<sup>2</sup> that little damage was caused by shortening contractions but significantly greater damage was found in muscles performing lengthening contractions. In addition, maximal isometric contractions performed at 90 degrees elbow flexion produce no muscle damage<sup>8</sup> but when they are performed at longer muscle lengths (20 degrees elbow flexion) muscle damage occurs<sup>9</sup>. Thus, it seems that the initial event producing muscle damage results from mechanical damage to the muscle fiber when it contracts at long muscle lengths or during lengthening contractions.

Mechanical factors that contribute to the amount of EIMD include the number of contractions, force, specific force, and contraction velocity. As the number of lengthening contractions increase, a greater amount of EIMD is found<sup>10</sup>. Force and specific force are particularly important factors

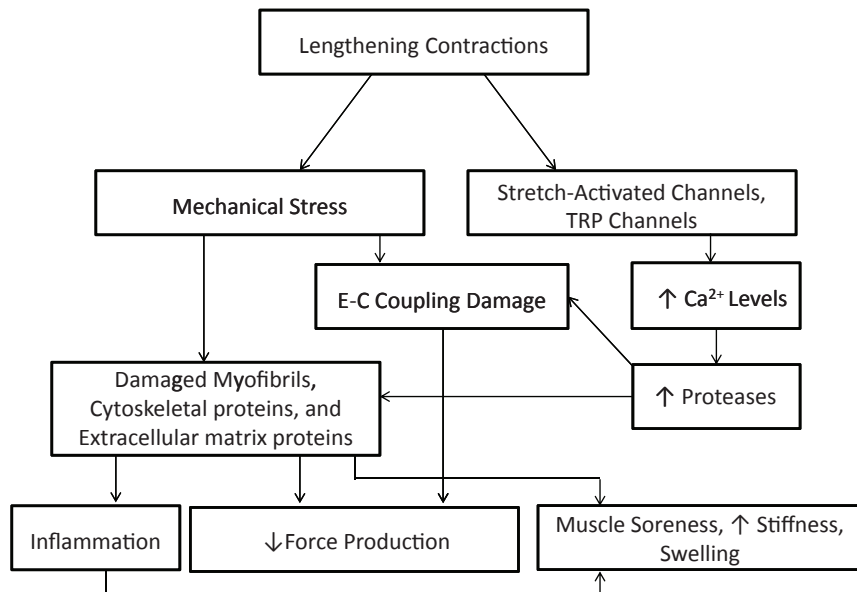
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**Figure 1.** Possible Mechanisms of Exercise-Induced Muscle Damage. E-C coupling=Excitation-contraction coupling. TRP=Transient receptor potential.

producing EIMD. For example, McCully and Faulkner<sup>11</sup> found that decreases in maximum isometric force were highly correlated with histological muscle damage and that this injury was related to the amount of peak force produced during eccentric contractions. Another study found that the peak total force produced during the eccentric contractions decreased muscle performance independent of lengthening velocity or muscle length change<sup>12</sup>. Lieber and Friden<sup>13</sup> also found that high forces did not necessarily dictate the amount of muscle damage produced but rather it was the muscle fiber strain produced during the lengthening contractions. In addition, they found that faster lengthening velocities produced more muscle damage than slower velocities. Another study reported that higher specific torque eccentric contractions resulted in greater amounts of muscle damage compared to lower specific torque eccentric contractions when matching contraction velocity, range of motion, active muscle, and contraction number<sup>14</sup>. All of these studies indicate that mechanical factors play a role in EIMD, and the mechanical damage produced by these factors translates into damage at the muscle fiber level.

