

# Resistance exercise, muscle damage and inflammatory response “what doesn’t kill you makes you stronger”

## Abstract

Exercises involving eccentric actions, mainly in untrained subjects, induce muscular damage to a higher extent than concentric actions. This damage arises from muscle injury and may cause rupture and inflammation of muscle, connective or nervous tissues. These changes in muscle morphology may occur as a direct consequence of exercise-induced mechanical stress or later due to activation of calcium-sensitive degradation pathways and inflammatory response. Later, this damage is exacerbated by the inflammatory response in the days after the exercise. However, an attenuated inflammatory response to a repeated bout reflects in an adaptation to avoid the proliferation of the mechanical disruption of myofibrils. Thus, muscle damage decreases when a person performs the same exercise consistently. This phenomenon is commonly known as the repeated bout effect or protective effect.

**Keywords:** Resistance exercise, skeletal muscle, muscle damage, muscle inflammation

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**Abbreviations:** EIMD, exercise-induced muscle damage; ILs, interleukins; MCP1, monocyte chemoattractant protein-1; CANP, calcium activated neutral proteases; RT, resistance training; MPS, muscle protein synthesis

## Introduction

Intense exercise, principally when a person is untrained or unaccustomed to it, can cause damage to skeletal muscle. This phenomenon, commonly known as exercise-induced muscle damage (EIMD), occurs particularly if the exercise involves a large amount of eccentric (muscle lengthening) contractions. There are different types of muscle actions: concentric, eccentric and isometric. The eccentric actions occur during the lowering phase of any weightlifting exercise and are defined as muscle actions at the places where the muscle lengthens because the contraction force is less than the resistive force.<sup>1</sup> Eccentric contractions occur frequently in everyday activities and in resistance exercise. They are characterized by the ability to achieve high muscle forces, an enhancement of the tissue damage that is associated with muscle soreness and perhaps require unique control strategies by the central nervous system.<sup>2,3</sup> Initial resistance exercise-induced stress mainly in the untrained state, affecting muscle homeostasis and promoting changes in muscle morphology, such as disturbances in cytoskeleton (e.g. Z-band streaming), loss of sarcomeric structural proteins (e.g. desmin and dystrophin), muscle fiber segmental necrosis, alterations in connective tissue, as well as in T-tubules and sarcoplasmic reticulum.<sup>4</sup> In addition, there is evidence of damages such as delayed onset muscle soreness, elevated intracellular enzymes in the blood (e.g., creatine kinase, lactate dehydrogenase and myoglobin), loss of calcium homeostasis decreased joint range of motion and edema. Additionally, eccentric exercise also shows a larger increase in plasma creatine kinase activity, whereas concentric and isometric exercise did not increase this enzyme.<sup>5</sup> However the decline in muscular force/torque is considered one of the most valid and reliable indirect markers of exercise-induced muscle damage.<sup>6</sup>

Delayed onset muscle soreness, that occurs 24 to 48 hours after unaccustomed exercise, appears to be related momentarily more to an inflammatory response than to the appearance of structural damage.<sup>2</sup> Furthermore, muscle soreness occurs only after eccentric exercise.<sup>5</sup>

## Discussion

Based on the cross-bridge theory of muscle contraction, the force exerted by muscle is generated by the interaction of actin and myosin, which results in the myofibrillar proteins translating relatively to one another. In this sense, when an eccentric contraction occurs, the muscle fibers are lengthened and the actomyosin bonds are probably disrupted mechanically rather than undergo an ATP-dependent detachment. This tension in the muscle may contribute to the tissue damage.<sup>2</sup> There are greater similarities between the acute inflammatory response to infection and the immune response to EIMD. After resistance exercise, neutrophils from the blood increase in number in the area of the myotrauma and the damaged myofibers release agents that stimulate and attract macrophages and lymphocytes to the injured tissue. The macrophages remove cellular debris, a crucial step for maintaining the structure of muscle during repair and also produce cytokines which activate myoblasts, macrophages and lymphocytes.<sup>3</sup> However, neutrophils and macrophages can influence muscle hypertrophy via their capacity to perform phagocytosis and to produce free radicals, cytokines and growth factors.<sup>7</sup> The inflammatory process caused by muscle damage has an overall beneficial or detrimental effect on muscle function depending on the magnitude of the response, the injury-specific interactions between the muscle and inflammatory cells and previous exposure to the applied stimulus.<sup>8</sup>

