

Physical Activity and Oxidative Stress - A Potential Role of L- Carnitine as an Antioxidant: A Review

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Abstract

Regular physical activity, along with a balanced diet, forms an important factor for the maintenance of good health. However, strenuous exercise increases the production of free radicals (FR) and reactive oxygen and nitrogen species (RONS), leads to toxicity, resulting in chronic fatigue, injuries. The overproduction of RONS is involved in muscular fatigue, many diseases, and aging. However, FRs are essential for the functioning of the immune system and certain metabolic functions. The increase in oxidants compared to antioxidant leads to oxidative stress. Nowadays, antioxidants are supplemented to reduce muscle damage incurred during exercise, which has drawn the attention of the athletic population. L- Carnitine being ergogenic, acts as an antioxidant during recovery from exercise, thereby attenuate oxidative stress, which may then decrease exercise-induced muscle damage. Despite increasing research on antioxidant properties for carnitine in several pathologies such as diabetes, hypertension, renal, neurodegenerative conditions, and liver disease, less has been documented on it against oxidative stress induced by exercise. This review may help researchers who are interested in athletic performance enhancement and sports nutrition.

Keywords: Physical training, Carnitine, Oxidative stress, Antioxidant, Free radicals

Introduction

Regular physical exercise is encouraged to prevent or to manage diseases like cardiovascular disease, cancer, diabetes, etc.(1). In contrast, prolonged intense exercise may cause oxidative damage to cellular constituents of contracting skeletal muscle due to the generation of free radicals (2-7). A certain level of oxidants in cells is essential to control various pathways such as gene expression or cell signalling, or production of energy in skeletal muscle. Now it is well established that a high level of free radicals can cause damage to cellular components (7-10).

However, exercise increases FR production, and hence enhanced oxidative stress during periods of intensive training (11, 12).

Reactive oxygen and nitrogen species (RONS) includes oxygen-derived, free radicals, and non-radicals. Primary free radicals like superoxide (O_2^-) and nitrogen monoxide (NO) trigger a chain reaction generating other oxidants such as hydrogen peroxide (H_2O_2), hydroxyl radicals ($\text{OH}^\cdot$), peroxynitrite (ONOO^-), and hypochlorous acid (HOCl) (13). Some tissues such as the liver, kidneys, heart, skeletal muscles are continuously producing FR even at rest, causing oxidative damage to these tissues (14, 15). To overcome the oxidative stress, organisms are equipped with antioxidant defence systems. It includes enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) and non-enzymes, such as vitamin C, vitamin E, glutathione, and bilirubin. They help in delaying or preventing oxidation of intracellular and extracellular biomolecules (7, 13). Dietary antioxidant supplements such as vitamins, minerals influence the antioxidant systems (12). Often it is reported that an insufficient supply of antioxidants in athletes, though some of it is provided through diets (16, 17).

By looking into the recent developments in the field of exercise and oxidative stress, we attempted to summarize the role of antioxidants such as carnitine to overcome exercise-induced oxidative stress.

Overview of Oxidative Stress and Physical Activity

Various stimuli such as radiation, alcohol use, smoking, and exercise moves in vivo redox system toward oxidation, leads to oxidative stress. In 1978, Dillard et al. reported first about the oxidative stress induced by exercise (18). They observed a rise in expired pentane, an oxidative biomarker, with 60 min of endurance exercise at 50% of $\text{VO}_{2\text{max}}$ in humans and was found to reduce at rest and during training with vitamin E, an antioxidant supplementation. Since then, various studies showed an increase in biomarkers of oxidative stress in both blood and skeletal muscle of humans and other animals subjected to either prolonged endurance exercise or short-duration high-intensity exercise. However, cellular antioxidants are found to adapt with regular exercise activity and thereby protecting muscle cells from oxidant damage (3). Jackson et al., Novelli et al., and Shindoh et al., (19-21) showed the contribution of free radicals to muscle fatigue in animals. Similar results were reported in various studies using non-human mammalian skeletal muscle as the experimental model (22-24). The mitochondria play a crucial role in producing superoxide and hydrogen peroxide. They attack other biomolecules thereby producing free radicals and are called reactive oxygen species (ROS) (7). An increased ROS level indicates oxidative stress and is associated with muscular fatigue during contraction and post-exercise muscular damage and suffering (25- 27).

Vitamin E was found to protect biological membranes from exercise-induced oxidative damage indicating adaptation of endogenous antioxidant systems of both cardiac and skeletal muscle in response to exercise training (2). Several studies confirmed that exercise training promotes an increase in antioxidant enzymes in skeletal muscles (24). Many have reported that acute aerobic exercise increases the markers of oxidative damage of biomolecules and influences antioxidant level as well as redox balance (28- 31).

Acute aerobic exercise increased oxidative stress levels in the blood, skeletal muscle, liver, and other tissues of animals (32, 33). The response to oxidative stress induced by acute aerobic exercise varies and depends on tissue type as its antioxidant level is different (34). Similar studies on human beings are also reported (7).

The anaerobic exercise also found to trigger the oxidative stress in animals. An increase in TBARS (biomarker of lipid peroxidation) level in the gastrocnemius muscle of rats after performing 15 sets of 30-s treadmill exercises at 35 m/min at a 5° slope with 10-s intervals is reported (35).

