

# Vitamin E, vitamin C, and exercise<sup>1-3</sup>

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**ABSTRACT** Exercise increases the generation of oxygen free radicals and lipid peroxidation. Strenuous exercise in a person who is unconditioned or unaccustomed to exercise will induce oxidative damage and result in muscle injury. However, aerobic exercise training strengthens the antioxidant defense system by increasing superoxide dismutase. Vitamin C and, especially, vitamin E are shown to decrease the exercise-induced increase in the rate of lipid peroxidation. No ergogenic effects of either vitamin C or E have been shown. Vitamin E was shown to significantly increase circulating neutrophils in older, but not younger, subjects performing eccentric exercise that causes an increase in skeletal muscle damage. In addition to its effect in augmenting the neutrophil response to eccentric exercise, vitamin E causes a greater increase in circulating creatine kinase activity, perhaps indicating increased skeletal muscle repair. Increased vitamin E intake has been associated with enhanced glucose tolerance and insulin action as well as improved lipoprotein status. Future research should examine the combined effects of exercise training and vitamins E and C on these health-related outcomes. *Am J Clin Nutr* 2000;72(suppl):647S–52S.

**KEY WORDS** Lipid peroxidation, free radicals,  $\alpha$ -tocopherol, muscle damage, exercise, vitamin E, vitamin C

## INTRODUCTION

Free radicals, which are atoms and molecules that have an unpaired electron, can damage molecules that are important for cellular function, leading to a total loss of cellular function. These deleterious free radical reactions can also be produced by various environmental factors. Superoxide radicals are formed during the reduction of oxygen, which takes place in the inner mitochondrial membrane. These radicals can trigger chain reactions in the fatty acids of phospholipids, leading to membrane lipid peroxidation and the loss of membrane bilayer organization, which is necessary for membrane-bound enzyme and receptor function. In conditions of oxidative stress, more oxygen radicals are produced, exceeding the cellular antioxidant defense system and resulting in the peroxidation of polyunsaturated fatty acids in membrane structures. Lipid peroxidation also releases reactive free radicals and toxic aldehydes, which can then completely inactivate enzymes and other cell components. Multiple enzymatic and nonenzymatic antioxidant defense systems are present in cells to protect the membranes and other cell organelles from the damaging effects of free radical reactions.

Exercise increases the generation of oxygen free radicals and lipid peroxidation. Strenuous exercise in an unconditioned individual or someone unaccustomed to exercise will induce oxidative damage and result in muscle injury. Prolonged submaximal exercise was shown to result in elevated amounts of both whole-body (1) and skeletal muscle (2) lipid peroxidation byproducts, with the former increase indicated by greater exhaled pentane but not ethane. These studies seem to indicate that the greatly increased oxygen consumption (up to a 100-fold increase in skeletal muscle) seen during exercise produces superoxide radicals that are associated with a host of deleterious effects.

The rate of oxygen consumption and the presence of cellular antioxidant systems influence the magnitude of oxidative damage occurring as a result of exercise (3, 4). Several in vivo and in vitro animal and human studies showed direct and indirect evidence of free radical generation during and after exercise (5, 6). The initial and early events in muscle injury are likely to occur as a result of the physical forces that act on the muscle cell and cause damage (7), and they occur before phagocytic cells enter the injury sites. In addition to the high specific tensions that take place during high-force muscle contractions, the metabolic events resulting from the initial damage result in muscle protein degradation and continued evidence of muscle damage well after the initial damaging exercise (5).

