Oxygen Free Radicals & Antioxidants

An overview of how antioxidants protect the body from disease.

By Merrily A. Kuhn, PhD, RN

Oxygen free radicals and antioxidants were a novel aspect of illness and its prevention to most nurses 15 years ago. But numerous exposés in the mainstream media in recent years—with titles such as "The Promise of Antioxidants" (*Saturday Evening Post,* January 1995), "Drinking Black Tea May Reduce Stroke Risk" (*New York Times,* March 1996), and "Vitamins E and C Called Alzheimer's Inhibitors" (*Los Angeles Times,* June 2002)—have turned *free radicals* and *antioxidants* into household words. In addition, researchers have begun to undertake serious study of the effects of antioxidants on health and illness. And while much of the research on oxygen free radicals and the beneficial effects of antioxidants has been conducted in animals, this research has nonetheless, generated much interest and many people are taking antioxidants in addition to conventional drugs. Although there aren't precise estimates of sales of antioxidants, it's known that Americans spend billions of dollars each year on a variety of dietary supplements.

More often than not, a nurse's concern with patients is in the management or cure of illness, which leaves little time to discuss prevention and health promotion. In order for nurses to give patients appropriate information on antioxidants, they must first understand how free radicals form and how they cause oxidative damage.

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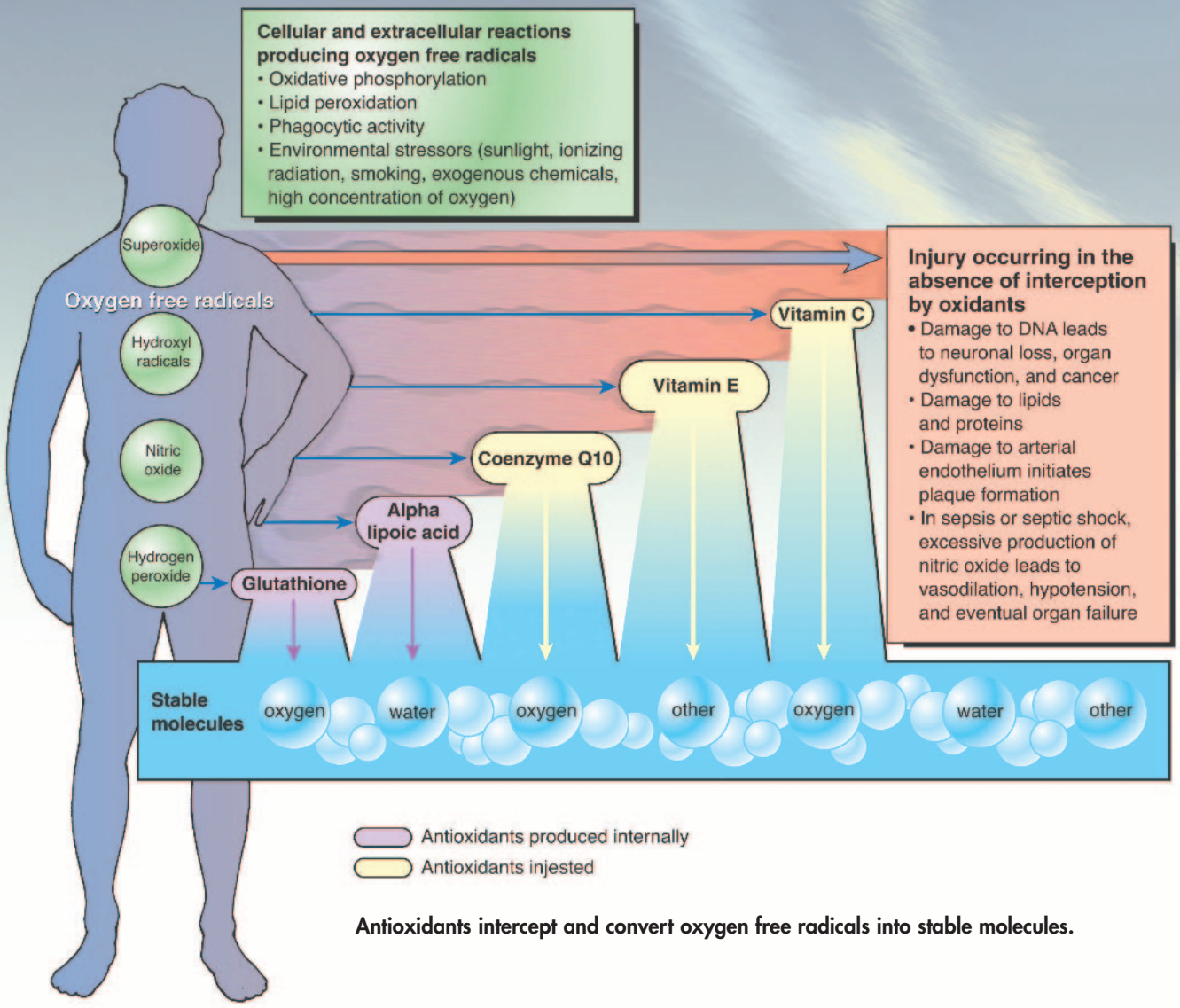
OXYGEN FREE RADICALS

