Dietary Antioxidants for the Athlete

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Physical exercise induces oxidative stress and tissue damage. Although a basal level of reactive oxygen species (ROS) is required to drive redox signaling and numerous physiologic processes, excess ROS during exercise may have adverse implications on health and performance. Antioxidant nutrients may be helpful in that regard. Caution should be exercised against excess antioxidant supplements, however. This article presents a digest for sports practitioners. The following three recommendations are made: 1) it is important to determine the individual antioxidant need of each athlete performing a specific sport; 2) multinutrient preparations, as opposed to megadoses of any single form of nutrient, seem to be a more prudent path to choose; and 3) for outcomes of antioxidant supplementation, performance should not be the only criteria. Overall well being of the athlete, faster recovery, and minimization of injury time could all be affected by antioxidant therapy.

Introduction

The benefits of exercise training in promotion of good health and in prevention of various diseases are well established. During heavy physical exertion, the oxygen flux to active skeletal muscles increases by two orders of magnitude and oxygen consumption increases 15-fold [1••]. Such acceleration in the rate of oxidative metabolism is associated with enhanced production of reactive oxygen species (ROS), and therefore, exercise itself may induce oxidative stress [2]. Free radical production occurs continuously in all cells as part of normal cellular function, and oxidative stress, an imbalance between the generation of ROS and antioxidant defense capacity of the body (Fig. 1), is closely associated with the natural aging and disease process [1••]. High concentrations of ROS are hazardous for living organisms and they damage all major cellular constituents. At moderate concentrations, however, ROS and other related reactive molecules such as hydrogen peroxide and nitric oxide play an important role in the regulation of signaling processes [3,4••]. ROS act as secondary messengers to control a variety of physiologic responses [4••]. Finally, endogenous ROS generated by the cells may function as survival and repair signals [5,6].

In biologic systems, a variety of antioxidant defense agents have evolved to cope with oxidative stress, acting in concert to detoxify ROS. Defense mechanisms against oxidative stress depend primarily on an orchestrated synergism between several endogenous and dietary antioxidants [7]. Exercise performance is an outcome that depends on multiple factors, of which antioxidant nutrients have emerged as important [1••]. Although management of exercise-induced ROS in tissues may help against fatigue [8], it takes much more to consistently improve performance in a field setting.

This article briefly discusses the need, advantages, and disadvantages of dietary antioxidant supplements with respect to exercise-induced oxidative damage and physical performance. This work is intended to serve as a digest for athletes and sports practitioners.

Dietary Antioxidants

Dietary planning to fend off exercise-induced oxidative stress may be broadly based on two important considerations: 1) avoidance of dietary contents that increase the risk of oxidative stress [9–11]; and 2) inclusion of nutrients with biologic antioxidant functions [1••,12–14]. For example, the Mediterranean diet not only produces favorable effects on blood lipids, but also protects against oxidative stress [14]. A diet rich in fruits and vegetables elevates plasma antioxidant vitamins and reduces the risk of oxidative stress-dependent diseases. Another important consideration in this respect is the observation that individuals are more predisposed to the risk of oxidative stress under postprandial conditions. Postprandial oxidative stress, as a subform of nutritional oxidative stress, ensues from sustained postprandial hyperlipidemia and/or hyperglycemia [15].

Research on individual antioxidant nutrients has led to a substantial volume of mechanistic insight. Such studies of isolated nutrients are of immense academic value but often fail to address the complex interaction between nutrients in a wholesome diet. Since the antioxidant network was proposed over a decade ago [2], there has been