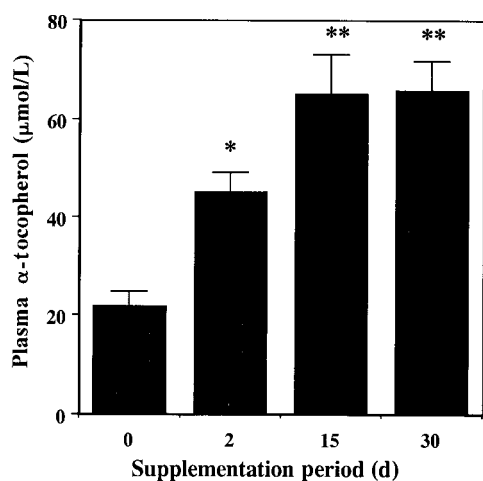
Loss of  $\text{Ca}^{2+}$  homeostasis may be an important event in exercise-caused muscle damage. Depletion of cellular thiols and an increase of intracellular  $\text{Ca}^{2+}$  may potentiate free radical generation, membrane lipid peroxidation, and leakage of intracellular enzymes. Cannon et al (8), using a single bout of downhill running in men and women, found a significant relation between superoxide radicals and plasma creatine kinase activity. In addition, exhaustive running was shown to decrease the oxidative capacity of brown adipose tissue mitochondria in rats (9).

Free radicals generated during or after exercise may come from several sources: 1) the mitochondria, from which oxygen radicals that have escaped scavenging enzymes present in the

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**FIGURE 1.** Effects of vitamin E supplementation (800 IU/d) (800 mg  $\alpha$ -tocopherol) on plasma vitamin E concentrations.  $n = 10$ . These data show that plasma concentrations reach their peak 15 d after the initiation of supplementation. Error bars denote SE. \*Significantly different from day 0,  $P < 0.05$ . \*\*Significantly different from day 0 and day 2,  $P < 0.05$ . Redrawn from reference 11.

mitochondria may leak into the sarcoplasm; 2) the capillary endothelium, where a hypoxia or reoxygenation process is created during exercise; and 3) an oxidative burst from inflammatory cells mobilized as a result of muscle or tissue damage.

## VITAMIN E

Vitamin E ( $\alpha$ -tocopherol) is found in virtually all cell membranes, but the major store of membrane-bound vitamin E is in the inner mitochondrial membrane, the site of the electron transport system (10). The vitamin E content of skeletal muscle is  $\approx 50\%$  of that seen in liver, heart, and lung tissue ( $\approx 20$ – $30$  nmol/g). Recently, Meydani et al (11) examined the effects of vitamin E supplementation on skeletal muscle vitamin E concentration. Subjects received 800 IU (800 mg) *all-rac*- $\alpha$ -tocopherol/d for 30 d. The plasma concentration of  $\alpha$ -tocopherol increased 300% and that of  $\gamma$ -tocopherol decreased 74% within 15 d of supplementation and was maintained at this plateau with continuous supplementation (Figure 1). Muscle biopsies taken after supplementation showed a significant increase in  $\alpha$ -tocopherol (53%) and decrease in  $\gamma$ -tocopherol compared with baseline values (from  $37.6 \pm 7.0$  to  $57.3 \pm 12.1$  nmol/g,  $P < 0.0001$ ).

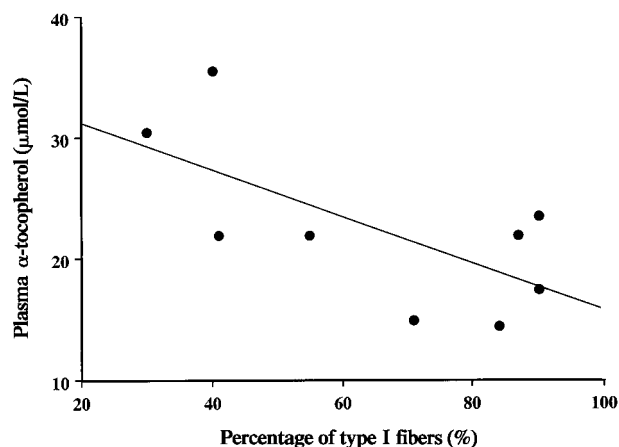
The investigators observed a significant inverse relation between plasma  $\gamma$ -tocopherol concentration and the percentage of type I muscle fibers before supplementation (Figure 2). This inverse relation may indicate that to minimize oxidative stress, physically active persons with a high percentage of type I fibers may have a greater requirement for vitamin E than those with more type II glycolytic fibers. Deficiency of vitamin E, the major antioxidant in cellular membranes, increases susceptibility to free radical damage in exercised rats and leads to premature exhaustion (40% decline in endurance capacity) and a greater fragility of lysosomal membranes (2). Vitamin E deficiency has also been shown to depress respiratory control of muscle mitochondria (4).