Oxygen is actually a toxic byproduct of the metabolism of lower cell organisms, and the body uses it to produce energy. The molecule adenosine triphosphate (ATP) carries energy and is the primary source of it for cells in all organs and tissues.[1]

How are oxygen free radicals made? Through a biochemical process at the cellular level, oxygen and glucose are used to produce ATP. This is called oxidative phosphorylation, a process during which electrons not bound to an oxygen molecule move from one such molecule to another seeking to bind to other unpaired electrons. These oxygen molecules that contain unpaired electrons are called *oxygen free radicals.*

One percent to 3% of the oxygen we breathe creates oxygen free radicals, as do natural aging and chronic disease. In small amounts, some oxygen free radicals help to clean cells by taking part in phagocytosis, a function of a normal immune system, but

Antioxidants Preventing or Repairing Oxygen Free Radical Injury



Antioxidants intercept and convert oxygen free radicals into stable molecules.

as production of these radicals increases, they begin to attack and destroy cells.

How do oxygen free radicals create disease? As their levels increase, oxygen free radicals attack and oxidize DNA, genetic molecular material that controls cell growth and development. Oxidation of DNA may lead to the adverse effects of aging, such as wrinkled skin, organ dysfunction, and cancer. As oxygen free radicals travel through the blood, they set the stage for heart, blood vessel, cerebrovascular, and skeletal muscle disease by making it more difficult for cells to repair themselves.

Free radicals can damage the intima in blood vessels, causing inflammation and thereby leading to increased plaque formation, which can contribute to stroke and cardiac disease.[2] Oxygen free radicals also free iron, which is usually tightly bound to protein molecules. Excessive levels of free iron are associated with Alzheimer disease, dementia, and Parkinson disease. In addition, oxygen free radicals cause an increase in neuronal loss by changing DNA structure. When a significant number of neurons are degraded, the central nervous system can no longer maintain homeostasis, and physiologic functions such as receptor-mediated signal transmission necessary to memory may become defective or be lost.[2]

What are the principal oxygen free radicals? There are many types of oxygen free radicals produced by cellular reactions, but four types seem to account for most of them: superoxide, hydrogen peroxide, hydroxyl radical, and nitric oxide.

Superoxide radicals are created during the production of ATP and are beneficial when produced in the immune system because they destroy virus, bac-

The Principal Antioxidative Foods

Oxygen radical absorbency capacity (ORAC) indicates the ability of a fruit or vegetable to prevent oxidation, the damage done by oxygen free radicals. The following table was created by the United States Dietary Association:

Fruits	ORAC units per raw serving
Prunes	1,939
Blueberries (1/2 cup)	1,740
Blackberries (1/2 cup)	1,466
Strawberries (1/2 cup)	1,170
Raisins (1/4 cup)	1,026
Raspberries (1/2 cup)	756
Oranges (1/2 cup, sections)	675
Plums (1)	626
Red grapes (1/2 cup)	591
Cherries (1/2 cup, pitted)	516