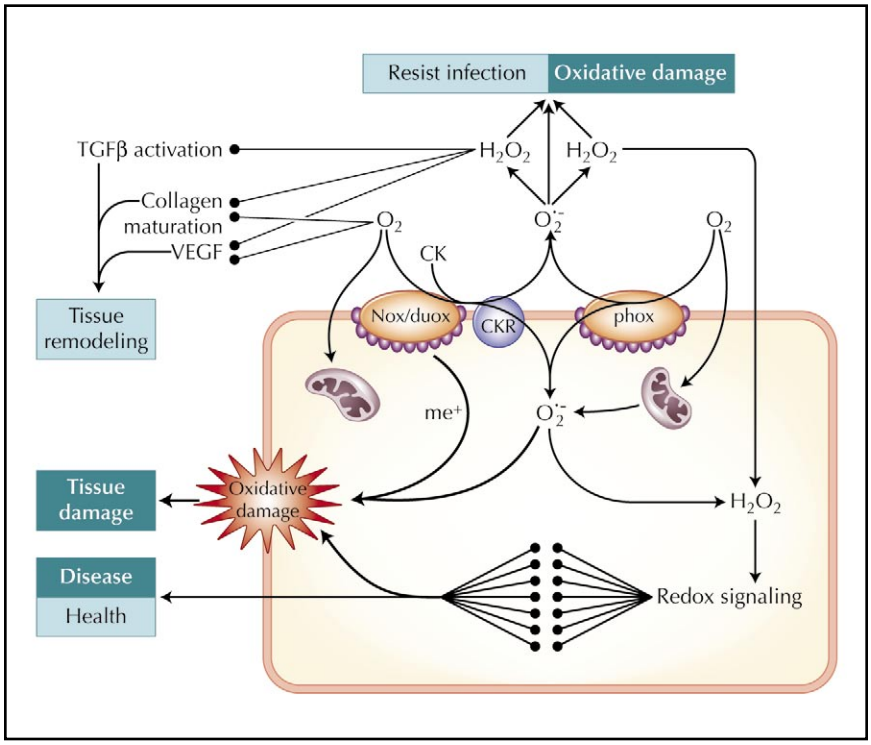

Figure 1. Schematic illustration of select possible pathways by which oxygen and its reactive derivatives may influence health and disease. ROS may be necessary for physiologic functions such as cell survival and tissue remodeling. Excess ROS, however, may trigger oxidative damage or damage caused by certain types of redox signaling. Such adverse effects of ROS may be managed by antioxidants. Redox signaling is integral to numerous physiologic processes. Indiscriminate total elimination of ROS by excessive antioxidants may not be desirable. CK—cytokine; CKR—cytokine receptor; me^+—free metal ions intensify oxidative damage; phox—phagocytic NADPH oxidases; nox/duox—nonphagocytic oxidases; ROS—reactive oxygen species; TGF—transforming growth factor; VEGF—vascular endothelial growth factor.

only a modest improvement of our understanding of the chemical, biochemical, and molecular interactions between nutrients. However, it is clear that low intake or impaired availability of dietary antioxidants including vitamins E and C, carotenoids, polyphenols, and other micronutrients (eg, selenium) weakens the antioxidant network [15].

Most of the available data on antioxidant supplementation in the prevention of exercise-induced oxidative stress have been obtained with vitamins E and C. Among the clinically relevant thiol-replenishing agents tested, N-acetyl-L-cysteine (NAC) and alpha lipoic acid (LA) are the best known [1••].

Vitamin C

Vitamin C (ascorbate) is a water-soluble vitamin that represents a major line of antioxidant defense in plasma. As with any vitamin, nutritional supply is essential. Under specific conditions, megadoses of vitamin C may prove to be harmful [16]. Persons exposed to brief periods of severe physical exercise and/or cold environments need high doses of vitamin C prophylaxis. Vitamin C promotes collagen synthesis, enhances carnitine biosynthesis, and facilitates glycogen storage. Vitamin C may also prevent exercise-induced oxidative changes [17], muscle soreness, and damage [18]. Furthermore, in three small randomized placebo-controlled trials with subjects under heavy acute physical stress, vitamin C supplementation markedly decreased the incidence of colds in physically active individuals [19].

Vitamin E

Vitamin E represents a family of major lipid-soluble chain-breaking antioxidants; it inhibits propagation of free radical formation, and prevents ROS-mediated lipid peroxidation in lipoproteins and biologic membranes. Vitamin E (alpha-tocopherol) supplements are unlikely to reliably reduce the severity of contraction-induced muscle damage but, in contrast, appear capable of modulating redox-regulated adaptive responses to contractions [20]. Alpha-tocopherol also does not appear to decrease exercise-induced lipid peroxidation in humans [21]. In general, studies of the use of dietary antioxidants such as alpha-tocopherol to reduce exercise-induced muscle injury have met with mixed success. The equivocal nature of these results appear to reflect a diversity of factors including the antioxidants tested, the nature and timing of the exercise, the age and fitness of the subjects, and the methodology for assessing oxidative stress [22]. Recent studies show that in some respects such as neuroprotection, certain vitamin E forms other than alpha-tocopherol, are more effective [23,24]. It would thus be prudent to test the tocotrienol form of natural vitamin E in a physical exercise setting.

