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Eccentric Exercise, Muscle Damage and Oxidative Stress

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1. Introduction

Participation in exercise has been linked with positive results on the cardiovascular system, metabolism, musculature etc. Some of these benefits are linked with reductions in blood pressure, increases in resting energy expenditure, changes in lipid profile, reductions in fat mass, increases in fat free mass etc. (Evans, 1999). There are different types of exercise that someone can participate in, i.e. walking, running, lifting weights, participating in organized sports which involve different muscular contractions. Isometric, concentric and eccentric muscle actions are the main muscular contractions involved in all exercise activities. Eccentric muscular contraction is this type of contraction where the length of the muscle is increased while tension is developed. Unaccustomed eccentric exercise has been linked with greater muscle damage compared to isometric or concentric muscular contractions. However this phenomenon is temporary and perturbations in functional and biochemical indices are back to normal within a week from the initiation of the trauma. Furthermore, the damage works as a protective mechanism since data indicates that the muscle damage is attenuated when a subsequent exercise bout of the same intensity is performed even a few months later. Eventhough eccentric exercise leads to greater muscle damage, recent data indicates that eccentrically induced muscle damage is related with positive changes in lipid profile that are evident for a few days following the initial event. Furthermore, the limited data from eccentric training studies indicate that this type of exercise is linked with positive changes in strength as well as in the metabolic profile of the exercise participant.

Oxidative stress indicates a condition where the cellular production of pro-oxidant molecules exceeds the ability of the antioxidant system to reduce reactive oxygen or nitrogen species (RONS). There are several studies that indicate that oxidative stress is evident following muscle damaging exercise. Its role has been related to cleaning the debris from the damaged tissue and providing the means for biochemical adaptations that lead to a stronger and more resistant to muscle damage muscular tissue. This phenomenon is transient and existing evidence suggests that oxidative stress indices are attenuated when a

subsequent exercise bout is performed a few weeks after the initial damaging protocol. Finally, eccentric exercise has been linked with health benefits that are evident either after an acute bout of exercise or following a training protocol.
This review highlights muscle damage and oxidative stress adaptations as well as the health benefits associated with acute and chronic eccentric exercise.

2. Benefits from exercise

Numerous experimental and epidemiological studies have documented a large number of health benefits derived from systematic engagement with cardiovascular exercise training such as enhanced physiologic, metabolic, and psychologic adaptations, as well as reduced risk for development of many chronic diseases and premature mortality (USA, 1996; Kesaniemi et al., 2001). It is well-established that physical activity and/or chronic exercise prevent the occurrence of adverse cardiac events, decreases the incidence of hypertension, atherosclerosis, stroke, osteoporosis, obesity, insulin resistance, type 2 diabetes, cancer, and depression, causes body weight and fat loss, and delays mortality (USA, 1996; Kesaniemi et al., 2001; ACSM, 2006; Feskanich et al., 2002; Leitzmann et al., 1999; Sahi et al., 1998; Rockville, 1995). Large-scale studies have also demonstrated that systematic exercise or switching from being sedentary to a more physically active life-style reduces disease rates and premature mortality (Hein et al., 1994; Paffenbarger et al., 1993; Blair et al., 1995; Erikssen et al., 1998). In fact, exercise-induced health benefits occur even at old ages (Paffenbarger et al., 1993).
Resistance exercise training (a form of which is eccentric training) also induces substantial health benefits, especially to older individuals. Strength training increases not only muscular strength and power but also improves bone mineral density as well as cardiovascular and psychological function (Ay and Yurtkuran, 2005; Takeshima et al., 2002; Wang et al., 2007). Although, the response to resistance exercise training is individualized, there is a consensus that a properly designed and supervised program should improve not only muscular fitness parameters (strength, muscular endurance, power, balance, speed) but the quality of life as well (Evans, 1999). These adaptations are particularly evident in the elderly. Resistance exercise training has been repeatedly shown to increase muscular strength and muscle mass which in turn improve the functional status (coordination, balance etc.) and limit sarcopenia in the aged (Evans, 1999; Fatouros et al., 2006; Fiatarone et al., 1993; Frontera et al., 1991; ACSM, 1998).