Inflammatory cells can also produce several interleukins (ILs). ILs is a class of cytokines released by numerous body tissues to control and coordinate immune responses.<sup>9</sup> IL-6 is a pleiotropic cytokine associated with the control and coordination of immune responses, inflammation, hematopoiesis and oncogenesis by regulating cell

growth, survival and differentiation. Skeletal muscle cells are a further important source of IL-6 and this cytokine is detected locally at elevated concentrations in actively contracting muscle fibers and after increased workload.<sup>10</sup> IL-6 has been shown to be one of the early inflammatory cytokines, which are produced in the first stages of exercise-induced muscular damage. The plasma concentration of IL-6 has been shown to increase gradually after strenuous eccentric exercises and exceed 4pg/ml within 90 minutes.<sup>11</sup> In addition; this cytokine is involved in proliferating satellite cells, supporting muscle regeneration.<sup>12</sup>

Another interleukin that promotes adaptation and has received considerable interest for having a potential role in skeletal muscle hypertrophy is IL-15. This interleukin is elevated in response to a single session of resistance exercise, in untrained and trained people.<sup>13</sup> Ostrowski et al.<sup>14</sup> demonstrated that IL-15 levels are upregulated in human skeletal muscle following strength training and the main mechanism involved in the anabolic effects of IL-15 relies on a decrease in the proteolytic rate. Moreover, other studies show that acute changes in IL-15 with exercise may be associated with the changes in blood supply requirements and neovascularization that occur with training, stimulating the angiogenesis.<sup>15</sup> Muscle damage initiates the release of growth factors that influence satellite cells in a cascade of regenerative events which ultimately leads to myofiber hypertrophy.<sup>3</sup> The satellite cells are muscle precursor cells that lie between the basal lamina and sarcolemma of skeletal muscle fibers. In normal adult muscle, satellite cells are mitotically and metabolically quiescent, which are known as stem cells. With appropriate environmental signals, satellite cells enter into the cell cycle, (i.e. are activated) to provide the precursors needed for new muscle formation in growth and repair.<sup>3</sup> Kadi et al.<sup>16</sup> have found that an increase in the area of muscle fibers can occur without the addition of new myonuclei, however, myonuclear addition is required when hypertrophy reaches 26%. Thus, these new myonuclei are able to increase their protein synthesis and support an enhancement of the cytoplasmic area. Thus, EIMD can enhance muscular adaptations and maximize the hypertrophic response to RT. However, Damas et al.<sup>4</sup> showed that initial increases in MPS post-RT are likely directed to muscle repair and remodeling due to damage and do not correlate with eventual muscle hypertrophy induced by several RT weeks. Increases in MPS post-RT session only contribute to muscle hypertrophy after a progressive attenuation of muscle damage and even more significantly when damage is minimal.

The severity of the inflammation depends on the type, duration and intensity of exercise. In addition, exercise with eccentric contractions will cause more damage and inflammation than concentric exercise of equal intensity and duration.<sup>17</sup> Stock et al.<sup>18</sup> found that in individuals beginning a resistance training program, small but detectable increases in hypertrophy may occur in the absence of eccentric muscle damage within seven training sessions. In addition, Damas et al.<sup>4</sup> showed that increases in muscle protein synthesis post resistance training session only contributes to muscle hypertrophy after a progressive attenuation of muscle damage and even more significantly when damage is minimal. Chen et al.<sup>19</sup> observed that upper-extremity muscles are more susceptible to muscle damage than leg muscles. The difference in the susceptibility to muscle damage seems to be associated with the use of muscles in daily activities.