Glutathione and selenium

Glutathione (GSH) is the most abundant intracellular thiol that has a key role in many physiologic functions [25]. GSH plays a central role in antioxidant protection directly and also by regenerating crucial exogenous antioxidants such as vitamins E and C from their respective oxidized forms [1••,26–28]. GSH is synthesized in the liver and also in skeletal muscle, but intact GSH is usually not transportable to intracellular compartments, and therefore, strategies to increase tissue GSH levels through various administration protocols ended up with failures [25,26].

GSH can either directly scavenge ROS or enzymatically via glutathione peroxidases (GSHPx) and GSH transhydrogenases; GSH is oxidized to glutathione disulfide (GSSG). Intracellular GSSG, thus formed, may be reduced back to GSH by GSSG reductase or released to the extracellular compartment [29]. Most of the GSHPx, but not all, are selenium dependent. The antioxidant function of selenium extends well beyond its ability to support the GSH system of antioxidant defense [30].

N-acetyl-L-cysteine

NAC is a thiol-derived antioxidant used clinically as a mucolytic and chemoprotective agent [25]. NAC is a potent antioxidant, reacting nonspecifically with a wide variety of ROS, and exerts its antioxidant functions by serving as a cysteine delivery agent for GSH synthesis. Reid et al. [31] were the first to report the ability of NAC supplementation to attenuate muscle fatigue in humans. We noted that NAC supplementation prevents exercise-induced blood GSH oxidation in humans [32]. Recently, NAC administration has been shown to enhance muscle cysteine and GSH availability, and to attenuate fatigue during prolonged exercise in endurance-trained individuals [8].

Beta-carotene

Beta-carotene, like other carotenoids, is a plant-derived fat-soluble pigment abundant in many fruits and vegetables, and efficient in quenching singlet oxygen and free radicals. Beta-carotene is also a precursor of retinol (provitamin A). In most studies related to physical exercise, beta-carotene has been studied in combination with other antioxidants making it difficult to determine the individual significance of this nutritional antioxidant. By itself, beta-carotene prevented exercise-induced asthma [33] and oxidative DNA damage in humans [34].

Lipoic acid

LA (thioctic acid or lipoate) is a natural thiol antioxidant with insulin-mimetic functions [25]. LA is able to favorably influence tissue antioxidant defenses and counteract lipid peroxidation at rest and in response to exercise [35].

The Need for Antioxidant Supplementation in Athletes

The literature on this subject is understandably equivocal making it challenging for athletes or their trainers to apply the knowledge to practice. As scientific evidence continues to build [18], it is important to take a practical view of the issue. Nutrition surveys in the United States reveal that athletes have generally adequate intake of vitamin C. Indeed, male athletes consume from 95 to 520 mg/d of vitamin C, and female athletes consume from 55 to 230 mg/d [36]; the current dietary reference intakes (DRI) of vitamin C are 75 to 90 mg/d for men and 65 to 75 mg/d for women of different age groups [37]. Some athletic groups, however, may have inadequate vitamin C intake and physiologic stressors, such as infection, cigarette smoking, altitude, and extreme environmental temperatures, increase vitamin C requirements [36]. Nonetheless, until now there has not been any conclusive evidence supporting the theory that regular exercise increases the requirement for vitamin C in athletes. In addition, plasma vitamin C levels of athletes are usually in the normal ranges, only a small portion of athletes have borderline or slightly low levels of vitamin C concentrations in the blood plasma [36].

Similar to vitamin C intake, nutrition surveys show that physically active people generally consume vitamin E within the limits of DRI or higher [38]. In addition, vitamin E intake is greater among athletes than sedentary people [39]. Nevertheless, a small group of athletes, including adolescent ballerinas, gymnasts, long-distance runners, and wrestlers, may have inadequate intake of vitamin E and other micronutrients because of the limitation of their food intake for esthetic purposes or competitive limitations [36,39]. Although vitamin E deficiency is rare in humans, physical activity and increased intake of polyunsaturated fatty acids may induce oxidative stress and need for vitamin E. The elderly population or physically active people with inadequate dietary intake of vitamin E may have marginal deficiency without developing clinical symptoms. In this context it is important to note that vitamin E refers to a family of eight natural molecules [24]. However, the only form of vitamin E tested under conditions of physical exercised is alpha-tocopherol. New results unequivocally suggest that alpha-tocopherol may have some adverse impact under specific conditions [40] and that the other natural forms of vitamin E have functions that are distinct from the effects of alpha-tocopherol [24]. For example, alpha-tocotrienol is clearly more neuroprotective than alpha-tocopherol [24,41]. It is time to consider forms of vitamin E other than alpha-tocopherol for studies addressing physical exercise.