3. Eccentric exercise

Daily movement involves different muscular contractions. Concentric type of contractions occurs when a muscle is activated and shortens. In contrast, eccentric contraction occurs when a skeletal muscle lengthens while it produces force. Both types of contractions occur during the day and the best example to differentiate between the two types of contraction is the ascending or descending the stairs. During the ascending of stairs leg muscles are working concentrically while during the descending of the stairs leg muscles are working eccentrically.
Eccentric exercise has been used as a means to develop muscle strength and size (Dudley et al. 1991). However, eccentric exercise training has been used lately as a novel rehabilitation modality in order to improve several conditions, i.e. tendinopathy, following anterior cruciate ligament reconstruction e.t.c. (Gerber et al. 2009) The health benefits derived from eccentric exercise training on metabolism will be discussed in a subsequent section.

4. Eccentric exercise and muscle damage

During eccentric exercise, force is generated when muscle fibers are lengthened. It is well documented that intense, unaccustomed eccentric exercise is associated with muscle damage (Clarkson et al. 1992). Evidence of damage includes morphological changes with ultrastructural damage to muscle fibers usually seen with microscopy Friden 1984), decrements in muscle force and the involved joint's range of motion (ROM) (Nosaka & Newton 2002), deterioration of running economy (Paschalis et al. 2005; 2008; Chen et al. 2007; 2009), alterations in position sense and reaction angle (Paschalis et al. 2007; 2010) elevated plasma proteins such as creatine kinase (CK) and myoglobin (Nosaka & Clarkson 1995; Jamurtas et al. 2000), elevation in inflammatory by products (Fatouros et al. 2010; McIntyre et al. 2001), connective tissue damage (Tofas et al. 2008), large increases in blood and muscle oxidative stress (Paschalis et al. 2007; Theodorou et al. 2010; 2011) and delayed onset of muscle soreness (Cheung et al. 2003). Eccentric exercises have been shown to produce the greatest amount of delayed onset muscle soreness (DOMS) and larger elevations of plasma CK compared to concentric or isometric exercises (Ebbeling & Clarkson 1989; Jamurtas et al. 2000).

Eccentric exercise results in greater muscle damage because fewer muscle fibers are recruited to exert a given amount of force as compared to concentric contractions. Since the force–velocity relationship indicates that each individual muscle fiber can exert a larger force while being stretched than it can while being shortened (Hill, 1938) and fewer fibers are activated during eccentric contractions, larger forces per muscle fiber are developed during eccentric actions thereby resulting in greater damage. Furthermore, during an eccentric contraction, some sarcomeres in muscle fibers are more resistant to stretching than others forcing weaker sarcomeres to absorb more stretch. With repeated eccentric contractions, the weaker sarcomeres first and then the stronger sarcomeres are overstretched. If the latter fail to withstand the stretching force during the relaxation phase, damage may occur. If the damage spreads to adjacent fibers, disruption of the membrane of the sarcoplasmic reticulum or sarcolemma may be seen. In that case intracellular Ca^{++} concentration increases leading to additional degradation of muscle fibers due to activation of calcium dependent proteolytic enzymes, such as the calpain mediated proteases, resulting in neutrophil infiltration to the injured site (Raj et al. 1998; Proske & Allen 2005).

Histological changes are evident following an intense bout of eccentric exercise and data indicates that approximately one third of the muscle fibers obtained from individuals who performed 300 maximal voluntary eccentric contractions of the knee extensors show intense myofibrillar disruptions, myofillament disorganization and loss of Z line integrity (Raastad et al. 2010). Changes in functional measurements are considered to be the best tool for quantifying muscle damage and monitoring exercise-induced muscle damage (Warren et al. 1999). Following eccentrically induced muscle damage, functional measurements (Maximal Voluntary Contractions, eccentric peak torque, jumping performance) demonstrate a marked deterioration reaching their lowest values approximately 72 hours post exercise and return to normal values within 7 days of recovery (Miyama & Nosaka 2004; Nikolaidis et al. 2008).