Vegetables	ORAC units per raw serving
Kale (1 cup)	1,186
Beets	571
Red bell peppers (1/2 cup)	533
Brussels sprouts (1/2 cup)	431
Corn (1/2 cup)	420
Spinach (1 cup)	360
Broccoli florets (1/2 cup)	320
Onions (1/2 cup)	360
Eggplant (1 cup)	320
Alfalfa sprouts (1/2 cup)	149

Source: USDA Agriculture Research Service, Food & Nutrition Research Briefs, April 1999.
http://www.ars.usda.gov/is/np/fnrb/fnrb499.htm#Antioxidant

teria, and cancer cells. Superoxide radicals also increase the activity of epinephrine and norepinephrine, which are necessary to the fight-or-flight response. Superoxide in large amounts, however, can damage lipids, proteins, and DNA.

Hydrogen peroxide is a by-product of the degradation of fats during energy production. It confers no benefit to the body, even at low levels. Because fat cells divide rapidly there is a greater risk of mutation in fatty tissue. Many hydrogen peroxide radicals form in the macula of the eye and may cause degeneration there.[3] Red wine (4 to 6 ounces per day) and purple grape juice (6 to 8 ounces per day) are hydrogen peroxide free radical scavengers that eliminate them, and drinking either daily may reduce the incidence or possibly the progression of such macular degeneration.[1,4]

Hydroxyl radicals. Direct exposure to radiation in the form of gamma rays or X-rays is harmful to the human body, yet we are exposed to constant radiation in the atmosphere through sunlight, for example. Hydroxyl radicals are most commonly produced by cells as a result of this exposure, and they are the most deadly and powerful of the oxygen free radicals, providing no benefit to the body, even in small amounts. The hydroxyl radical is highly reactive, destroying everything in its path by altering DNA and contributing to plaque formation in blood vessels.

Nitric oxide is produced in the body through enzymatic reactions. Although it is an oxygen free radical, it is beneficial to the body at low levels because it regulates both blood flow in the vessels and blood pressure. A form of nitric oxide, nitroglycerin, is used as a drug to dilate the blood vessels of patients with chest pain. Nitric oxide in excess, however, can cause damage. When a patient is in septic shock, the body can produce too much nitric oxide, and along with other vasoactive substances, this can cause vasodilation, low blood pressure, and eventual multiple organ failure.

ANTIOXIDANTS

Oxygen free radicals are counterbalanced by the activities of enzymes and monoenzymes called antioxidants. Normally, there is a balance between the production of oxygen free radicals and antioxidants, but when the body is overwhelmed, either by aging or disease, the unchecked oxidants lead to cellular changes and critical illness.

Antioxidants act as catalysts in a biomedical reaction, which means they react to oxygen free radicals but are not damaged or changed by them. Such a reaction results in a stable molecule, and the unchanged antioxidant is ready to continue its helpful work in transforming oxygen free radicals into harmless molecules.

Antioxidants are found in food or taken as supplements and can significantly decrease the adverse effects of oxygen free radicals. They are derived from vitamins, minerals, and phytochemicals, beneficial nutrients found in foods such as fresh fruits and vegetables.

When we are young, and mild oxidative stress

occurs in the form of a cold, tissues respond by producing additional antioxidants. But under severe oxidative stress associated with acute or chronic disease, chronic stress, or aging, the body can't produce antioxidants sufficient to protect against cellular injury.

There are hundreds of antioxidants; but five of them, working synergistically, seem to be the most powerful. They are:

- alpha lipoic acid
- vitamins C and E
- coenzyme Q10
- glutathione

Vitamins C and E are not produced in the body, but are easily obtained from food such as citrus fruits and nuts, respectively. Alpha lipoic acid, coenzyme Q10 (CoQ10), and glutathione are produced by the body at the cellular level, but levels of them decline with age. Vitamin E and CoQ10 are fat-soluble and protect cell membranes. Vitamin C and glutathione are water-soluble and protect the cytoplasm within cells. Each antioxidant is completely dependent on the others, having its own particular function and the inability to perform the function of another.

