Causes of muscle damage

An antioxidant has been defined as a substance that reduces oxidative damage such as that caused by free radicals (Halliwell 1984). Oxygen-centred free radicals known as Reactive Oxygen Species (ROS) may contribute to exercise induced muscle damage (Mc Ginley 2009). Due to this, it has been widely accepted over the past 20 years that increasing antioxidants in the body will provide greater protection against ROS (Sastre 1992; Hathcock 2005). However, the significance of exercise-induced oxidative stress is open for discussion (Cabrera 2008) with unclear conclusions in literature. This has led to the recent investigation on the possibility of increased production of free radicals during exercise and the effects of antioxidant supplementation in athletes (Finaud 2006; Gomez-Cabrera 2008; Ristow 2009). Free radical proliferation is a widely suggested mechanism in the damage response to exercise by process of phacocytosis and activation of the respiratory burst by neutrophils during the inflammatory response (*Pyne 1994*). The most commonly used antioxidants in the sporting world are vitamin C (ascorbic acid) and vitamin E (tocopherol) with an astonishing 84% of athletes using antioxidants during the 2008 Beijing Olympics (International Olympic Committee 2008).

It has been well documented that high intensity exercise results in damage to active muscle fibres resulting in soreness, stiffness and a reduction in the muscles force producing capabilities (Allen 2001; Armstrong 1990; Clarkson 2002). Peroxidation of muscle fibre lipids causes disturbance in cellular homeostasis which may result in muscle fatigue or injury, possibly implicating free radical formation as a major cause of delayed-onset muscle soreness (*Byrd 1992*). Preventing muscle tissue damage during exercise

training may help optimize the training effect and eventual competitive sports performance (Sen 2001). In order to minimise tissue & cell damage, there must be an equilibrium maintained between oxidants (ROS) and antioxidants (reductants). ROS increases with intense physical exercise (*Fig 1*) which can exceed the capacity of the body's natural antioxidant defence (*Reid 2001*). This was illustrated by *Davis* (*1982*) and *Ebbeling (1990*), whereby strenuous activity led to increased levels of malondialdehyde (MDA), a 3-carbon-chain aldehyde. Measurement of MDA has become the most commonly used indicator of lipid peroxidation (*Mc Bride 1999*). Thus, the ingestion of exogenous antioxidants has been proposed to attenuate this increase in ROS. *Evans (1990)* noted that several antioxidants, including vitamin C and especially vitamin E, have been shown to decrease the exercise-induced increase in the rate of lipid peroxidation, which could help prevent muscle tissue damage.

The effects of Vitamin E have been more extensively researched than Vitamin C due to some promising results in the literature. Vitamin E is the main lipidsoluble, chain-breaking antioxidant (*Ji 1996*) which accumulates in the phospholipid bilayer of cell membranes and helps attenuate lipid peroxidation (*Sjodin 1990*) within the cell membrane acting as an important scavenger of superoxide and lipid radicals (*Powers 2000*). Vitamin E supplementation has been shown to significantly decrease the amount of lipid peroxidation (Kanter 1993) and membrane damage associated with single bouts of low and high intensity submaximal exercise aswell as resistance exercise (*Mc Bride 1998; Ashton 1999*). *Sumida (1989)* stated that 300 mg of vitamin E given for 4 weeks reduced exercise-induced lipid

peroxidation . *Mc Bride (1998)* reported the effectiveness of vitamin E supplementation in reducing MDA and creatine kinase (CK) levels. *Cannon (1990)* reported a decrease in CK and a faster recovery after supplementation of vitamin E. Furthermore, *Kanter (1997)* recently reported a 35 % increase in T-lag time (indicative of a diminished LDL oxidation rate) in subjects who consumed 1000 mg d-a-tocopherol acetate daily for 1 week before exercise.

Various studies have also demonstrated beneficial physiological effects of vitamin C supplementation in physically-active people. *Jakeman and Maxwell (1993)* found that supplementing vitamin C showed less strength loss (*Fig 2*) in the triceps surae post-exercise, and a faster recovery (*Fig 3*) compared to placebo. The force response to tetanic stimulation was less in the vitamin C group also, indicating a reduction in contractile function. *Kaminski and Boal (1992)* pre-supplemented subjects for 3 days with 1 g of vitamin C 3 times a day and then induced damage in the posterior calf muscles. Supplementation continued for 7 days post-exercise with vitamin C group reporting reduced soreness ratings ranging from 25-44% less than the control group. *Peters (1993)* noted fewer cases of upper respiratory tract infection in runners who consumed 600 mg vitamin C/d for 3 weeks before a 42 km road race. *Bryer (2006)* reported lower DOMS in a high-dose Vitamin C supplementation group 2 weeks prior and 4 days post eccentric exercise Studies which have used combinations of antioxidants (consumed 300-800 mg d-cr-tocopherol plus 200 mg vitamin C/d for 4-8 weeks) reported post-exercise declines in serum enzymes indicative of muscle tissue damage in subjects (*Sumida 1989; Rokitzi 1994). Kanter (1993)* reported that a mixture