When the muscle is lengthened, the amount of overlap between myosin and actin decreases in individual sarcomeres with a greater stretch produced particularly in weaker sarcomeres<sup>7</sup>. Lengthening contractions produce greater levels of force than shortening contractions while recruiting fewer motor units. This can therefore substantially increase the tension on individual muscle fibers<sup>15</sup>. The high levels of tension in stretched sarcomeres can cause the overlap between myofilaments to become disrupted. Due to a disruption in the overlap between actin and myosin in some sarcomeres, the cytoskeletal protein matrix of the muscle fiber, especially the z-disk area, will bear the added tension<sup>7</sup>. Muscle biopsies clearly demonstrate disruption of the sarcomeres after lengthening contractions, particularly at the z-disks<sup>2,16,17</sup>. The

disruption in the z-disks results in damage to cytoskeletal proteins that are crucial to maintaining the structure of the sarcomere such as desmin<sup>18</sup>. Other potentially damaged z-band related proteins may be Rab-35 (z-band assembly protein) and LDB3 (co-localized with alpha-actinin to stabilize the z-band)<sup>19</sup>. With repetitive lengthening contractions and higher-intensity contractions, the tension in the muscle fiber will increase and muscle damage will spread to other z-bands and sarcomeres in the muscle fiber as fewer sarcomeres remain intact. The disrupted sarcomeres will then result in a shift in the optimum length-tension relationship of the muscle<sup>20</sup>.

The mechanical stress to the muscle fiber may not only damage the sarcomere structure but can damage the excitation-contraction (EC)-coupling complex resulting in a loss of force. Warner et al.<sup>21</sup> suggested that the EC-coupling complex is disrupted specifically in the connection between the t-tubules and the ryanodine receptors of the sarcoplasmic reticulum membrane. One type of protein involved in this connection is the junctophilin protein which allows a direct connection between the t-tubule and ryanodine receptors<sup>22</sup>. Corona et al.<sup>22</sup> found that after performing 50 lengthening contractions, junctophilin levels were significantly reduced and that the junctophilin damage was significantly associated with the decline in force. The authors concluded that damage to the EC-coupling complex, specifically junctophilin, may play a role in the early force deficits that occur after lengthening contractions.

Mechanical stress is not the only mechanism producing damage in the muscle fiber, but activation of calpains seems to play an important role. Activation of ionic channels such as stretched-activated calcium channels or transient receptor potential channels can increase intracellular calcium levels<sup>6</sup>. It has been reported that intracellular calcium levels significantly increase after lengthening contractions while the

tetanic intracellular calcium decreases<sup>23</sup>. As the intracellular calcium levels rise, calcium proteases called calpains, become activated and these proteases can then cleave proteins such as titin, desmin, nebulin, troponin, tropomyosin, kinases and other signaling molecules producing more damage to the muscle<sup>6</sup>. However, the complete role of calpains in producing muscle damage is still not completely understood. For instance, one study found a threefold increase in calpain activity 30 minutes after eccentric exercise but the increase in calpain activity did not correlate well with myofibrillar disruptions<sup>16</sup>. As the damaged fibers continue to accumulate, inflammation increases such that neutrophils and macrophages enter the muscle fibers<sup>24</sup>. Tidball et al.<sup>25</sup> suggest that M1 macrophages and neutrophil fibers increase during the early stages of muscle damage followed by increases in M2 macrophages which help activate satellite cells and to later promote skeletal muscle repair.

Muscle damage thus appears to initially be dependent on the mechanical stress placed on the sarcomeres. The mechanical stress on the muscle fiber puts strain on the muscle fiber elements which includes the cytoskeleton, z-disks, myofibers, plasma membrane and sarcoplasmic reticulum. In addition, the mechanical stress can activate stretch-activated calcium channels or transient receptor potential channels which increase intracellular calcium levels. The rise in calcium then activates calcium proteases which promote further destruction of proteins in the myofiber. The accumulation of damaged proteins will then initiate an inflammatory response. The end result of muscle damage is a decrease in force production, muscle soreness, increased blood proteins (CK and myoglobin) and swelling in the exercised limb.

