Chula Med J Vol. 64 No. 3 July - September 2020;347-354 DOI : 10.14456/clmj.2020.43

Review article

Mechanism of muscle injury from eccentric exercise induced free radicals and protection with antioxidants

Kultida Klarod[a,b], Pornprom Surakul[a,*]

[a]*Department of Physical Therapy, Faculty of Allied Health Science, Burapha University, Chonburi, Thailand*
[b]*Molecular Medicine Research Group, Faculty of Allied Health Sciences, Burapha University Chonburi, Thailand*

Eccentric contraction exercise causes more muscle injury and damage than concentric exercise. The mechanism of muscle damage is divided into primary and secondary damages. One of the importance sources of secondary damage is derived from reactive oxygen species (ROS), which an increase of ROS results in the destruction of muscle tissue. Eccentric exercise is not only indicated adverse effect, but also suggested a positive effect with regular training. As a result of eccentric exercise promotes adaptation and prevention, thus some interventions should be taken into consideration for ameliorating negative effects. Antioxidant supplementation has been observed to be a method for relieving negative effect at the beginning of eccentric exercise. Antioxidant has been illustrated as molecules that control the adverse effect from ROS-induced muscle damage. An improved antioxidant level is believed to be a beneficial aspect against oxidative stress which develops from adaptation through exercise training. Previous studies observed the positive consequences of increased vitamin levels, however, several investigations have reported controversial results. In addition, enzymatic antioxidants are able to be controlled by effector cells that are induced, stimulated, and activated, which an increasing or decreasing of these antioxidants are still be disputed. Besides, the responsiveness of free radicals and antioxidants to eccentric exercise also depends on the intensity and duration of exercise.

Keywords: Eccentric exercise, oxidative stress, antioxidants, muscle damage, oxidative stress induced-muscle injury.

Physical exercise has been introduced into several characters including isometric and isotonic contractions.(1) Isotonic contraction consists of concentric and eccentric contractions. The concentric contraction causes muscle to shorten during contraction, whereas active muscle is lengthened during eccentric contraction. (1) In the year 1925, Hill AV. noted an aspect of eccentric contraction by investigating the association between heat production and stretched muscle during contraction, which indicated that during eccentric contraction induced less energy release.(2) The muscle contraction in different types are illustrated in Figure 1. The character of concentric contraction describes as muscle tension increases to obtain a load of resistance, following by constant sustaining while muscle shortens. Whereas, eccentric contraction defines as muscle length is increased while resistance overcomes muscle force.(3) Additionally, eccentric contraction has been observed to be activated larger oxidative stress than concentric contraction, as a result of increased production of reactive oxygen species (ROS). (4)

Mechanisms of muscle injury from eccentric contraction during exercise

The mechanisms of muscle injury due to eccentric contraction has been suggested by disruption of myofibrillar, abnormality of excitation-contraction uncoupling, and propagation process related inflammation (5), as well as, free radicals induce oxidative stress.(6) They have been separated into primary and secondary damages. (7)

***Correspondence to: Pornprom Surakul,** Department of Physical Therapy, Faculty of Allied Health Science, Burapha University, Chonburi 20131, Thailand.
E-mail: pornprol@go.buu.ac.th
Received: November 3, 2019
Revised: December 4, 2019
Accepted: January 10, 2020