Even the intensity of exercise directly influences exercise-induced oxidative stress. The oxidative stress markers in blood increased with the duration when young men and women were subjected to a cycle ergometer exercise for 30, 60, or 120 min at a constant intensity (70% VO₂ max), and is highest in them who exercised for 120-min (36). Similar results have been reported in several studies which are carried out on both humans and animals (37, 38).

It is interesting to note that the adaptation of the antioxidant defence system takes place along with physical training. A regular physical activity found to increase SOD and GPX activity, significantly (39). However, too intense exercise can compromise the antioxidant response, even in athletes. Attempts are made to reduce oxidative stress by supplying dietary antioxidant supplements thereby enhancing the performance of athletes.

However, the moderate training is more beneficial than selenium supplementation (an antioxidant), where the antioxidant system getting adapted, thereby decreasing exercise-induced oxidative damage (41, 42).

Antioxidants Supplementation on Exercise-induced Stress

An antioxidant is a substance that helps to delay or prevents oxidative stress either by breaking chain reaction induced by FR on biomolecules or by forming a less active radical (42). The enzymes SOD, CAT, and GPX form part of the enzymatic antioxidant system. Vitamin A (retinol), vitamin C (ascorbic acid), vitamin E (tocopherol), flavonoids, thiols (including glutathione –GSH), ubiquinone (ubiquinone Q10), uric acid, bilirubin, ferritin, and micronutrients (act as cofactors) such as iron, copper, zinc, selenium, manganese as a part of non-enzymatic antioxidants (43, 44). The nutritional intakes (vitamins and micronutrients), exercise, and physical training found to modulate the efficiency of the antioxidant system (45).

Nowadays, an intense study on the role of antioxidants in acute physical exercise and exercise training is undergoing in sports nutrition (46-50). During the past few decades, studies on the effects of antioxidant supplements on reducing RONS produced during strenuous exercise have drawn attention (47, 50, 51). Antioxidant supplements are routinely given to athletes thinking that it may improve performance by reducing oxidative stress and promote recovery (52). A pioneering study on exercise-induced production of RONS and counteraction of vitamin E was reported by Davies et al. in the early 1980s (7).

Various antioxidant supplements such as vitamin C, vitamin E, β -carotene, coenzyme Q10, α -lipoic acid, N-acetylcysteine (NAC), quercetin, resveratrol, and polyphenols, individually or in combination, were investigated. Supplements were administered for a different time duration, such as one day to several days or several months at different doses before, during, or after exercise. Some of the studies have reported the beneficial role of vitamin E and C against secondary oxidative stress induced by exercise and found to delay the onset of muscle soreness (12, 53, 54). On the contrary, the conclusion of many of these studies is that the intake of antioxidants is not influencing exercise performance (55, 56).

Carnitine as Supplement

L-Carnitine [LC, 3-hydroxy-4-(trimethyl ammonio) butanoate] is an endogenous molecule with well-established functions in intermediary metabolism. It facilitates β -oxidation of fatty acids by transporting activated long chain fatty acids into the mitochondria of mammalian cells. LC may occur as free LC, acetyl-L-carnitine (ALC), and other carnitine esters. It exhibits a cytoprotective role along with ergogenic action. Abdul and Butterfield (2007), Hinerfield (2004), in different studies, reported the cell-protecting activity of LC against oxidative damage seen during neurodegenerative disorders such as in Parkinson's and Alzheimer's diseases (57, 58). Studies have shown that LC

reduces oxidative stress significantly during aging (59, 60). LC was found to enhance the activities of antioxidant enzymes, thereby decreasing the lipid peroxidation and formation of superoxide radicals in the heart of spontaneously hypertensive rats (61).

LC was found to delay the fatigue of rat skeletal muscle subjected to electrical stimulation in vitro (62). It has also been reported that LC supplementation reduces oxidative stress induced by strenuous exercise (63). The in vitro studies have shown that LC is an efficient superoxide anion radical and hydrogen peroxide scavenger (64). Dutta et al. (2008) have reported that LC supplementation reduces muscle damage caused by oxidative stress induced by hypobaric hypoxia (65). However, further investigations are required to show the beneficial effect of LC on the antioxidant system and use as a dietary supplement to athletes.

Summary: Exercise, the Antioxidant System and Carnitine

Under various conditions, cells experience oxidative stress. Exercise, whether it may be aerobic or anaerobic, was found to induce the formation of RONS, leading to oxidative damage. The level of RONS depends on the intensity of exercise given to the subjects. There are enzymatic and non-enzymatic antioxidant systems found to protect tissues from excessive oxidative damages [43]. Studies have shown that antioxidant supplements do not improve performance but improve antioxidant status [40]. LC is an ergogenic molecule and improves the antioxidant system on its supplementation, as seen in neurodegenerative disorders and other clinical trials (61). LC supplementation has been considered safe and with a low risk of adverse effects, which makes it a promising candidate for the prevention and treatment of oxidative alterations due to excess physical activity (66). Hence the supplementation of LC may help the athletes to recover after strenuous exercise. Therefore, studies are required to decide duration and dose (depending on nutritional intakes) to enhance the health and performance of athletes. Additional research is essential to define antioxidant requirements during exercise training, taking into account of nutrigenomic issues.

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