### **Muscle Damage and Detrimental Effects**

Since the early 1980's, researchers have examined muscle damage using a variety of populations and methods. Some studies have used animals<sup>23,24</sup>, humans<sup>26,27</sup>, downhill running<sup>19</sup>, stair-stepping<sup>2</sup>, and resistance exercises (elbow and knee flexors and knee extensors)<sup>16, 28, 29</sup>. Exercise-induced muscle damage occurs when an exercise bout is performed that damages the myofibrils, most notably at the z-lines<sup>5</sup>. Specifically, it happens after lengthening contractions or isometric contractions at long muscle lengths. Markers of EIMD include delayed-onset soreness that peaks approximately 24-72 hours following exercise, decreased force production, decreased range of motion, swelling of the exercised limb, increased muscle proteins in the blood (creatinase kinase and myoglobin), increased MRI T2 relaxation time, and increased ultrasound echo intensity levels<sup>30, 31</sup>. Of these indirect markers, the most reliable marker indicating muscle damage is sustained decreases in force production<sup>32</sup>. This decrement in muscle force production is also highly correlated with myofibrillar disruptions (myofilament disorganization or z-disk damage)<sup>16</sup>.

However, a common misunderstanding of muscle damage is that the amount of muscle damage is equivalent to the amount of soreness that develops following exercise. Nosaka et al.<sup>33</sup>

examined the association between indirect markers of muscle damage (maximal isometric force, range of motion, upper arm circumference, and creatine kinase levels) and soreness levels in individuals who performed 12, 24, or 60 maximal lengthening contractions. No differences were found between soreness levels despite the fact that force decrements were significantly different for the different number of contractions performed. Furthermore, soreness levels did not correlate well with other indirect markers of muscle damage. Hence, these results demonstrate that using DOMS alone to assess the magnitude of muscle damage would not be correct as DOMS does not always correlate well with other indirect markers of muscle damage.

### **Exercise performance and muscle damage**

Despite the many symptoms associated with EIMD, detrimental consequences of EIMD include a decrease in force production<sup>5</sup>, a decrease in muscle power,<sup>34</sup> and a decrease in exercise performance<sup>35</sup>. In an athletic competition, optimal exercise performance is the goal but muscle damage can impair the athlete's performance. In particular, endurance performance is modified with muscle damage. For example, men and women who performed a muscle damaging protocol of 100 drop jumps experienced a 12% decrease in knee extensor force production and increased muscle soreness<sup>36</sup>. Subsequently, 48 hours after the muscle damaging exercise, the amount of distance ran in a 30 minute time-trial significantly decreased (6631 m vs. 6781 m)<sup>36</sup>. Another study also found that 48 hours after a muscle damaging protocol of bench press exercise that arm-cranking time to exhaustion was significantly decreased by 27%<sup>37</sup>.

Not only can muscle damage impact endurance performance but other events requiring more power seem to be affected by muscle damage. One study found that 48 hours after performing 100 vertical jumps to elicit muscle damage, 5-minute cycle time-trial peak power output, mean power output, and distance covered were significantly reduced<sup>35</sup>. In addition another study by Highton et al.<sup>38</sup> reported that 24 and 48 hours after performing 100 vertical jumps, 5 and 10 m sprint time was significantly increased and agility performance time was significantly increased. Overall, EIMD impairs exercise performance which could be detrimental in a competitive sports event. Therefore, in the days preceding sports competitions, exercises that induce muscle damage should be avoided to reduce potential decrements in exercise performance.

### **Exercise-induced rhabdomyolysis**

Another detrimental effect of muscle damage is when it is too extreme and results in exercise-induced rhabdomyolysis. Exercise-induced rhabdomyolysis is the destruction of muscle cells from exercise and is associated with myalgia, muscle weakness, muscle swelling, myoglobinuria, and elevated CK levels (greater than 70,000 U/L)<sup>3, 39, 40</sup>. Creatine kinase levels may become extremely high but it is myoglobinuria that can be dangerous especially when it is accompanied by dehydration, heat stress or hypotension. When the amount of

myoglobin in the blood surpasses the ability of the kidney to filter it, myoglobin will enter the urine resulting in the myoglobinuria, or a dark-colored urine. If the pH of the blood goes below 5.4, myoglobin can disassociate to globin and ferrihennate which is toxic to the renal tubules in the kidney and can lead to acute kidney failure.<sup>39</sup> However, only 5 to 7% of rhabdomyolysis cases produce this acute kidney failure.<sup>39</sup> In addition, it can also lead to compartment syndrome especially in the lower body which if not corrected can cause nerve compression and potentially reduce muscle function.<sup>39</sup>