Following eccentrically induced muscle damage, changes in running economy appear to depend on the intensity of exercise used to asses this parameter. Reports indicate no changes in running economy following eccentric exercise when a moderate intensity exercise is used to assess running economy (Paschalis et al. 2005; 2008; Chen et al. 2009) whereas others report significant perturbations when higher intensities are used (Braun & Dutto 2003; Chen

et al. 2007; 2009). For example, Chen et al. reported significant changes in running economy during level running when the intensity of exercise was set at 80% and 90% of VO2max but not at 70% VO_{2max} (Chen et al. 2009). When submaximal intensities (55% and 75% of VO2max) were used to assess changes in running economy following eccentrically induced muscle damage it was found that running economy indicators remained unaffected throughout recovery (24-96 hours post exercise) (Paschalis et al. 2005; 2008). Perhaps there is an impairment in the fast twitch fibers, which are the ones that are mainly affected by intense eccentric exercise thereby leading to changes in running economy and kinematic measures (Paschalis et al. 2007; Tsatalas et al. 2010).

As it was indicated earlier, eccentric exercise may cause a disruption to the plasma membrane of a muscle fiber. Disruption of the sarcolemma results in the release of intracellular proteins (CK, myoglobin) into circulation. The time frame of entry of various muscle proteins into the circulation following sarcolemma damage may depend on the size of the protein. For instance, there is a difference in the peak between CK and myoglobin (Nosaka, 2011). Small proteins such as myoglobin (the molecular weight of myoglobin is 18 kD) enter the circulation through capillaries whereas large proteins such as CK (the molecular weight of CK is 80 kD) enter the circulation via the lymph (Lindena et al. 1979).

One of the main characteristics of the unaccustomed eccentric exercise is the development of muscle soreness. Muscle soreness needs to be differentiated between the temporary soreness and DOMS. Temporary soreness is usually felt during the final stages of fatiguing exercise and is a product of metabolic waste accumulation (Friden J 1984). DOMS is characterized by a sensation of dull, aching pain that is usually felt during movement or palpation of the affected muscle (Clarkson et al. 1992). DOMS appears 24 hours after exercise and peaks 48-72 hours post-exercise. DOMS subsides and dissipates slowly and does not fully disappear until 7-10 days after exercise. The delayed response of DOMS seems to be related to an initial insult to the muscle due to mechanical reasons and this insult sets off a chain of events that leads to more damage while regeneration processes are also activated. Inflammatory responses to eccentric exercise play a role in the degeneration and regeneration of the damaged muscle (Peake et al. 2005). Following the initial insult, neutrophils are released into the circulation and enter the damaged muscle tissue within several hours (Beaton et al. 2002). Natural killer cells and lymphocytes are also released into the circulation during and after eccentric exercise. Macrophages and proinflammatory cytokines are produced in the muscle within 24 hours and can be present for several days following exercise. These responses are important for the acute phase response of the immune system and the removal of the damaged muscle tissue. Reactive oxygen and nitrogen species (RONS), such as superoxide produced by neutrophils and nitric oxide generated by macrophages, contribute to muscle damage (Close et al. 2005). The role of RONS on muscle damage will be discussed in a following section.

5. Oxidative stress

Oxidative stress may be defined as a condition in which cellular production of prooxidants exceeds the physiological ability of the system to quench reactive species. It is an imbalance between the production of reactive oxygen and nitrogen (RONS) species and antioxidant defense mechanisms. When the imbalance is in favor of RONS it can lead to biomolecular damage (Sies, 1991). RONS include several molecules such as superoxide ($O_2^{\cdot-}$), hydroxyl radical ($\cdot OH$) and nonradical derivatives of oxygen such as hydrogen peroxide (H_2O_2), nitric

oxide ($NO\cdot$) and nonradical derivatives of $NO\cdot$ such as peroxynitrite ($ONOO^-$). These molecules have a singlet electron in the outer membrane and often are called free radicals. RONS occur as a consequence of normal cellular metabolism and have an effect on important biological processes such as gene expression (Pendyala & Natarajan 2010), signal transduction (Santos et al. 2011) and posttranslational modifications (Radak et al. 2011). Therefore, it appears that low levels of RONS are important for normal physiological function and homeostasis. RONS seem to be increased under conditions of psychological and physical stress (Sen et al. 1994). Evidence also indicates that enhanced production of RONS can lead to cardiovascular diseases and cancer due to chronic inflammation (Halliwell B, 1993).