Alpha lipoic acid is an oxygen free radical scavenger and the most versatile and powerful antioxidant of all, often called the super antioxidant because it is both water- and fat-soluble. It works to promote synergy among other antioxidants, including vitamins E and C, glutathione, and CoQ10. Most research to date on alpha lipoic acid has been performed on animals, and some of it has revealed that it protects and increases neurotransmitters, thereby improving memory.[5] Other research shows that alpha lipoic acid may decrease complications in patients with types 1 and 2 diabetes.[6,7] Spinach and red meat contain alpha lipoic acid, but it's difficult to obtain enough of it in the diet; supplementation at 100 mg daily is recommended.[6]

Vitamin E. In the 1930s vitamin E was used to keep food from becoming rancid, as it was found to stop lipid peroxidation, a chain reaction that causes cells to degrade. Since that time, much more has been learned about the benefits of vitamin E. It recycles vitamin C, alpha lipoic acid, and CoQ10, which means that after it changes the oxygen free radical into a stable molecule, these other antioxidants rejuvenate vitamin E, reinstating it to fighting form. The antioxidants remain unchanged and continue transforming oxygen free radicals into stable molecules by working together to recycle one another to maintain the ability to fight oxygen free radicals. Vitamin E is found in many foods, such as vegetable oils, nuts, nut butters, sunflower seeds, kale, wheat germ, dried apricots, sweet potatoes, and mangos.

Antioxidants seem to be more powerful when obtained from food sources, rather than from supplementation.

Observational studies indicate that vitamin E may aid in reducing the incidence of heart disease by lowering cholesterol levels and preventing blood clots that could induce a heart attack.[8] (A 2002 study of 423 postmenopausal women with coronary disease who took either hormone replacement therapy or a combination of vitamins E and C revealed no benefit conferred by either.[9]) A study conducted in the Netherlands from 1990 to 1999, of people older than 55 without dementia, concluded that high doses of both vitamin E and vitamin C may lower the risk of developing Alzheimer disease. The researchers conceded that more research in this area must be conducted.[10] The National Institutes of Health recommends 15 mg as the daily dosage for adults older than 19.[8] However, an antioxidative dose is probably 400 IU daily.

Vitamin C, also known as ascorbic acid, helps the body regenerate vitamin E and assists in the absorption of iron. It also performs a critical function in the immune system by improving the body's response to infection. Vitamin C is found in many fresh fruits and vegetables, but citrus fruits and juices are particularly rich in it.

The current recommended daily dosage of vitamin C is 60 mg to 90 mg (smokers should take 100 mg),[11,12] although researchers in a 1999 study recommend a daily dosage of 100 mg to 200 mg.[13] Because vitamin C is water soluble, taking too much of it may cause diarrhea and gastric disturbance.[14]

CoQ10, a powerful lipophilic antioxidant and oxygen free radical scavenger found in mitochondrial enzymes,[15] improves the function of mitochon-

dria, which produce energy in cells. It's found in relatively high concentrations in the heart, kidney, liver, and pancreas. The daily recommended dosage is 50 mg taken with food but can vary to three or more times that amount, depending on whether it's being taken for a specific condition. Possible benefits of CoQ10 include improving cardiomyopathy,[16] and it may improve survival after myocardial infarction if administered within three days (120 mg per day).[16, 17] Contraindications include pregnancy and lactation, and CoQ10 may interfere with warfarin's efficacy. Taking statin drugs may necessitate an increased daily intake of CoQ10 because such drugs may inhibit its absorption, which, generally, can be enhanced by taking one 5-mg dose of piperine (Bioperine [black pepper]) with each CoQ10 dose.

Glutathione is the cell's primary antioxidant and the one most commonly produced in the body. Glutathione, vital to proper liver function, is also known to fight infection, but levels of it decrease with age. Excessive intake of alcohol, as well as large, continuous doses of acetaminophen, deplete glutathione in the liver. Acetaminophen labeling warns against the combination with alcohol because it increases the production of oxygen free radicals, depleting glutathione in the liver even further. Environmental toxins, such as cigarette smoke and overly processed foods laden with chemicals, such as luncheon meats that contain nitrites, reduce levels of glutathione as well.