The exact cause is not completely understood but clinically significant exercise-induced rhabdomyolysis can happen in healthy individuals. Sayers and Clarkson<sup>39</sup> suggested that the primary factor producing rhabdomyolysis is the exercise itself but secondary factors such as hypoxia, genetics, high temperature, high humidity, alcohol, nutritional supplements containing ephedrine or androstenedione, drugs, sickle cell trait, hypokalemia or training status may actually increase the response of the muscle damage and, therefore, produce exercise-induced rhabdomyolysis. Most often it happens after exercising beyond the point of fatigue in group settings such as basic military training<sup>41</sup>, athletic training<sup>42</sup>, or personal training<sup>43</sup>. Sayers et al.<sup>40</sup> even noted six cases of subjects exhibiting signs of rhabdomyolysis when performing eccentric exercise in a lab setting with one case being clinically diagnosed as rhabdomyolysis. Surprisingly, one of those cases reported high levels of myoglobin after only performing exercise in one arm. Thus, care should be taken especially when performing whole body exercises that include multiple muscle groups. Overall, exercise-induced rhabdomyolysis is an extreme form of muscle damage that is a rare occurrence but when conditions are right, can lead to acute kidney failure or even nerve damage.

### **Beneficial Effects of EIMD?**

Despite the negative consequences associated with muscle damage, the plasticity of muscle allows it to adapt to this damage and become “stronger”. Most notably, muscular strength and size increase after eccentric exercise, and the muscle becomes less prone to future damage from exercise. However, are these adaptations dependent upon damaging the muscle? The next few sections will discuss the role of muscle damage in producing these potential benefits.

### **Repeated bout effect**

One of the most recognized and studied adaptations to muscle damage is the “repeated bout effect”. The repeated bout effect refers to the protection or attenuation in muscle damage markers observed following a second bout of exercise. It is well known that a damaging bout of exercise through eccentric actions will result in a protective effect in subsequent repeated bouts<sup>44-46</sup>. Researchers continue to examine what produces this protective effect and various exercise modes and intensities that can minimize subsequent muscle damage. Interestingly, this protective effect is provided by exercise that does not produce severe muscle damage. Therefore, this

section will focus on the influence of exercise intensity and muscle damage on the repeated bout effect and evidence that suggests muscle damage may not be needed for the repeated bout effect to happen.

Intensity plays a large role in the repeated bout effect and can determine the amount of protection that results. Chen et al.<sup>45</sup> examined the influence of intensity on the repeated bout effect. Subjects performed a total of 30 lengthening contractions at 40%, 60%, 80% or 100% MVC during the first bout followed by a second bout of 30 maximal lengthening contractions 2-3 weeks later. Analyzing the protection of the first bout on markers of muscle damage, they determined that the larger the exercise intensity at the first bout, the greater the protective effect. Also, even a low-intensity of 40% MVC provided protection ranging from 20%-60% for range of motion (ROM), creatine kinase (CK), myoglobin (Mb), circumference (CIR), and muscle soreness; however, it did not provide a protective effect for MVC. In addition, markers of muscle damage were not totally abolished despite the same intensity being used for the first and second bout but it provided the greatest amount of protection.

Interestingly, studies demonstrate that intensities lower than 40% MVC provide protection at a subsequent bout despite not producing evidence of muscle damage after the first bout. For example, Lavender et al.<sup>47</sup> found that a 10% MVC lengthening exercise bout did not result in any significant changes in MVC, ROM, CIR, CK and muscle soreness. Two days after the first bout, subjects performed a bout of 40% MVC lengthening contractions. Another group performed only a 40% MVC lengthening exercise bout and the groups were compared. Performing a bout of 10% MVC lengthening contractions two days prior to a greater intensity bout of exercise provided a significant attenuation in MVC decline, ROM, and muscle soreness but no significant differences were found between groups for upper arm circumference and CK levels. Despite performing a low-intensity bout that produced no muscle damage, some protection is provided. This is an important point and demonstrates that muscle damage is not needed to provide a protective effect. Although it is a minimal protection, for someone beginning a resistance training session or during detraining periods, he or she could gradually increase the exercise intensity to minimize potential muscle damage at future training sessions.