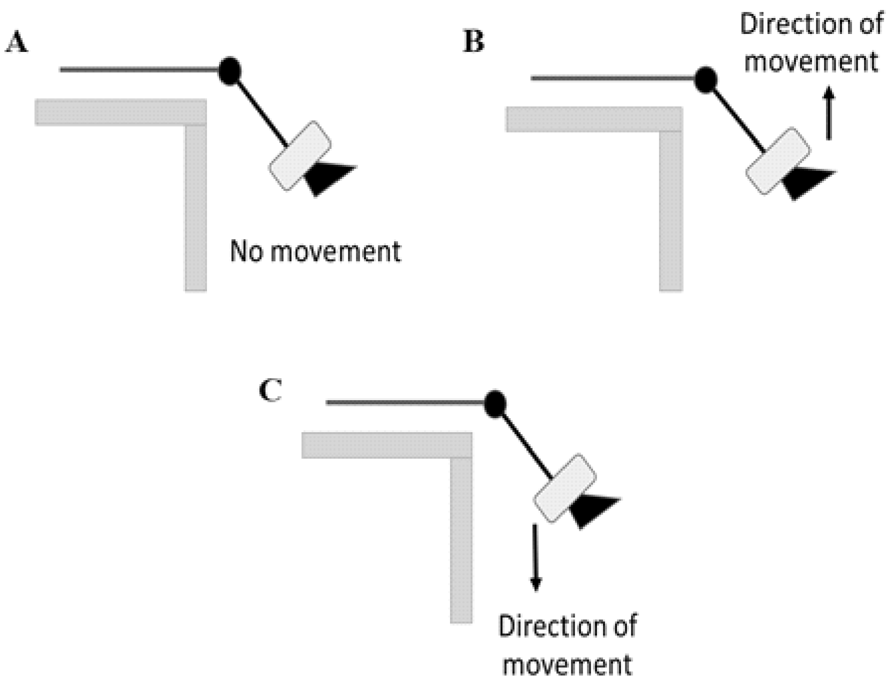

Figure 1. Types of muscle contraction (A) Isometric contraction, (B) Concentric contraction, and (C) Eccentric contraction.

Primary damage

The two pathways have been proposed to be involved including, metabolic and mechanical muscle damages. Ischemia during exercise for a long period is considered to be the essential exacerbated causes of metabolic muscle damage.(8) This induces an alteration of ion concentration, an aggregation of metabolic disuses, and insufficiency of adenosine triphosphate (ATP).(9) However, the main cause of direct damage is suggested to be mechanical loading by causing a direct disruption of myofibers from eccentric contraction.(10) The two possible mechanisms are introduced that one is abnormality of excitation - contraction uncoupling and another is passive structures in a sarcomere are weak.(5, 10) A decline of maximal Ca^{2+} activated force has been found after muscle damage, which is noticed a disruption of the force-bearing components as a result of a decreasing of muscle strength.(11) The sarcomeres length non-uniformities are believed to be under eccentric contraction, which induces weak sarcomere to be extended above actin and myosin filament overlapping.(12) Therefore, the tension stress with repeated eccentric contraction is able to provoke the disruption of the structures. This is characterized by a declined in force generation in muscle.(10, 13) The mechanisms can be concluded in Figure 2.

Secondary damage

This mechanism has appeared after the primary damage. It has been started with imbalance of calcium by disturbance of calcium level within cells. The increasing of intracellular calcium in cytosol has been proposed to be from external cell which followed by promoting a deficit of sarcoplasmic reticulum, and damage of mitochondrial and membrane myofibrillar.(14) The calcium has been involved by stimulating of proteolytic and lipolytic pathways resulting in degeneration of sarcolemma and cell membrane causing rupture of protein and its structures.(10) However, secondary damage mechanisms are still needed an elucidation. Since, this damage is included consequences of reactive oxygen metabolism of phagocyte leukocytes, oxidative stress, loss of calcium homeostasis, and inflammation.(15) The possible sources of oxidative stress that resulting from ROS have associated with eccentric exercise. It could be separated into primary and secondary sources. Primary sources are mainly inside muscle as endogenous section. On the other hand, secondary sources are an exogenous site of muscle.(16) The particular primary sources of ROS is the leakage of electron during electron transport and oxidative phosphorylation in mitochondria.(17) Another is over superoxide generation by xanthine oxidase in capillary