of vitamin E (592 mg), vitamin C (1, 000 mg), and 30 mg of beta carotene resulted in a decreased level of a lipid peroxidation marker after exercise. All the previously mentioned studies suggest tangible benefits of antioxidant supplementation in combating detrimental physiological processes that may be initiated by physical activity thus appearing beneficial to sports and exercise participants.

Exercise exhibits numerous positive effects on general health *(Wartburton 2006)* , most notably improving glucose metabolism. It is well documented that exercise increases ROS production (*Powers 2008)* , however it is unknown whether this may influence the health promoting effects of exercise. The effects of antioxidant supplementation on the health-promoting effects of exercise have recently been investigated *(Gomez-Cabrera 2008; Ristow 2009)* . Exercise helps initiate mitochondrial metabolism, with a reduction of this metabolism linked with type 2 diabetes (*Simoneau 1997)* . Since mitochondria are the main source of ROS, it's been proclaimed that ROS may be a factor in some health promoting effects (*Schulz 2007; Birringer 2007). Ristow (2009*) investigated this theory and hypothesized that antioxidant supplementation may repeal certain health promoting benefits of exercise and oxidative stress. Thus, if increases in oxidative stress exhibit a counteracting effect on insulin-resistance, then the prevention of ROS activation by antioxidants may increase the risk of disease such as type 2 diabetes.

Ristow (2009) proposed an essential role for ROS formation in increasing insulin sensitivity in exercising humans. The study found that vitamin C and vitamin E blocked many of the beneficial effects of exercise such as insulin

sensitivity (glucose infusion rates-GIR) and the promotion of muscle antioxidant defence post-exercise. *James (1984)* found non-supplemented subjects showed significant increase in GIR after 4 weeks training whereas antioxidant group found no significant change (Fig 4). In addition, the non supplemented group also increased adiponectin levels compared to the supplemented group (*Fig 5*). Adiponectin (secretory protein) has been shown to have a positive correlation with insulin sensitivity and is inversely correlated with risk of type 2 diabetes *(Spranger 2003)* . A recent meta-analysis of 232, 550 participants suggests use of antioxidants may increase all-cause mortality *(Bjelakovic 2007)* . Of the 136, 023 receiving antioxidants, 13. 1% died (17, 880) whereas of the 96, 527 controls, 10. 5% died (10, 136).

Studies in healthy subjects show that low aerobic capacity is a strong predictor of mortality (*Myers 2002; Yusuf 2004*). Impaired regulation of mitochondrial function is an important mechanism for low aerobic capacity (*Wisloff 2005*). *Gomez-Cabrera (2008*) found that mitochondrial content is a key determinant of endurance capacity and that vitamin C decreases exercise-induced mitochondrial biogenesis in muscle. Free radicals serve as signals to adapt muscle cells to exercise through gene expression (*Khassaf 2003*). Vitamin C was found to prevent beneficial training effects to occur due to their prevention of activation of two major antioxidants (Mn-SOD and GPx) (Gomez- *Cabrera 2008*). The aforementioned study also concluded that endurance capacity is directly related to mitochondrial content, which is negatively affected by antioxidants.

Antioxidant supplementation is extremely popular among athletes, but data indicating beneficial effects on functional capacity of muscle are elusive. There is no strong evidence from literature for the use of antioxidant supplementation in athletic populations as there are many poor controlled studies involving unusually high doses, involving low muscle damaging activity and more recent research has alleviated to minimal if any benefits. Antioxidants do not seem beneficial in preventing DOMS, increasing recovery time or protect against muscle damage but in fact long term supplementation (with vitamin E in particular) may increase mortality (*Bjelakovic 2007*). Most notably for athletes, not only does supplementation appear ineffective in preventing against exercise induced muscle damage, but interferes with the ROS signalling which are needed for adaptation to occur (*Gomez-Cabrera 2008*).

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