However, the length of this protective effect for such a low intensity may be relatively short lived. Indeed, Chen et al.<sup>26</sup> tested how long a protective effect would last when a bout of 10% MVC lengthening contractions was performed prior to a bout of 100% MVC lengthening contractions. Subjects repeated the second bout at 2, 7, 14, or 21 days after the first bout. The greatest attenuation of upper arm circumference, ROM, CK levels, Mb levels, muscle soreness, echo intensity, and MVC happened following 2 and 7 days but decreased by 14 days and did not provide a protective effect at 3 weeks. These findings demonstrate that the protective effect of a low-intensity bout is short lived and abolished by 3 weeks. Because the level of protection increases with exercise intensity, it was hypothesized that the length of protection may



also increase with a higher intensity. Indeed, while a 10% MVC eccentric exercise did not provide a protective effect 3 weeks later, a bout of 20% MVC eccentric contractions did provide protection<sup>48</sup>.

Another interesting aspect of the repeated bout effect is that isometric contractions produce some protection. Chen et al.<sup>48</sup> investigated how low-intensity eccentric contractions or maximal isometric contractions performed at different muscle lengths would influence the repeated bout effect. Subjects were placed into one of five groups and during the first exercise bout performed 30 contractions of either maximal eccentric actions, 10% of maximal voluntary isometric contractions (MVIC) eccentric exercise, 20% MVIC eccentric exercise, 90 degrees maximal isometric contractions, or 20 degrees maximal isometric contractions. After the first bout, all the groups had significantly smaller changes in indirect markers of muscle damage when compared to the maximal eccentric contraction group. However, no significant differences in the changes between the 20 degree maximal isometric and 20% MVIC eccentric contractions were found. Three weeks later all groups performed maximal eccentric actions. The greatest protection occurred when the maximal eccentric actions (64-98%) were performed at the first bout. After that, the largest protection was produced by the 20 degree maximal isometric contractions (27-63%) then 20% MVC eccentric actions (17-55%), 10% MVC eccentric contractions (0%-36%) and lastly the 90 degree maximal isometric contractions (0%-11%). From these findings, it seems apparent that as the intensity increases, the protective effect is greater. In addition, an isometric contraction performed at long muscle lengths produced little damage but provided a significant protective effect.

Despite differences in intensities during the first bout, the muscle adapts to exercise making the muscle less prone to future damage. Some muscle damage may be beneficial in this regard as greater exercise intensities provide a greater protective effect. Yet, low to moderate intensities that produce little muscle damage performed previous to a higher intensity bout provide some protection and could provide a useful training strategy for individuals beginning resistance training for the first time. The exact mechanism producing this protective effect is not clearly understood but the initial exercise stimulus may induce cellular or neural adaptations that produce a protective effect by decreasing the mechanical stress or proteolytic response at the second bout of exercise. One possible adaptation to an exercise bout may be the expression of heat shock proteins. Heat shock proteins (HSPs) may protect the muscle from future damage by aiding in the refolding of damaged proteins and folding of newly synthesized proteins after exercise<sup>49</sup>. Paulsen et al.<sup>49</sup> found that HSP27 and HSP70 levels significantly increased after 2 bouts of exercise particularly at the z-disks and at sites of myofibrillar disruption and suggested they played a role in protecting the muscle from future damage. Another possible adaptation may be increases in cytoskeletal proteins such as desmin, titin, and dystrophin. Using the proteomic technique, a damaging bout of downhill running significantly increased

desmin and actin protein expression<sup>19</sup>. Furthermore, Lehti et al.<sup>50</sup> found an increase in desmin, dystrophin, and titin mRNA levels after downhill running in rats. These findings suggest that the cytoskeletal proteins may play a role in future protection of the muscle. However, future studies should examine the response of these cytoskeletal proteins and HSPs to low-intensity exercise that provides a protective effect.