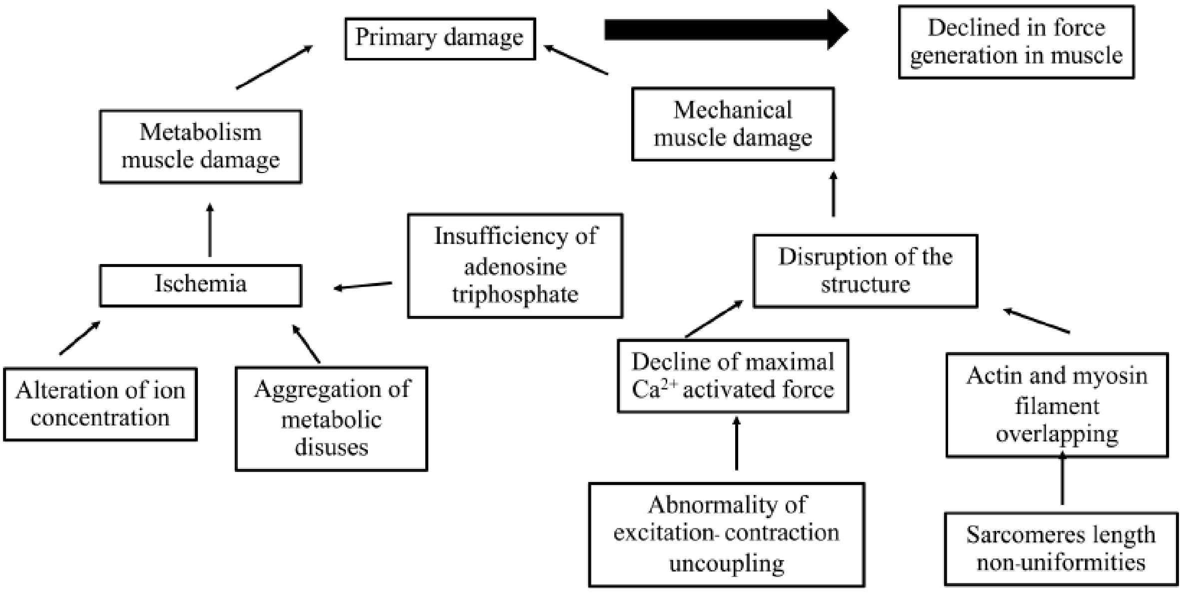

Figure 2. Diagram shows mechanisms of primary muscle damage.

endothelium. It has been developed by temporary ischemia or hypoxia in a specific part of the body, leading to ATP turned into hypoxanthine at the end.(18)

The secondary sources of ROS are consisted of radical generation by phagocyte, calcium accumulation in muscle, and disruption of iron-containing protein.(19) Phagocytic cells as neutrophils develop ROS during inflammatory process.(19) The injuries from eccentric contraction exercise tend to be followed by delayed onset muscle soreness (DOMS) after 24 - 72 hours of exercise.(20) The symptoms explain as tenderness points, swelling, and fatigue (10, 20), however, an established mechanism is still uncertain.

The eccentric and concentric exercise were employed in either acute or training exercise. It has been reported that eccentric exercise obtains more muscle injury and damage than concentric exercise.(21) Eccentric contraction exercise causes an increase of ROS which results in destruction of muscle tissue.(22, 23) The increased ROS derives from several mechanisms as xanthine oxidase and NADPH oxidase, ischemia/ reperfusion, Prostanoid metabolism, respiratory burst by phagocyte, disruption of iron-containing protein, increased intracellular Ca^{2+} due to high energy using in eccentric exercise (22 - 24), and neutrophils and macrophage infiltration to damage tissue (25), as illustrated in Figure 3.