Due to short half-life of RONS an indication of their presence is monitored by the measurement of by-products resulting from damage of various macromolecules such as proteins, lipids and nucleic acids. Oxidative damage to proteins involves the oxidation of amino acids and the most often utilized index of protein oxidation is protein carbonyls (Vincent & Taylor 2006). Lipid peroxidation markers include lipid hydroperoxides, conjugated dienes, malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), and isoprostanes, with the level of F_2-isoprostanes in blood or urine to be widely regarded as the reference marker for the assessment of oxidative stress (Nikolaidis et al. 2011). Significant alterations to normal physiological function can be induced due to elevated lipid peroxidation and loss of membrane fluidity and cytosolic membranes are examples of this modification. Strand breaks and single base modifications of DNA are examples of RONS associated DNA damage. 8-hydroxy-2'-deoxyguanosine (8-OHdG) represents the most frequently marker used to assess DNA damage (Vincent & Taylor 2006).

RONS are quenched through molecules that are called antioxidants. The main purpose of these molecules is to delay or prevent oxidative stress and damage. Antioxidants donate one of their electrons in order to reduce the formed oxidizing agent. Antioxidants are separated into the ones that have enzymatic activity and those with non-enzymatic activity. The main enzymatic antioxidants include superoxide dismutase, glutathione peroxidase and catalase. Non enzymatic compounds include vitamins (e.g. vitamin C, vitamin E), proteins (e.g. ferritin, transferrin, ceruloplasmin) or peptides (e.g. glutathione).

6. Eccentric exercise, oxidative stress and muscle damage

It was stated in a previous section that eccentric exercise leads to DOMS. At the same time numerous evidence suggests that eccentrically induced muscle damage appears concurrently with changes in oxidative stress. Paschalis et al. had 10 healthy females with no previous history of eccentric training perform five sets of 15 eccentric maximal voluntary contractions of the knee extensors and assessed indices of muscle function and muscle damage (isokinetic peak torque, ROM, CK) as well as indices of oxidative stress and the antioxidant system (glutathione, TBARS, protein carbonyls, catalase, uric acid, total antioxidant capacity) (Paschalis et al. 2007). The results showed that eccentric exercise resulted in significant loss of torque, decreases in ROM and elevation in CK concentration for several days following the exercise bout. These changes coincided with marked elevations of selected oxidative stress indices manifested in a uniform and prolonged pattern. Oxidative stress indices peaked at 48 hours of recovery and remained significantly elevated for 72 hours post exercise (Paschalis et al. 2007). The authors also report a moderate relationship between muscle damage and oxidative stress indices that may indicate a link between muscle damage and oxidative stress.

Nikolaidis et al. assessed also oxidative stress following eccentric exercise in healthy females and found significant perturbations in all assessed indices (Nikolaidis et al. 2007). Subjects had to perform five sets of 15 eccentric maximal voluntary contractions of the knee flexors and indices of muscle function and muscle damage (isokinetic peak torque, ROM, CK) and indices of oxidative stress and the antioxidant system (glutathione, TBARS, protein carbonyls, catalase, uric acid, total antioxidant capacity) were assessed before the exercise session and 1, 2, 3, 4 and 7 days post exercise. Eccentric exercise caused muscle damage and uniformly modified the levels of the selected oxidative stress indices in the blood. Oxidative stress indices peaked at 72 hours and returned toward baseline after 7 days post exercise (Nikolaidis et al. 2008).

Results from another study from our laboratory (Theodorou et al. 2010) performed in healthy males provided similar results with the aforementioned studies. In Thedorou et al. study, nine healthy males performed five sets of 15 eccentric maximal voluntary contractions of the knee extensors and indices of muscle function and muscle damage and oxidative stress were also assessed. Indices of oxidative stress in this study were assessed in plasma and erythrocyte lysate before, as well as 1, 2, 3, 4, and 5 days post-exercise in order to determine whether there was a different response between the two blood compartments (plasma and red blood cells) as well. The results showed that eccentric exercise markedly increased muscle damage, oxidative stress and hemolysis indices that peaked at 2 and 3 days post exercise (Theodorou et al. 2010).