Another possible adaptation producing the repeated bout may be the strengthening of the extracellular matrix. Mackey et al.<sup>51</sup> used intermittent electrical stimulation of the gastrocnemius medialis muscle to produce muscle damage and found a significant decrease in heat shock proteins and tenascin C after the second bout of exercise when compared to the first bout of exercise 30 days earlier. Also, 30 days after the first bout satellite cells were significantly elevated and also extracellular matrix lamin-B1 and collagen types I and II were elevated 6-9 fold. The authors concluded that after the muscle damage, a breakdown in the connective tissue happens followed by an anabolic response that increases the connective tissue strength in the muscle, thereby, providing protection at the subsequent bout.

Interestingly, there is some evidence that protection can be provided without the need of causing direct damage to the muscle. This is considered the repeated bout cross-transfer effect. A cross-transfer effect refers to the idea that when one limb increases in strength after unilateral training, the contralateral limb will also increase in strength<sup>52</sup>. The first study to examine if a similar type of cross-transfer effect would occur with regards to protection from a second bout of muscle damage reported no cross-transfer protective effect in the contralateral limb after performing two bouts of quadriceps eccentric exercise<sup>53</sup>. However, several other studies have noted a cross-transfer protective effect after a repeated bout. Howatson et al.<sup>54</sup> investigated if a protective effect would be found in the contralateral arm 2 weeks after performing 3 sets of 15 maximal eccentric exercises of the elbow flexors in the ipsilateral arm. Following 2 weeks of rest, a bout of exercise performed in the contralateral arm produced levels of creatine kinase, delayed-onset muscle soreness and maximal isometric torque that were significantly attenuated when compared to the first bout. The authors also reported that the attenuation in markers of muscle damage in the contralateral group were smaller when compared to the group that performed both bouts with the ipsilateral arm.<sup>54</sup>

Another study by Starbuck and Eston<sup>55</sup> found similar results. They had subjects perform six sets of 10 maximal eccentric contractions of the elbow flexors with the ipsilateral arm during the first bout. Then after 2 weeks, the second exercise bout was performed with either the ipsilateral or contralateral arm. A significant attenuation of muscle damage markers was reported in the contralateral arm and ipsilateral arms. In addition, the authors also reported similar reductions in median frequency in both the ipsilateral and contralateral arms from bout 1 to bout 2 suggesting similar neural adaptations between the two arms. More recently, Newton et al.<sup>56</sup> also determined that when a second bout of exercise is performed with the contralateral arm that creatine kinase

levels, maximal isometric torque, and upper arm circumference were significantly attenuated when compared to the first bout of exercise performed 4 weeks earlier.

These studies provide evidence that the repeated bout effect is produced under conditions in limbs where little muscle damage is produced. In addition, the cross-transfer repeated bout effect demonstrates that part of the repeat bout effect is produced irrespective of mechanical damage. This protective effect is most likely provided through neural mechanisms as suggested by Starbuck and Eston<sup>55</sup>. A complete understanding, however, of the involvement of the neural system in producing this repeated bout effect is still not clear. For example, Black and McCully<sup>57</sup> found that when muscle was voluntarily activated or electrically stimulated to perform lengthening contractions that no differences were found in the repeated bout effect between conditions for T2 relaxation time, MVC or soreness levels. The authors concluded that changes in muscle recruitment may not be an underlying adaptation with the repeated bout effect. In addition, Muthalib et al.<sup>58</sup> found no difference in muscle activation between the first and second bout and no differences in muscle oxidative metabolism. However, Dartnall et al.<sup>59</sup> determined that motor unit synchronization increased after the first bout of eccentric exercise but following the second bout of eccentric exercise motor unit synchronization declined indicating a neuromuscular adaptation.