## VITAMIN C

Vitamin C (ascorbic acid), which is water soluble and present in the cytosolic compartment of the cell, serves as an electron donor to vitamin E radicals generated in the cell membrane during oxidative stress (12). Plasma vitamins E and C and uric acid, all of which have potential antioxidant activity, have been reported to increase after exercise (10, 13–15). In rats, acute submaximal exercise has been shown to decrease vitamin E concentrations in skeletal muscle (16).

Only a few human studies have examined the interaction between vitamin E and exercise. The data suggest that vitamin E supplementation does reduce oxidative stress and rates of lipid peroxidation and that vitamin E requirements may increase with exercise. Lipid peroxidation is increased after exercise (as measured by increased amounts of exhaled pentane), and vitamin E supplementation reduces this increased lipid peroxidation (17). Sumida et al (15) found that supplementation with vitamin E decreases the exercise-induced increase in circulating glutamic-oxaloacetic transaminase (aspartate transaminase),  $\beta$ -glucuronidase, and rate of lipid peroxidation. Meydani et al (18) examined the protective effect of vitamin E on exercise-induced oxidative damage in young and older men and in women. In all 3 groups, these researchers showed that 48 d of vitamin E supplementation [800 IU (800 mg)  $\alpha$ -tocopherol/d] lowered an exercise-induced increase in oxidative injury, as indicated by a sparing of muscle fatty acids (which dampened the production of muscle lipid-conjugated dienes) and by decreased excretion of urinary thiobarbituric acid adducts. This study confirmed that the antioxidant protection provided by vitamin E may reduce the amount of membrane damage following exercise in untrained subjects but that there is little evidence that vitamin E benefits high-performance athletes. Although circulating concentrations of vitamins E and C were significantly increased in this study, the differences were no longer significant when the values were corrected for changes in plasma volume. These data indicate that previously observed increases in these vitamins (none of which were corrected for plasma volume changes) were most likely a result of exercise-induced hemoconcentration (13, 15, 19).

To date, no well-controlled study has shown an ergogenic effect of vitamin E supplementation. As reviewed by Clarkson (20), the



**FIGURE 2.** Inverse relation between plasma vitamin E concentrations (in unsupplemented subjects) and muscle fiber type.  $r = -0.69$ ,  $P < 0.05$ . Redrawn from reference 11.

performance of neither standard exercise tests (21) [such as measurements of maximal oxygen uptake, muscle strength (22), swimming endurance, or blood lactate concentrations (23)] nor any cardiorespiratory fitness test (21) has been shown to be affected by long-term vitamin E supplementation in double-blind, placebo-controlled experiments. The data of Simon-Schnass and Pabst (24) suggest a potential ergogenic effect of vitamin E; these investigators reported an enhanced anaerobic threshold and decreased expired pentane production during cycle ergometry in high-altitude environments.

The overwhelming consensus of a fairly large number of well-conducted investigations is that vitamin C has no ergogenic effect in persons who are not vitamin C deficient. However, vitamin supplements may have important effects on athletes that are much more subtle than simply an improvement in time to run a specific distance or increased maximal oxygen uptake.

### EXERCISE-INDUCED MUSCLE DAMAGE AND AGE-ASSOCIATED CHANGES

Muscle contraction and shortening produces a concentric action; in contrast, when skeletal muscle lengthens as it produces force, the result is an eccentric muscle action. For example, lifting a weight is a concentric action, and lowering the weight is an eccentric action. At the same power output, the oxygen cost is lower for eccentric than for concentric exercise (25), but even so, eccentric exercise is a potent cause of muscle damage (26, 27), delayed-onset muscle soreness, and increased circulating creatine kinase activity (28).