Glutathione is found in fresh fish, vegetables, and fresh cooked meat, but most of it is lost in digestion, and supplements of it are also destroyed in the gut. Because cells must therefore produce their own glutathione, which requires the presence of precursors and cofactors such as alpha lipoic acid, it's recommended that 100 mg of the latter be taken daily.

CONSIDER THE SOURCE: FOOD OR SUPPLEMENTS?

In April 2000 an expert panel at the Institute of Medicine concluded that there was not enough evidence at that time to support the use of high doses of antioxidants, including vitamins C and E, to combat chronic diseases like cancer, heart disease, macular degeneration, cataracts, Alzheimer disease, and Parkinson disease.[12] But the panel did set upper levels of recommended dosages of vitamins C and E higher than had been suggested previously.

Despite the many studies of antioxidants conducted to date, more research is necessary to clarify several issues.[18] Antioxidants seem to be more powerful when obtained from food sources, rather than from supplementation.[18] Some research has suggested that high supplementary doses of antioxidants may be harmful, as this may change the delicate balance in the body that protects against cellular injury. To keep the antioxidant network strong and effective, there must be constant daily replenishment of antioxidants or antioxidant precursors. For that purpose, the ingestion of five to nine daily servings of fresh whole fruits and vegetables is the best option. A medium-size fruit or ? cup of raw or cooked vegetables is considered a serving. To minimize pesticide and wax consumption, wash and scrub produce well. ▼

REFERENCES

1. High KP. Nutritional strategies to boost immunity and prevent infection in elderly individuals. *Clin Infect Dis* 2001;33 (11):1892-900.
2. Shigenaga MK, et al. Oxidative damage and mitochondrial decay in aging. *Proc Natl Acad Sci U S A* 1994;91(23): 10771-8.
3. Jampol LM. Antioxidants, zinc, and age-related macular degeneration: results and recommendations. *Arch Ophthalmol* 2001;119(10):1533-4.
4. Schmitt CA, Lowe SW. Apoptosis and therapy. *J Pathol* 1999;187(1):127-37.
5. Hager K, et al. Alpha-lipoic acid as a new treatment option for Alzheimer-type dementia. *Arch Gerontol Geriatr* 2001; 32(3):275-82.
6. Packer L, et al. Molecular aspects of lipoic acid in the prevention of diabetes complications. *Nutrition* 2001;17(10): 888-95.
7. Evans J, Goldfine I. Alpha-lipoic acid: a multifunctional antioxidant that improves insulin sensitivity in patients with type 2 diabetes. *Diabetes Technol Ther* 2000;2(3):401-13.
8. Clinical Nutrition Service, National Institutes of Health. *Vitamin E* [Website]. 2002. http://www.cc.nih.gov/ccc/supplements/vite.html.
9. Waters DD, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA* 2002;288(19):2432-40.
10. Engelhart MJ, et al. Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA* 2002;287(24):3223-9.
11. *JAMA* patient page: Vitamin C. *JAMA* 1999;281(15):1460.
12. Institute of Medicine. *Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids*. Washington, DC: National Academy Press; 2000.
13. Levine M, et al. Criteria and recommendations for vitamin C intake. *JAMA* 1999;281(15):1415-23.
14. Kaur B, et al. Vitamin C supplementation for asthma. *Cochrane Database Syst Rev* 2001;4.
15. Kontush A, et al. Plasma ubiquinol-10 is decreased in patients with hyperlipidaemia. *Atherosclerosis* 1997;129(1):119-26.
16. Singh RB, Niaz MA. Serum concentration of lipoprotein(A) decreases on treatment with hydrosoluble coenzyme Q10 in patients with coronary artery disease: discovery of a new role. *Int J Cardiol* 1999;68(1):23-9.
17. Singh RB, et al. Randomized, double-blind, placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction. *Cardiovasc Drugs Ther* 1998;12(4):347-53.
18. Warnholtz A, Munzel T. Why do antioxidants fail to provide clinical benefit? *Curr Control Trials Cardiovasc Med* 2000;1(1):38-40.