In conclusion, the repeated bout effect increases with increasing intensity resulting in the greatest protective effect. However, muscle damage is not necessarily needed to provide a protective effect as low-intensity exercise that produces little evidence of muscle damage results in protection. Even after isometric exercises at long muscle lengths this protective effect is produced. The protective effect may be through cellular mechanisms that improve the muscle fibers ability to handle mechanical stress through HSPs, increased levels of cytoskeletal proteins, or increased extracellular matrix components. Neural adaptations may also provide some protection as evidenced by the cross-over repeated bout effect. More research is needed to clarify the possible underlying cellular and neural adaptations that result in some protection after low-intensity eccentric and isometric exercise.

### Muscle Hypertrophy

Another idea associated with muscle damage is that it may be needed for muscle hypertrophy. This is an interesting topic to both recreational and professional athletes and can influence how they train to maximize muscle hypertrophy. A recent review article suggests that muscle damage may play an important role with muscle hypertrophy<sup>60</sup>. Evidence supporting this notion is typically found by the effect that eccentric resistance training has on muscle hypertrophy and strength. Eccentric resistance training, which is known to produce more muscle damage than concentric resistance training, seems to produce greater strength and muscle mass gains compared to concentric resistance training<sup>61</sup>. For example, Hortobagyi et al.<sup>62</sup> had subjects perform either isokinetic concentric or isokinetic eccentric exercise consisting

of 4-6 sets of 8-12 repetitions over a period of 12 weeks. After 12 weeks, type II fiber area was 10 times greater in the eccentric training group than the concentric training group.

However, an important point to consider when examining muscle hypertrophy between conditions is to examine the total work or amount of volume being performed. Moore et al.<sup>63</sup> did an interesting study and compared changes in muscle hypertrophy and strength when both lengthening and shortening training conditions were matched for work and training intensity (maximal contractions). The lengthening contraction limb performed significantly greater work per repetition compared to the shortening contraction limb (68 kJ/rep vs. 42 kJ/rep) and the shortening contraction limb performed 40% more repetitions in order to match the total work of the lengthening contraction limb. After 9 weeks of training, both conditions had similar increases in muscle hypertrophy (7% vs. 5%). Thus, the authors came to the conclusion that when eccentric and concentric training protocols are work and intensity matched then similar muscle hypertrophy results. The possibility then exists that it is the exercise stimulus itself that is producing the changes in hypertrophy and not necessarily the lengthening contractions which are well known to produce muscle damage.

If muscle damage is necessary for muscle hypertrophy, then one would expect that damaging bouts of downhill running or stair stepping would promote muscle hypertrophy. Downhill running and stair stepping which accentuate eccentric movements produce significant muscle damage although to a lesser degree than lengthening resistance exercise<sup>2, 19, 64</sup>. While downhill running may not induce severe muscle damage, regeneration of myofibers and increased muscle fiber hypertrophy signaling after an acute bout of downhill running have been reported in mice<sup>65, 66</sup>. However, little muscle hypertrophy may result from this type of training. Recently, Zou et al.<sup>67</sup> investigated the influence of downhill training in wild type mice and mice with an overexpression of  $\alpha 7$ -integrin. Integrins are transmembrane receptors that allow chemical and mechanical signals to be transmitted from the outside of the cell to the inside of the cell and could play a role in the muscle hypertrophic response<sup>68</sup>. Consistent with this idea, the mice that overexpressed  $\alpha 7$ -integrin significantly increased muscle hypertrophy after 4 weeks of downhill running<sup>67</sup>. On the other hand, wild-type mice without overexpression of  $\alpha 7$ -integrin that performed downhill running for 4 weeks did not significantly increase in muscle size. This supports the idea that downhill running training may not be beneficial to muscle hypertrophy but that part of the hypertrophy response normally found with exercise may be through  $\alpha 7$ -integrin.

Unfortunately, very few studies have investigated the changes in muscle hypertrophy and muscle damage<sup>60</sup>. The difficulty in developing a training program that produces muscle damage and continuing to produce muscle damage is the repeated bout effect and training design. One study tried to examine how muscle damage would affect muscle hypertrophy in mice. Komulainen et al.<sup>69</sup> electrically stimulated the anterior tibialis muscle of mice during lengthening or

shortening exercise. One contraction was performed every 3 seconds for a total of 240 contractions. Markers of muscle damage included beta-glucuronidase and desmin loss of the muscle fibers. At 4 days, lengthening contractions significantly increased beta-glucuronidase levels compared to shortening contractions; however, at no other time points were levels statistically different from each other. After 80 days muscle hypertrophy was not statistically different between conditions but both were significantly greater than the control limb. The authors concluded that muscle damage was not needed to provide greater amounts of muscle hypertrophy.