Antioxidant Supplementation and General Health

When considering the cellular mechanisms, current knowledge supports the role of antioxidant nutrients in the intracellular management of excess ROS. Several physiologic and pathologic conditions ranging from pregnancy to cardiovascular diseases and cancer have been investigated to elucidate the effects of antioxidant supplementation. Given the complexities in the nature of each disease and in the biochemical issues related to redox biology, it is not simple to deduce straightforward conclusions from most studies. With more insight into fundamental mechanisms this situation is improving. Epidemiologic evidence suggests protection of cardiovascular disease by dietary intake of flavonoids [42]. Observational studies have also shown an inverse asso-

ciation between dietary intake of vitamin C, vitamin E, and beta-carotene and cardiovascular disease, although the net result of published trials on vitamin E and beta-carotene do not unequivocally support a protective effect of these antioxidant nutrients on overall mortality.

Many nutritional antioxidants such as carotenoids, vitamins C and E, selenium, and polyphenols have been investigated in various types of cancer [43,44]. Although equivocal data exist, most clinical trials tend to show that nutrition has an important role in the prevention of various types of cancer and overall mortality. The antioxidant vitamins and trace elements in fruits and vegetables account for a part of the beneficial effects.

Antioxidant Supplementation and Performance

Physical performance is regulated by multifactorial processes and may not serve as a good indicator to comprehensively test the effect of antioxidant supplementation. In most of the studies, a complete set of parameters for measuring performance including time to exhaustion, strength or torque changes for resistance training, changes in body composition, hormone concentrations, race times, mood changes, and neuromuscular changes were lacking [36]. Performance was determined either using one or few of these parameters or have been simply based on the subjective ability of the subject to endure repeated bouts of exercises. Therefore, this type of performance measurements may be somewhat misleading especially when a double-blind study design was not used.

In a population-based analysis, a significant positive correlation between plasma antioxidant concentrations and physical performance and strength in elderly people has been noted [45]. Supplementation with vitamin E has been used among athletes to increase endurance performance, although to date there has not been satisfactory experimental evidence to conclusively support this. In agreement with these effects of vitamin E, vitamin C supplementation also does not seem to improve exercise performance per se; it may be useful, however, in attempts to reduce exercise-induced muscle damage [18]. Antioxidant deficiency models in animals have helped to realize the significance of antioxidants in physical exercise. Planned depletion of tissue antioxidant levels enhance exercise-induced tissue damage and impair performance. In our earlier study, we noted that GSH depletion in rats decreased endurance time to exhaustion by 50% [26].

Caution Against Overdoses

Low-level ROS serve as important mediators of the signal transduction pathways [4••] for several physiologic functions that may be directly related to exercise-induced adaptations. Ex vivo animal studies have shown that dietary consumption of excessive high doses of antioxidants impairs muscle force production [46]. The widespread belief that more of a good nutrient is even better, does not always hold true with antioxidant nutrients. The optimum intake is one that minimizes the incidences of both deficiency and toxicity. Common antioxidants such as vitamins C and E, and beta-carotene are generally well tolerated even at doses several-fold higher than the DRI. However, at very high doses, vitamins and minerals can be as toxic as any other compounds present in food. For example, high doses of vitamin E may interfere with vitamin K metabolism and platelet function. High doses of selenium, and vitamins C and E can act as pro-oxidants. This is also the case with zinc, high doses of which have been associated with depressed immune response [47]. Epidemiologic studies indicated that prolonged high-dose supplementation of micronutrients such as selenium compounds are associated with several adverse health effects [48]. Current data caution against the use of antioxidants in excessive doses [49].

Conclusions

It is important to determine the individual need of each athlete. Oxidative stress markers should be used as a tool to identify the antioxidant needs of an athlete training for a specific type of sports. Because endogenous antioxidant defenses are dependent on genetic factors and exogenous antioxidant defenses are dependent on lifestyle, it is reasonable to expect significant individual variation. Professional athletes should address their need for antioxidant supplementation on a personalized basis.