Silva et al. reported significant elevation in lipid peroxidation (TBARS) and protein carbonylation indices following eccentric exercise (Silva et al. 2010). Subjects performed three sets of eccentric exercise of the elbow flexors at an intensity of 80% of maximum repetition until exhaustion. A point of interest is the significant elevated TBARS and protein carbonyls for 7 days after the eccentric exercise which is in contrast with previous reports indicating a return of oxidative stress indices at baseline levels within five to seven days post exercise (Nikolaidis et al. 2007; Theodorou et al. 2010). Goldfarb et al. reported significant elevations in protein carbonyls and MDA up to 72 hours post exercise in subjects that performed four sets of 12 maximal repetitions of eccentric actions at an angular velocity of $20^{o} \cdot s^{-1}$, with 60 s of rest between sets using their nondominant arm elbow flexors (Goldfarb et al. 2011). Eccentric exercise resulted also in significant changes in force and muscle damage indices. Other reports also indicate significant elevations in indices of oxidative stress (i.e. protein carbonyls) following eccentric resistance exercise (arm elbow flexors) performed by humans (Goldfarb et al. 2005; Lee et al. 2002) or downhill running (Close et al. 2004; 2005; 2006).

Eventhough the previously reported studies suggest that eccentrically induced muscle damage is accompanied with changes in oxidative stress indices for some days after exercise there are reports indicating no changes in oxidative stress following eccentric exercise. Kerksick et al. showed no changes in lipid peroxidation (F2-isoprostanes) and superoxide dismutase following eccentric exercise (10 sets of 10 repetitions at an isokinetic eccentric speed of $60^{o} \cdot s^{-1}$ on an isokinetic dynamometer) that caused muscle damage (Kerksick et al. 2010). In Goldfarb et al. study no changes in lipid hydroperoxides and glutathione levels were observed (Goldfarb et al. 2011). Saxton et al. also did not find significant changes in oxidative stress measures immediately post and two days following exercise of the forearm flexors (Saxton et al. 1994).

Taken collectively, the results from the aforementioned studies suggest that muscle damaging exercise seems to increase lipid peroxidation and protein oxidation in blood of humans. These results also indicate that disturbances in indices of blood oxidative stress may persist for several days following muscle-damaging exercise. This response is different compared to non-

muscle damaging exercise where the disturbances in oxidative stress indices are not uniform and return towards baseline within hours after the end of exercise (Michailidis et al. 2007).

Direct comparisons of different studies are difficult. It has to be stated here that only human studies were presented in this section. A point of consideration relates to the mode of exercise used to cause muscle damage and the muscle groups used to perform the exercise. Eccentric exercise on an isokinetic device and downhill running are primarily the two main modes of exercise used to induce muscle damage following which oxidative stress markers were assessed. These two modes differ considerably since eccentric exercise on an isokinetic device isolates the muscle group used to perform the exercise whereas downhill running integrates the action of multiple muscle groups besides quadriceps in order to perform the exercise. In addition, the aerobic component of downhill running might be an additional confounding factor in causing oxidative stress (through electron leakage from mitochondrial respiration and other mechanisms).

Another point of consideration that relates to eccentrically induced muscle damage is the cause of the enhanced appearance of RONS following eccentric exercise. Muscle mitochondria (through electron leakage in the electron transport chain) could be one source of RONS during or shortly after muscle damaging exercise. However, that mild elevation of RONS production is unlikely to contribute to the delayed increased oxidative stress response that appears hours or days following exercise. Ischemia-reperfusion could be another cause of RONS elevation during exercise. It is well-known from cardiac physiology that reperfusion in cardiac tissue following angioplasty operations leads to elevated myocardium damage that is partly attributed to elevated RONS production (Zhao et al. 2000). Blood flow redistribution during exercise is a well-known adaptation in exercise physiology and describes the vasodilation of the vascular system of the active muscle and the vasoconstriction of the vasculature of the non-active muscle tissue. The hypoxic non-active tissue receives a greater quantity of blood after exercise and enhanced formation of RONS is possible due to the xanthine oxidase mechanism (Finaud et al. 2006; Veskoukis et al. 2008). This mechanism of RONS production seems also unlikely to account for the increased oxidative stress that appears days following eccentrically-induced muscle damage. Oxidation of hemoglobin and myoglobin during exercise can also cause RONS formation (Finaud et al. 2006) but this mechanism is also unlikely to be responsible for the delayed response of oxidative stress when muscle damage is present.