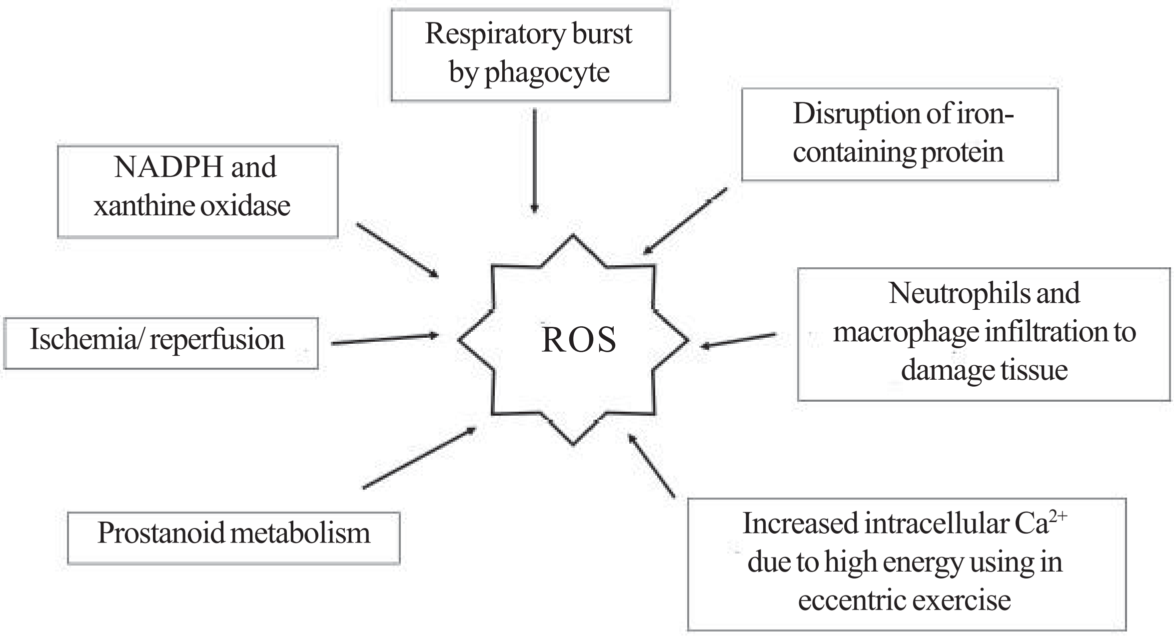

Figure 3. The mechanisms leading to increased ROS due to eccentric exercise.

The benefits of eccentric contraction exercise

It has been indicated that the eccentric exercise has more increased muscle size but less energy utilization than concentric contraction exercise.[26] Also, it has evidenced that this exercise is relatively less stress on cardiovascular system. This exercise is able to maintain and/or increase muscle strength, while reducing stress in cardiovascular system during exercising.[27] Thus, it is an exercise suitable for the elderly and those patients with pathology of heart and blood circular systems. As a result of this type of exercise appears to obtain negative effect as muscle injuries, however, while using as exercise training, it introduces an adaptation effect, contributing in increased endurance, higher exercise capacity, and improved physical performance.[28] The eccentric contraction exercise not only shows negative side effects, but also reports the positive side. It demonstrates several beneficial aspects. Since eccentric exercise promotes adaptation and prevention, thus some interventions that could ameliorate the negative effects on short time of starting eccentric exercise, should be considered as a promising method to get the beneficial effects from regular training in elderly and patients with various diseases.[29] Regarding receive protective effect with eccentric exercise, it should be used by controlling deteriorated response at the beginning, then, obtaining improvement due to training exercise. Therefore, it would be suggested positive aspect through eccentric exercise.

Researches related to eccentric contraction exercise induced oxidative stress

In 1990, Zerba E, *et al.* found that the extensor digitorum longus muscle in mice had injured on function as eccentric contraction. They observed that ROS caused secondary damage phase as well as muscle pain after exercise. The evidence suggested by mice with antioxidant supplement alleviated the secondary damage phase.[30] There are ROS releases during muscle contraction into extracellular cavity which is leaded to secondary damage.[31] Additionally, there are not only ROS, but also reactive nitrogen species (RNS) that appear to demonstrate an important role during exercise.[32] Nitric oxide (NO) develops by muscle and enhances during muscle contraction.[32] Regarding nitric oxide reacts with ROS which results from peroxynitrite, leading to muscle damage and protein nitration production.[33] ROS and cytokines are able to induce an upregulation of inducible nitric oxide synthase (iNOS) though an activation of nuclear factor kappa B (NF-kB).[34] NF-kB is essential in control responsiveness of immune and inflammatory process. [34] Previous study from Lima-Cabello E, *et al.* in 2010 observed that after eccentric exercise, there was a direct relationship between NF-kB and an expression of NOS in skeletal muscle.[35] Current study suggested that activation of NF-kB and expression of gene related to inflammation inducible nitric oxide synthase (iNOS, cyclooxygenase-2 COX-2, interleukin-6; IL-6) increased these levels on mononuclear leukocyte in elderly with acute eccentric exercise. In contrast to regularly trained with eccentric exercise was the protective process against inflammatory response induced by eccentric exercise.[36]