Multinutrient preparations, as opposed to mega doses of any single form of nutrient, seem to be a more prudent path to choose. For outcomes of antioxidant supplementation, performance should not be the only criteria. Overall wellbeing of the athlete, faster recovery, and minimization of injury time could all be desirably affected by antioxidant therapy.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• Sen CK, Packer L, Hänninen O: *Handbook of Oxidants and Antioxidants in Exercise.* Amsterdam: Elsevier; 2000.
A comprehensive treatise on the subject designed for readers who are new to the subject or who are looking for itemized "take home" messages.

2. Sen CK: **Oxidants and antioxidants in exercise.** *J Appl Physiol* 1995, **79:**675–686.
3. Sen CK, Packer L: **Antioxidant and redox regulation of gene transcription.** *Faseb J* 1996, **10:**709–720.
4.•• Stone JR, Yang S: **Hydrogen peroxide: a signaling messenger.** *Antioxid Redox Signal* 2006, **8:**243–270.
Comprehensively reviews how reactive oxygen species may drive cell signaling processes central to health and disease.
5. Roy S, Khanna S, Nallu K, et al.: **Dermal wound healing is subject to redox control.** *Mol Ther* 2006, **13:**211–220.
6. Sen CK: **Antioxidant and redox regulation of cellular signaling: introduction.** *Med Sci Sports Exerc* 2001, **33:**368–370.
7. Sen CK: **Antioxidants in exercise nutrition.** *Sports Med* 2001, **31:**891–908.
8. Medved I, Brown MJ, Bjorksten AR, et al.: **Effects of intravenous N-acetylcysteine infusion on time to fatigue and potassium regulation during prolonged cycling exercise.** *J Appl Physiol* 2004, **96:**211–217.
9. Lenda DM, Boegehold MA: **Effect of a high salt diet on microvascular antioxidant enzymes.** *J Vasc Res* 2002, **39:**41–50.
10. Skrha J, Kunesova M, Hilgertova J, et al.: **Short-term very low calorie diet reduces oxidative stress in obese type 2 diabetic patients.** *Physiol Res* 2005, **54:**33–39.
11. Dierckx N, Horvath G, van Gils C, et al.: **Oxidative stress status in patients with diabetes mellitus: relationship to diet.** *Eur J Clin Nutr* 2003, **57:**999–1008.
12. Choi EY, Cho YO: **Allium vegetable diet can reduce the exercise-induced oxidative stress but does not alter plasma cholesterol profile in rats.** *Ann Nutr Metab* 2006, **50:**132–138.
13. Miquel J: **Can antioxidant diet supplementation protect against age-related mitochondrial damage?** *Ann N Y Acad Sci* 2002, **959:**508–516.
14. Galli C, Visioli F: **Antioxidant properties of Mediterranean diet.** *Int J Vitam Nutr Res* 2001, **71:**185–188.
15. Sies H, Stahl W, Sevanian A: **Nutritional, dietary and postprandial oxidative stress.** *J Nutr* 2005, **135:**969–972.
16. Duarte TL, Lunec J: **Review: When is an antioxidant not an antioxidant? A review of novel actions and reactions of vitamin C.** *Free Radic Res* 2005, **39:**671–686.
17. Ashton T, Young IS, Peters JR, et al.: **Electron spin resonance spectroscopy, exercise, and oxidative stress: an ascorbic acid intervention study.** *J Appl Physiol* 1999, **87:**2032–2036.
18. Clarkson PM, Thompson HS: **Antioxidants: what role do they play in physical activity and health?** *Am J Clin Nutr* 2000, **72:**637S–646S.
19. Hemila H: **Vitamin C and common cold incidence: a review of studies with subjects under heavy physical stress.** *Int J Sports Med* 1996, **17:**379–383.
20. Jackson MJ, Khassaf M, Vasilaki A, et al.: **Vitamin E and the oxidative stress of exercise.** *Ann N Y Acad Sci* 2004, **1031:**158–168.
21. Viitala P, Newhouse IJ: **Vitamin E supplementation, exercise and lipid peroxidation in human participants.** *Eur J Appl Physiol* 2004, **93:**108–115.
22. Sacheck JM, Blumberg JB: **Role of vitamin E and oxidative stress in exercise.** *Nutrition* 2001, **17:**809–814.
23. Sen CK, Khanna S, Roy S: **Tocotrienol: the natural vitamin E to defend the nervous system?** *Ann N Y Acad Sci* 2004, **1031:**127–142.