Inflammatory responses to eccentric exercise play a major role in the degeneration and regeneration of the damaged muscle (Peake et al. 2005). Following the initial insult neutrophils are released into the circulation and enter the damaged muscle tissue within several hours (Beaton et al. 2002). Therefore, infiltrating white blood cells into skeletal muscle may be another source of RONS production following the insult caused to skeletal muscle due to eccentric exercise. Indeed activated neutrophils and other phagocytic cells are a major cause of RONS production leading to tissue damage and if remain unchecked can destroy adjacent healthy tissue (Close et al. 2005). Therefore, RONS can assist in repairing damaged tissue via phagocytosis and white blood cell respiratory burst activity. Production of RONS when muscle damage is present may serve a secondary role which is not other than the induction of the antioxidant activity of the damaged tissue in order to prevent harm when a subsequent exercise session is performed. Figure 1 illustrates a simplistic approach to the events that takes place following an eccentrically induced muscle damage exercise session. In brief, eccentric exercise due to mechanical stress causes injury to the sarcolemma and muscle damage is induced. The inflammatory

processes that take place lead to enhanced production of RONS which serve a dual purpose: first, they clean the debris and repair the damaged tissue and secondly upregulate several transcription factors that lead to increased antioxidant activity of the remaining healthy muscle fibers that become more resistant to muscle damage when a bout of similar exercise is performed.

7. Eccentric exercise, oxidative stress and the repeated bout effect

As it has been mentioned earlier unaccustomed eccentric exercise results in muscle damage. Furthermore, it was eluded that the initial injury to muscle tissue leads to changes in its structure that make it more resistant to a subsequent bout of exercise. This process is referred in the literature as the "repeated bout effect". Numerous studies have shown an attenuation of indices related to muscle damage due to the repeated bout effect (Chen et al. 2007; McHugh et al. 2003). In regards to oxidative stress similar changes (i.e. attenuation) to indices of muscle damage have been observed. Nikolaidis et al. had 12 females perform two sessions of eccentric exercise, separated by three weeks, and assessed muscle damage and oxidative stress indices prior to exercise and 1, 2, 3, 4, and 7 days after exercise (Nikolaidis et al. 2007). The two exercise sessions were identical in intensity and duration and consisted of five sets of 15 maximum eccentric voluntary contractions of the knee flexors. The first exercise bout changed significantly all muscle damage and oxidative stress indices indicating that severe muscle damage and increased oxidative stress had occur. Nevertheless, the second exercise bout resulted in significant attenuation in the perturbations of muscle damage and oxidative stress indices. Assessment of the increase or decrease area under the curve for the oxidative stress indices revealed a 1.8-6.1-fold less change in oxidative stress compared to the changes induced by the first bout (Nikolaidis et al. 2007). One possible explanation for the reduced oxidative stress following the second bout of exercise relates to the less muscle damage and less invasion of white blood cells in the damaged tissue. Data from animal work supports this idea since no significant changes in the concentration of $ED1^+$ and $ED2^+$ macrophages were found after a second bout of lengthening contractions (Lapointe et al. 2002) and treatment with diclofenac, a widely used non-steroidal anti-inflammatory drug (NSAID), affected in parallel the concentration of macrophage subpopulations and the adaptive response after the second bout of exercise (Lapointe et al. 2002). Therefore, inflammation plays a significant role in repair or strengthening of the muscle and might

be the basis for the repeated bout effect. Results from human data are needed in order to substantiate the results obtained from the animal studies.

8. Health benefits from eccentric exercise

Participation in exercise has been linked with positive results on the cardiovascular system, metabolism, musculature etc. Some of these benefits are linked with reductions in blood pressure, increases in resting energy expenditure, changes in lipid profile, reductions in fat mass, increases in fat free mass etc. The majority of the studies that examined the positive effects of exercise have used either endurance exercise or resistance exercise with both types of exercise showing beneficial effects on health (Booth et al. 2000).

It has been mentioned previously that pure eccentric contractions lead to increased muscle damage and soreness levels. This phenomenon is transient, lasts a few days and can make the muscle more resistant to further damage when a repeated bout is performed. However, due to appearance of muscle soreness and the associated changes in muscle function eccentric exercise was viewed as the "bad guy" in the exercise physiology area. Besides the negative effects on muscular function eccentrically induced muscle damage was associated with impaired insulin action (Kirwan et al. 1992) and impaired muscle glycogen resynthesis (O'reilly et al. 1987). The transient augmented insulin responses to hyperglycaemia resulting from muscle damaging exercise seems to serve a dual purpose, i.e. to maintain glucose homeostasis and provide an anabolic environment for the damaged muscle, at least in muscles predominately composed of fast twitch fibres (Flucke et al. 2001).