Supplementation with antioxidants for reducing negative effects non-enzymatic and enzymatic antioxidants

Antioxidants play an important role in protecting cells from exercise-induced oxidative stress. The depletion of antioxidant system might be leaded to tissue injury.[37] Particular types of oxidants need particular type of antioxidant protection. Antioxidants can be divided into non-enzymatic and enzymatic antioxidants. Non-enzymatic antioxidants are such as carotenoids, vitamin C, vitamin E, albumin, uric acid etc. Enzymatic antioxidants are superoxide dismutase, glutathione peroxidase, catalase, glutathione reductase.[38]

Non-enzymatic antioxidants

The study of Cannon JG, *et al.* in year 1991 conducted in sedentary men by vitamin E supplementation for 48 days (800 IU per day) before downhill running on treadmill. They found that after exercise for 24 hours a decreased IL-6 was on supplement group, which IL-6 responded to muscle damage. Additionally, IL-1β and prostaglandin E_2 were positively correlated with excretion of 3-methylhistidine, which associated with protein breakdown. This is implied that vitamin E is possibly modified cytokines responsiveness that involved with muscle damage.[39] In the year 1993, Maxwell SR, *et al.* indicated an enhanced antioxidant capacity in people's blood plasma supplemented with vitamin C and E in eccentric contraction exercise by box-stepping for one hour. These were demonstrated the responsiveness of antioxidants in plasma to eccentric exercise.[40] In contrast to Jakeman P, Maxwell S. evidenced that supplementation with vitamin E did not improve muscle damage and declined muscle power. However, vitamin C supplementation group indicated favorable effects on muscle recovery and muscle power after 24 hours with eccentric exercise. This investigation suggested a protective effect of vitamin C against eccentric contraction exercise-induce muscle injury.(41) The year 2003, Sacheck JM, *et al*. performed investigation by supplementation vitamin E (1,000 IU per day) among young and elderly people in downhill exercise on a treadmill compared to those without taking supplements. Vitamin E supplementation groups showed to reduce creatine kinase in adolescents and F_2-isoprostanes in the elderly. Creatine kinase is a substance that is involved in muscle damage. While F_2-isoprostanes is an indicator of an increase in oxidative stress. Regarding this study, it could imply that vitamin E has a positive effect on reducing injury and damage to muscle cells due to eccentric exercise.(42) Vitamin C supplementation for 800 mg in the study of Nie J. and Lin H. focused on reducing muscle injury in people who performed squash jumping exercise regularly. The results indicated that supplementation group had a higher level of vitamin C, whereas the increase of creatine kinase was declined compared to control in immediately and 24 hours after exercise. The oxidative stress level as malondialdehyde level and perception of muscle soreness was no significant difference between groups. This study concluded that vitamin C acts as a preventive substance for muscle damage from exercise-induced injury, but does not involved with muscle damage induced by oxidative stress and perception of muscle soreness.(43) In 2007, Paschalis V, *et al*. demonstrated that eccentric exercise could alter the changing of oxidative stress. There were a decreased glutathione level and glutathione to oxidized glutathione ration, but increased oxidized glutathione level, protein carbonyl level, total antioxidant level, thiobarbituric acid reactive substance level in eccentric exercise. They suggested that eccentric exercise individually differed from other exercise types by oxidative stress responsiveness.(44) The study by Sliva LA, *et al*. in 2010 performed supplementation with vitamin E (800 IU per day) 14 days before exercise session and 7 days after exercise in eccentric exercise as elbow flexion and extension. They demonstrated that on days 4 and 7 in exercise group decreased muscle injury, lactate dehydrogenase level and lipid peroxidation, and protein carbonylation level in supplemented group compared to control group. In contrast, there was an increased inflammatory-related substances level in both supplemented and control groups. This study suggested that vitamin E could prevent muscle injury and injury-related oxidative stress, except injury-related inflammatory. (45) However, the study by Theodorou AA, *et al*. in the year 2011 conducted the investigation by supplementation vitamin E (400 IU per day) and C (1 g) for 11 weeks. They reported that no effect of vitamin E and C supplementation on muscle injury, oxidative stress and antioxidant levels in people who performed eccentric exercise in both acute and training exercise.(46) In accordance with Theodorou AA, *et al*, the investigation by Yfanti C, *et al*. in 2017 found that supplementation with 1g of vitamin C and 400 IU vitamin E did not induce an alteration on apolipoproteins and insulin sensitivity. They supplemented those vitamins for 9 weeks in people who attended eccentric exercise at week 5th - 9th. (47) Additionally, the study by Klarod K, *et al*. in year 2017 illustrated that ration of antioxidant and oxidative stress levels in people who performed eccentric exercise under hypoxia had increased but did not improve exercise performance. On the other, there was no change in the ration of antioxidant and oxidative stress levels in exercise under normal conditions, but improved in exercise performance was seen. This investigation appeared that under hypoxia environment was possibly increased the ration of antioxidant and oxidative stress levels before an improved performance occurred. (48) Besides, supplementation with taurine, which is an amino acid cysteine with a thiol group and high ability as an antioxidant. It is found in muscle structures. Taurine supplemented before eccentric exercise with a dose of 0.1 grams per kilogram of body weight for 3 days appeared to have effects on muscle recovery after exercise.(49)