Running a marathon can cause extensive skeletal muscle damage (29, 30) similar to the ultrastructural changes in skeletal muscle resulting from eccentric exercise. When studying muscle biopsy samples taken in the days after a race, Warhol et al (30) found a characteristic pattern of muscle damage in marathon runners, with tearing of sarcomeres at the Z-band level followed by movement of fluid into the muscle cells. Mitochondrial and myofibrillar damage showed progressive repair by 3–4 wk after the marathon. Biopsy samples taken later (8–12 wk after the race) showed central nuclei and satellite cells characteristic of a regenerative response.

Ultrastructural evidence of damage is greater well after the initial damaging exercise. For example, Friden et al (31) found more damaged muscle fibers 3 d after than 1 h after high-tension eccentric exercise. In addition, Newham et al (26) showed that eccentric exercise caused immediate damage but that biopsies performed 24–48 h after the exercise revealed more marked damage. These data indicate an ongoing process of skeletal muscle repair consisting of increased degradation of damaged proteins and an increased rate of protein synthesis.

After only one bout of high-intensity eccentric exercise (32), previously sedentary men showed a prolonged increase in the rate of muscle protein breakdown, as evidenced by a higher urinary ratio of 3-methylhistidine to creatinine, which peaked 10 d later. In addition, circulating interleukin 1 (IL-1) concentrations in these subjects increased 3 h after the exercise. Endurance-trained men performing the same exercise did not display increased circulating IL-1 concentrations, but their preexercise plasma IL-1 concentrations were significantly higher than those seen in the untrained subjects.

Damage to tissue, as well as infection, stimulates a wide range of defensive reactions known as the acute-phase response (33). This response is important for its antiviral and antibacterial actions

as well as for promoting the clearance of damaged tissue and subsequent repair. Within hours of injury or exercise (34), the number of circulating neutrophils can increase manyfold. Neutrophils migrate to the site of injury, where they phagocytize tissue debris and release factors such as lysozyme and oxygen radicals that are known to increase protein breakdown (35). Greater neutrophil increases are observed after eccentric exercise than after concentric exercise (36). Although neutrophils have a relatively short half-life (1 or 2 d) within tissue (37), the life span of monocytes may be 1–2 mo after migration to damaged tissue (38).

Substantial monocyte accumulation in skeletal muscle was found after completion of a marathon by runners aged 20–50 y who ranged from elite (world record holder) to those who took longer than 3 h to finish (30). Each runner, however, achieved a time close to his personal best. In another study, monocyte accumulation in muscle was not seen until 4–7 d after eccentric exercise (39, 40). In addition to the ability to phagocytize damaged tissue, monocytes secrete cytokines such as IL-1 and tumor necrosis factor (TNF). These and other cytokines mediate a wide range of metabolic events that affect virtually every organ system in the body. Fielding et al (41) found that after downhill running, muscle IL-1 $\beta$  of subjects was increased by 135% immediately and by 250% 5 d later; intramuscular neutrophil accumulation was positively correlated with muscle IL-1 $\beta$ . In addition, with use of ultrastructural analysis these investigators noted a significant relation between the percentage of damaged Z-bands and neutrophil accumulation, indicating that the tissue accumulation of neutrophils after eccentric exercise may be associated with observed exercise-induced muscle injury. It is unclear whether the injury releases a chemoattractant that leads to increased muscle neutrophils or whether invading neutrophils release oxygen radicals that lead to further damage.