Eccentric exercise has been used as means of training for several pathological conditions showing positive results in patients with Parkinson disease (Dibble et al. 2006), older cancer survivors (LaStayo et al. 2010), patients undergone anterior cruciate ligament reconstruction (Gerber et al. 2007) etc. Lately there has been an attempt to elucidate the acute and chronic effects of eccentric exercise on metabolism. Eventhough previous reports have attempted to examine the acute effects of muscle damaging exercise on blood lipids only total cholesterol was used as an index of blood lipid profile in these studies (Smith et al. 1994; Shahbazpour et al. 2004). In a study that was performed in our laboratory, the acute effects of muscle damaging exercise on time-course changes of blood lipid profile and the effect of the repeated bout on blood lipids were assessed (Nikolaidis et al. 2007). Twelve healthy females participated in this study. They performed two isokinetic eccentric exercise sessions (five sets of 15 eccentric maximal voluntary contractions at an angular velocity of $60^{o} \cdot s^{-1}$) during the luteal phase. The two exercise sessions were separated by 24-30 days, depending on the duration of their menstrual cycle. Markers of the lipid profile and muscle damage indices were assessed before, immediately, 1, 2, 3, 4, and 7 days after exercise. The results revealed that eccentric exercise uniformly modified the levels of the lipids and lipoproteins (triglycerides, total cholesterol, HDL and LDL). The repeated bout effect affected the assessed variables in a way that the response of lipids and lipoproteins were higher after the first session of exercise compared to those induced by the second identical session performed 4 weeks later. Those changes in the blood peaked at 2 to 4 days post exercise (Nikolaidis et al. 2007). Beneficial changes in lipid profile after eccentric exercise in overweight and lean women were observed in another study performed in our laboratory (Paschalis et al.

2010b). Subjects performed again five sets of 15 maximal voluntary contractions and energy expenditure, respiratory quotient (RQ), muscle damage and lipid and lipoprotein (triglycerides, total cholesterol, HDL and LDL) changes were assessed prior to, immediately after, 12, 24, 48 and 72 hours post exercise. The results revealed increased energy expenditure at all time-points following exercise, lower RQ at 24 hours post exercise andsignificant changes in muscle damage indices and lipids and lipoproteins at 24, 48 and 72 hours post exercise. These changes were exacerbated in the overweight group probably due to the higher muscle damage that was induced by the eccentric exercise protocol in this group of participants (Paschalis et al. 2010b). Similar results with the aforementioned studies were obtained from another study where significant lower triacylglycerol total area under the curve by approximately 12% and significantly elevated insulin incremental area under the curve, indicating transient insulin resistance, were also found 16 hours and 40 hours following an acute bout of eccentric exercise (Pafili et al. 2009).

Eccentric training seems also to improve muscle performance and diminishes the reductions in muscle performance, the elevation in muscle damage indices and the oxidative stress responses (Theodorou et al. 2011). The chronic effects of eccentric training on metabolism have been examined and show promising results in regards to this type of training. Drexel et al. had two groups of subjects hiking either upwards or downwards, three times a week, and assessed metabolic and inflammatory indices (Drexel et al. 2008). The results showed a reduction in total cholesterol (4.1%), LDL (8.4%), apolipoprotein B/apolipoprotein A1 ratio (10·9%), homeostasis model assessment of insulin resistance (26·2%) and C-reactive protein (30.0%) in the eccentric group. These results indicate favorable metabolic and anti-inflammatory results following this type of exercise. Paschalis et al. examined also the effects of a weekly bout of eccentric versus concentric exercise on health parameters of healthy women (Paschalis et al. 2011). Subjects performed an isokinetic eccentric or concentric exercise protocol once per week for eight weeks. Subjects had to complete five sets of 15 concentric or eccentric maximum voluntary contractions in each of their lower limbs with a 2-min rest between sets. The results showed that eccentric training improved the resting levels of blood lipid profile. More specifically, triglygerides, total cholesterol (TC), LDL and TC/HDL ratio decreased by 12.8%, 8.8%, 16.4% and 17%, respectively whereas HDL levels increased by 9.3%. No changes in apolipoprotein A1, apolipoprotein B and lipoprotein (α) were seen. Eccentric training resulted also in significant reductions in glucose, insulin, HOMA and glycosylated hemoglobin levels (Paschalis et al. 2011). However, Marcus et al. did not find any significant changes in insulin sensitivity in overweight or obese postmenopausal women with impaired glucose tolerance (Marcus et al. 2009). Subjects performed three exercise sessions per week for 12 weeks. The exercise was performed on a high-force eccentric ergometer and ranged from 5 minutes in the beginning to 30 minutes at the end of training. Eventhough the eccentric training resulted in significant positive changes on body composition, strength, and physical function no significant changes were found in insulin sensitivity following a hyperinsulinemic-euglycemic clamp test. The different modes of exercise (isolated isokinetic eccentric exercise vs. aerobic type eccentric exercise on an ergometer) might account for the difference in the results obtained in the latter study compared to the former studies.