24. Sen CK, Khanna S, Roy S: **Tocotrienols: Vitamin E beyond tocopherols.** *Life Sci* 2006, **78:**2088–2098.
25. Sen CK, Packer L: **Thiol homeostasis and supplements in physical exercise.** *Am J Clin Nutr* 2000, **72:**653S–669S.
26. Sen CK, Atalay M, Hanninen O: **Exercise-induced oxidative stress: glutathione supplementation and deficiency.** *J Appl Physiol* 1994, **77:**2177–2187.
27. Atalay M, Laaksonen DE, Khanna S, et al.: **Vitamin E regulates changes in tissue antioxidants induced by fish oil and acute exercise.** *Med Sci Sports Exerc* 2000, **32:**601–607.
28. Sen CK: **Update on thiol status and supplements in physical exercise.** *Can J Appl Physiol* 2001, **26 Suppl:**S4–12.
29. Rahman I, Biswas SK, Jimenez LA, et al.: **Glutathione, stress responses, and redox signaling in lung inflammation.** *Antioxid Redox Signal* 2005, **7:**42–59.
30. Burk RF: **Selenium, an antioxidant nutrient.** *Nutr Clin Care* 2002, **5:**75–79.
31. Reid MB, Stokic DS, Koch SM, et al.: **N-acetylcysteine inhibits muscle fatigue in humans.** *J Clin Invest* 1994, **94:**2468–2474.
32. Sen CK, Rankinen T, Vaisanen S, et al.: **Oxidative stress after human exercise: effect of N-acetylcysteine supplementation.** *J Appl Physiol* 1994, **76:**2570–2577.
33. Neuman I, Nahum H, Ben-Amotz A: **Prevention of exercise-induced asthma by a natural isomer mixture of beta-carotene.** *Ann Allergy Asthma Immunol* 1999, **82:**549–553.
34. Sumida S, Doi T, Sakurai M, et al.: **Effect of a single bout of exercise and beta-carotene supplementation on the urinary excretion of 8-hydroxy-deoxyguanosine in humans.** *Free Radic Res* 1997, **27:**607–618.
35. Khanna S, Atalay M, Laaksonen DE, et al.: **Alpha-lipoic acid supplementation: tissue glutathione homeostasis at rest and after exercise.** *J Appl Physiol* 1999, **86:**1191–1196.
36. Lukaski HC: **Vitamin and mineral status: effects on physical performance.** *Nutrition* 2004, **20:**632–644.
37. *US Department of Health and Human Services and the US Department of Agriculture: Dietary Guidelines for Americans 2005.* Washington, DC: US Government Printing Office; 2005.
38. Economos CD, Bortz SS, Nelson ME: **Nutritional practices of elite athletes. Practical recommendations.** *Sports Med* 1993, **16:**381–399.
39. Guilland JC, Penaranda T, Gallet C, et al.: **Vitamin status of young athletes including the effects of supplementation.** *Med Sci Sports Exerc* 1989, **21:**441–449.
40. Miller ER, 3rd, Pastor-Barriuso R, Dalal D, et al.: **Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality.** *Ann Intern Med* 2005, **142:**37–46.
41. Khanna S, Roy S, Slivka A, et al.: **Neuroprotective properties of the natural vitamin E alpha-tocotrienol.** *Stroke* 2005, **36:**2258–2264.
42. Zern TL, Fernandez ML: **Cardioprotective effects of dietary polyphenols.** *J Nutr* 2005, **135:**2291–2294.
43. Clark LC, Combs GF Jr, Turnbull BW, et al.: **Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group.** *Jama* 1996, **276:**1957–1963.
44. Hercberg S, Galan P, Preziosi P, et al.: **The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals.** *Arch Intern Med* 2004, **164:**2335–2342.
45. Cesari M, Pahor M, Bartali B, et al.: **Antioxidants and physical performance in elderly persons: the Invecchiare in Chianti (InCHIANTI) study.** *Am J Clin Nutr* 2004, **79:**289–294.
46. Coombes JS, Powers SK, Rowell B, et al.: **Effects of vitamin E and alpha-lipoic acid on skeletal muscle contractile properties.** *J Appl Physiol* 2001, **90:**1424–1430.
47. Chandra RK, McBean LD: **Zinc and immunity.** *Nutrition* 1994, **10:**79–80.
48. Vinceti M, Wei ET, Malagoli C, et al.: **Adverse health effects of selenium in humans.** *Rev Environ Health* 2001, **16:**233–251.
49. Willett WC, Stampfer MJ: **Clinical practice. What vitamins should I be taking, doctor?** *N Engl J Med* 2001, **345:**1819–1824.