Elevated amounts of cytokine during infection or injury have different and selective effects. During infection, IL-1 mediates an elevated core temperature (42). In laboratory animals, IL-1 and TNF increase muscle proteolysis and liberation of amino acids (43), possibly providing substrate for increased hepatic protein synthesis. In humans, although circulating IL-1 was shown to increase acutely as a result of eccentric exercise (44), by 24 h after the exercise, it returned to resting amounts. Biopsies of the vastus lateralis taken before, immediately after, and 5 d after subjects performed downhill running showed an immediate and prolonged increase in IL-1 $\beta$  (45). Results from this study implicate muscle IL-1 $\beta$  in the postexercise change in protein metabolism. More recently, Jeng et al (46) investigated supplementation with vitamin E [400 (400 mg) IU *all-rac*- $\alpha$ -tocopherol acetate], vitamin C (1 g ascorbic acid), or both vitamins and found that the combination had a greater effect on stimulating IL-1 $\beta$  and TNF- $\alpha$  than did each vitamin alone. These data may indicate that after muscle-damaging exercise, a combined course of vitamins E and C causes a greater increase in circulating and muscle cytokines and, as a result, an improved adaptive response.

Eccentric exercise increases the amounts of both circulating and skeletal muscle neutrophils (34). Muscle neutrophils and mononuclear cells can serve as a source of oxygen free radicals, which may partially cause the delayed increase in ultrastructural damage (2). Free radical processes may also be directly related to delayed functional impairment in muscle after damage. Zerba et al (47) examined the extensor digitorum longus muscles in young, adult, and old mice after in situ muscle damage by lengthening contractions. Muscle injury was assessed by measuring maximum



isometric tetanic force ( $P_o$ ) as well as by looking at morphologic damage. Three days after the injury, muscle  $P_o$  of the old mice was  $\approx 15\%$  lower than that of the young and adult mice. These researchers also found that mice treated with a free radical scavenger, polyethylene glycol-superoxide dismutase (PEG-SOD) showed less delayed injury and significantly greater muscle  $P_o$ . Interestingly, they found that PEG-SOD afforded some protection from damage 10 min after exercise in the old animals. These data indicate that 1) muscle of old mice is more susceptible to muscle damage from lengthening contraction than is muscle of young and adult mice, 2) a free radical scavenger provides some measure of protection from delayed muscle damage, and 3) free radicals as well as mechanical forces contribute to the initial damage.

Manfredi et al (48) found significantly more ultrastructural muscle damage in older men performing 45 min of high-intensity eccentric exercise than in young men performing eccentric exercise at a similar intensity. Considerable evidence is available to support the idea that old skeletal muscle may be more susceptible to eccentric-exercise-induced injury than young skeletal muscle. First, when compared with young people, older men typically are less active and fit (49), and lower physical activity may increase the degree of eccentric-exercise-induced muscle damage. Second, skeletal muscle in older individuals may have more intrinsic damage than that seen in young subjects before exercise. Byrnes et al (50) showed that 1 bout of eccentric exercise significantly reduces muscle damage after subsequent bouts of exercise for up to 6 wk. Armstrong et al (51) noted that among the recruited muscle fibers, some showed more damage than others, suggesting that some muscle fibers may be more susceptible to injury. Muscle from older subjects may have more of these susceptible fibers. This intrinsic damage seen in older subjects also may be due to the accumulation of oxidized forms of proteins (52). With advancing age, rates of skeletal muscle lipid peroxidation (as well as antioxidant enzyme activities) have been shown to increase (53). The accumulation of oxidized proteins in muscle may indicate that with age the increase in the rate of lipid peroxidation is greater than the increase in the activities of antioxidant enzymes.

Cannon et al (34) reported a greatly attenuated neutrophil response in untrained older men (mean age: 55–74 y) when they were compared with young men (aged 22–29 y) during the 24-h period following 45 min of downhill running. In addition, older men had a significantly reduced and delayed increase in plasma creatine kinase activity than seen in young subjects, which may have been due to a reduced ability of the elderly to mount an acute-phase response to muscle damage. In this study, vitamin E supplementation [800 IU/d (800 mg  $\alpha$ -tocopherol) for 2 mo before the exercise] had the effect of significantly increasing the postexercise rise in circulating neutrophils and creatine kinase activity in the older subjects only. Vitamin E supplementation of the young men had no effect; thus, there were no significant age-associated differences in the response to exercise. At the time of peak concentrations in the plasma, creatine kinase correlated ( $r = 0.751$ ,  $P < 0.001$ ) with superoxide release from neutrophils. The association of this circulating skeletal muscle enzyme with neutrophil mobilization and function supports the concept that neutrophils are involved in the delayed increase in muscle membrane permeability after damaging exercise. These data indicate that vitamin E supplementation may affect the rate of repair of skeletal muscle after muscle damage and that these effects may be more pronounced in older subjects.