Another study using humans tried to create two similar training programs with similar volume where one program would produce muscle damage and the other would not<sup>70</sup>. To do this, subjects exercised on a recumbent ergometer with pedals that pushed towards the subject producing lengthening contractions. One group started training 3 weeks prior to the other group and gradually built up the duration and intensity of exercise to not induce any muscle damage. In this group significant increases in levels of CK and muscle soreness never occurred but in the group that started exercise for 20 minutes at the beginning of training, they experienced significant increases in CK levels and significant soreness. After several weeks of training no differences were found between increases in strength and muscle hypertrophy<sup>70</sup>.

From these studies, little evidence is found that supports the notion that muscle damage is needed for hypertrophy or increases the muscles ability to increase in size. An interesting exercise intervention that may also support this idea is blood flow restriction (BFR) resistance exercise. Blood flow restriction involves blocking venous return and decreasing arterial flow to the exercising limb. Blood flow restriction combined with low-load resistance exercise (20-30% 1RM) produces significant strength and muscle size gains similar to high-intensity resistance training<sup>71</sup>. Some studies suggest that muscle damage is happening during BFR<sup>72,73</sup>. However, other studies have demonstrated that indirect markers of muscle damage such as CK levels and ROS are not significantly elevated following blood flow restriction exercise<sup>74,75</sup>. Furthermore, one study found that when leg extension exercise was combined with BFR at 30% 1RM that maximal torque returned to baseline values by 24 hours<sup>76</sup>.

Unpublished data from our lab also shows little if any change in muscle damage markers following low-load resistance exercise when combined with BFR. For example, when performing either lengthening or shortening contractions of the elbow flexors at 30% 1RM, no significant decreases in force were found and only the lengthening condition had significant soreness levels peaking at 24 hours (unpublished data). Interestingly, when young men train for 6 weeks using the same BFR exercise protocol, a significantly greater amount of muscle hypertrophy occurs in the shortening contraction condition which produces no muscle damage (unpublished data). Overall, it seems unlikely that BFR resistance exercise is causing any significant amounts of muscle damage, yet still produces significant gains in muscle mass.

The increases in muscle size following resistance exercise in

combination with blood flow restriction could be attributed to various mechanisms. In older and young adults, BFR resistance exercise concurrently activates both the mammalian target of rapamycin (mTOR) and mitogen activated kinase (MAPK) pathways.<sup>77,78</sup> In addition, BFR resistance exercise increases myogenic stem cells and myonuclei in muscle which could contribute to the increased muscle hypertrophy<sup>79</sup>. Other possible mechanisms producing the increased levels of muscle hypertrophy with little muscle damage include cell swelling or increased activation of type II fibers.<sup>80,81</sup>

Overall, muscle damage does not seem to be needed to increase muscle hypertrophy. However, more studies examining microtears and molecular events not necessarily evidenced by indirect markers such as CK, force and soreness are needed. Rather than increasing muscle size, the muscle damage produced after a damaging exercise bout results in a chain of events that strengthen the extracellular matrix and connective tissue to protect the muscle from tearing at a subsequent exercise bout which have been noted in studies examining the repeated bout effect.

## Conclusion

In conclusion, muscle damage is detrimental in the fact that it produces significant declines in muscle force, decreases power output, decreases exercise performance, and when severe can lead to acute kidney failure. Despite the negative consequences of muscle damage, muscle damage may be beneficial in the fact that the muscle increases its ability to recover faster from a second bout of exercise, although, muscle damage is not needed to provide a protective effect. Furthermore, evidence substantiating that muscle damage is needed or increases the muscles ability to increase muscle mass is lacking.

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