Enzymatic antioxidants

According to the study by Paschalis V. and colleagues in the year 2007 appeared that catalase level was increased after eccentric exercise.(44) In year 2010, Hanachi P. and Shemshaki A. studied activity of glutathione peroxidase (GPx) and glutathione reductase. They found that there was a development of GPx after both concentric and eccentric exercises. This implied that exercises induce a protective effect on the responsiveness of antioxidant system.

Nonetheless, the intensity and duration of exercise must take into account.(50) In year 2013, da Silva LA, *et al*. performed an experiment in mice which demonstrated that eccentric exercise resulted in increased antioxidants. Although, there was a non-effect on oxidative stress level.(24) The study of da Silva LA, *et al*. in year 2014 conducted experiment with taurine supplementation for 21 days (supplemented 14 days before exercise and continuing throughout 7 days after exercise). They observed that taurine supplementation improved muscle strength, decreased muscle soreness, and oxidative damage markers. However, superoxide dismutase, catalase, and GPx and inflammatory markers did not differ during the recovery period between exercise and control groups. This study concluded that taurine supplementation acts as a significant component for improved exercise performance and decreased muscle damage and oxidative stress but does not involve with the inflammatory responsiveness after eccentric exercise.(51)

Conclusion

Eccentric contraction exercise has relatively clear mechanisms for inducing muscle injury that consists of primary and secondary damages. Regarding muscle injury, primary damage contains metabolic and mechanical mechanisms follow by secondary damage which includes an imbalance of calcium level and consequence of reactive oxygen species. Eccentric exercise believed to augment muscle injury and damage which results from an increase of ROS cause destruction of muscle tissue. On the other hand, the positive side of eccentric exercise training showed to improve adaptation and prevention effects. However, treatment for reducing adverse effects from eccentric exercise such as supplementation with antioxidants are still controversial. Regarding enzymatic antioxidants that have been suggested the stimulation of the production of enzyme antioxidants in response to the increase of oxidative stress. But it is not conclusively clear for establishing the certain mechanism. Additionally, the responsiveness depends on factors such as the intensity and duration of eccentric exercise.

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