9. Eccentric exercise programming

Latest research indicates that systematic eccentric exercise can lead to positive changes in physical capabilities, improved rehabilitation and health outcome measures. It has been also reported that unaccustomed eccentric exercise produces greater muscle damage and pain which subsides in a few days. Therefore, it is of great importance to develop exercise programs that incorporate eccentric actions that minimize muscle damage and the associated pain discomfort. Initial low intensity, short duration and progression are key elements in designing eccentric exercise programs. Rate of perceived exertion (RPE) is an important element that could be used in the exercise program. An example of how the aforementioned elements could be appropriately used is presented in an elegant study by Lastayo where older cancer survivors participated in an eccentric exercise intervention study (Lastayo et al. 2011). Subjects begun the intervention program participating in an exercise regimen of low intensity (7, very very light on an RPE scale) and short duration exercise (3-5 minutes per session) that progressed to a higher intensity (11-13, fairly light to somewhat hard on an RPE scale) and longer duration (16-20 minutes) after 12 weeks which was the duration of the exercise program. The program proved to be efficacious since increases in muscle size, strength and power along with improved mobility were noted. Another area where eccentric training could be applied is rehabilitation. Program designing in this area should also follow the same principles as the ones outlined previously. Lorenz & Reiman have outlined the role of eccentric training in various injuries in the athletic field and the reader is encouraged to read their review (Lorenz & Reiman 2011). In conclusion, eccentric training could be an effective means of increasing performance and lead to better health. Incorporation of basic principles in exercise program development (load, volume, intensity, frequency and progression) is essential in order to avoid unwanted outcomes (i.e. muscle damage).

10. Conclusion

Unaccustomed eccentric exercise can cause muscle damage that is evident by morphological changes of the muscle fiber, reductions in physical performance, elevation in inflammatory products and muscle soreness. These responses are significantly attenuated when a second exercise bout of the same intensity is implemented, a phenomenon known as the repeated bout effect. Oxidative stress indices follow the same pattern of response as the one previously mentioned. Significant perturbations in oxidative stress are evident following an eccentrically induced muscle damage exercise protocol that are attenuated due to the repeated bout effect. Elevation in oxidative stress seems to be related with cleaning the debris from damaged muscle fibers and upregulating the antioxidant activity of healthy fibers making them more resistant to muscle damage. Finally, strong evidence indicates that eccentric training can induce health-promoting effects.

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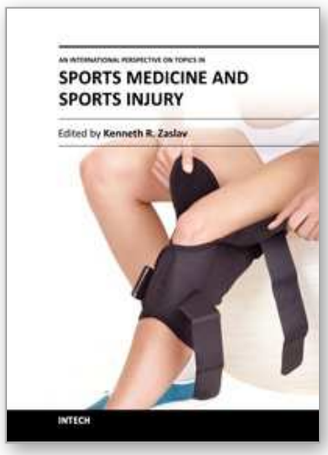

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For the past two decades, Sports Medicine has been a burgeoning science in the USA and Western Europe. Great strides have been made in understanding the basic physiology of exercise, energy consumption and the mechanisms of sports injury. Additionally, through advances in minimally invasive surgical treatment and physical rehabilitation, athletes have been returning to sports quicker and at higher levels after injury. This book contains new information from basic scientists on the physiology of exercise and sports performance, updates on medical diseases treated in athletes and excellent summaries of treatment options for common sports-related injuries to the skeletal system.

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