Moreover, Hortobagyi et al.<sup>20</sup> compared changes in muscle strength, muscle fiber size and surface electromyography (EMG) activity of the quadriceps muscle between eccentric and concentric isokinetic actions with untrained young subjects. After 36 sessions,

over 12 weeks of training, the eccentric strength increased 3.5 times more than concentric strength. Eccentric training increased EMG activity 7 times more than concentric training. Type I fibers did not change significantly, but type II fiber areas increased 10.3 times more in the eccentric than in the concentric group. According to these authors, training with maximal eccentric contractions are specific to eccentric muscle actions and are associated with greater neural adaptation and higher muscle hypertrophy than concentric exercise.

Another characteristic of muscle damage is the strength loss after eccentric exercise. This trait is considered to be one of the most valid and reliable indirect measures of muscle damage in humans.<sup>21</sup> Vijayan et al.<sup>22</sup> showed that when fast-twitch, slow-twitch and hybrid muscle fibers are actively submitted to eccentric exercises, fast-twitch fibers are intrinsically more susceptible to damage than slow-twitch fibers. This occurs possibly due to their lack of oxidative capacity, the higher levels of tension generated during exercise and structural differences between fiber phenotypes.<sup>23</sup> In addition, initial RE-induced stress (i.e. in the untrained state) increases the intracellular calcium concentration following the initial contraction-induced injury contributing to the progression of muscle damage. Increases in intracellular calcium may contribute to the progression of muscle damage by stimulating CANP such as calpain (high calcium affinity and low calcium affinity forms). These proteases may initiate proteolysis by cleaving susceptible Z-line-associated proteins such as desmin and  $\alpha$ -actinin.<sup>4,24</sup>

When a person performs the same exercise consistently, the EIMD decreases, this phenomenon is commonly known as the “repeated bout effect” or “protective effect”. This effect occurs after a single training session and this benefit is found within a period as short as 24 hours and can remain for up to six months.<sup>25</sup> Chen et al.<sup>19</sup> observed that when performing eccentric training sessions with different intensities (40%, 60%, 80% and maximal strength) all damage markers analyzed were more attenuated at higher intensities (80% and 100%) in a second training session performed 2-3 weeks later. This result shows that, the higher the intensity of the first exercise session, the higher the “protection” granted. According to Brentano et al.<sup>25</sup> several factors are thought to be responsible for the repeated bout effect, including an adaptive strengthening of connective tissue, increased efficiency in the recruitment of motor units, enhanced synchronization of motor units, a more even distribution of the workload among fibers and a greater contribution of muscle synergists. McHugh<sup>26</sup> showed that the initial inflammatory response to the initial bout may contribute to the induction of a protective mechanism. In addition, Hubal et al.<sup>27</sup> suggest that one key feature for adaptation may be an increase in MCP1 that co-localized with macrophages and satellite cells, which could play a role in promoting recovery.

## Conclusion

The inflammatory process following EIMD is fundamental to the adaptation of the skeletal muscle to resistance exercise. This inflammatory response coincides with muscle repair, regeneration and growth and the initial RT-induced muscle damage possibly drives enhance of MPS towards muscle remodeling, not hypertrophy. Thus, the damage caused by exercise in skeletal muscle enhances the adaptive response or at least initiates the signaling pathways that mediate anabolism. The knowledge about EIMD is of great relevance, from the application in studies of muscular adaptation and hypertrophy to possible applications in therapies and treatments. Although studies have been growing in this sense, much research is still necessary to determine the full extent and mode of action of these

factors. In summary, paraphrasing Nietzsche, “what doesn’t kill you makes you stronger”.

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## Conflict of interest

None.

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