According to Jacob and Burri (54), the “increased production

of reactive oxygen species is a feature of most, if not all, human disease, including cardiovascular disease and cancer” (page 987). Use of the antioxidants vitamins E and C has been associated with several positive adaptations; for example, taking vitamin C appears to decrease the risk of developing cataracts and certain cancers.


Borkman et al (55) described a strong relation between the fatty acid composition of skeletal muscle and insulin sensitivity. In 1 of 2 experiments they conducted, samples of the rectus abdominis muscle were taken from 27 patients undergoing coronary artery surgery and the fatty acid composition of these samples was correlated with fasting serum insulin concentrations. Insulin concentrations were negatively correlated with the percentage of individual long-chain polyunsaturated fatty acids in the phospholipid fraction of muscle, particularly arachidonic acid ( $r = -0.63$ ,  $P < 0.001$ ). The second experiment involved a similar analysis of biopsies taken from 13 healthy men (aged  $30 \pm 11$  y). In this experiment, muscle polyunsaturated fatty acids were strongly correlated with insulin sensitivity assessed by a euglycemic glucose clamp (120 min at a rate of  $40 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$ , or  $278 \text{ pmol} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$ ). The authors of this study suggested that variations in insulin sensitivity are related to differences in the membrane content of long-chain polyunsaturated fatty acids within skeletal muscle phospholipids and that abnormalities in the fatty acid composition of membranes may be involved in the pathogenesis of a cluster of disorders linked to insulin resistance and hyperinsulinemia. Type 2 diabetes is associated with increased free radical production (56), lipid peroxidation, and a reduction in plasma vitamin E and superoxide dismutase (57). It has also been shown that pharmacologic doses of vitamins E and C increase insulin-stimulated glucose uptake (58–60). Perhaps the observed effect of vitamin E on carbohydrate metabolism is a result of decreased rates of lipid peroxidation and greater preservation of polyunsaturated fatty acids in muscle membranes. Paolisso et al (60) stated that their study showed that vitamin E supplements may reduce oxidative stress in persons with type 2 diabetes and thus improve the physical characteristics of membranes and related activities.

## CONCLUSIONS

In summary, exercise greatly increases the production of oxygen radicals in humans. In untrained persons, older men and women, and those with an inadequate antioxidant system, the increased rates of lipid peroxidation resulting from oxygen radical production may cause skeletal damage. The overwhelming consensus of the literature is that long- or short-term supplementation with vitamins E or C has no ergogenic effect on submaximal exercise performance, aerobic capacity, or muscle strength. However, the effects of these antioxidant vitamins may be subtle, and previous studies may not have examined appropriate endpoints. The protection against the generation of oxygen radicals and lipid peroxidation observed in untrained persons performing exercise and the enhanced acute-phase response to eccentric exercise observed in untrained older subjects indicate that vitamin E may be of some benefit in the adaptive response to exercise. In addition, the positive health benefits of using vitamins E and C may suggest an additive or synergistic effect when combined with regular exercise. New research initiatives should examine the following:





- the effects of vitamin E, vitamin C, or vitamins E and C together on the adaptive response to strength training;
- the combined effects of exercise and vitamin E on improved glucose homeostasis;
- the combined effects of exercise and vitamin C on diabetes risk factors including cataract formation as a complication of diabetes;
- the combined effects of exercise and vitamin E on lipoprotein status and risk factors for cardiovascular disease. 

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