Antioxidants

Dr Victoria Jewell

Oxidant stress

Oxidant stress has been implicated in a large number of important human diseases including cancer, cardiovascular disease and stroke.[1] The term 'reactive oxygen species' (ROS) is used to describe free radicals or oxidants etc that are capable of damaging cells in the body. Damage from ROS can eventually kill the cell. ROS are formed through trauma or injury, as well as air pollution, radiation, chemicals or toxins, alcohol consumption, cigarette smoke, drugs, some foods we eat and environmental toxins. Some ROS are also formed as a by-product of many of the body's natural biochemical processes.

Oxidative stress is probably caused when damage arising from ROS is not repaired rapidly enough. All of the major classes of biomolecules (lipids, proteins etc) are vulnerable to free radical damage. Free radicals cause strand breaks in DNA, which potentially can lead to subsequent disrepair and tumour cell formation.[2]

Antioxidants

Antioxidants make free radicals incapable of causing damage to cells. The primary antioxidant defences of the body include nutrients such as vitamins (e.g. vitamins C and E), carotenoids (e.g. beta-carotene and lycopene), thiols (e.g. glutathione), flavanoids and polyphenols (found in tea, red wine and herbs). Antioxidants can be obtained from fruit and vegetables in the diet including ascorbate (vitamin C), α-tocopherol (vitamin E), carotenoids and polyphenolic flavanoids. In addition, several micronutrients function as integral components within the endogenous antioxidant defences of the body (e.g. selenium in the metalloenzyme glutathione peroxidase).

Links have emerged between diets rich in antioxidant nutrients and a lower incidence of diseases (e.g. cancer, cardiovascular disease and effect on immune function).[3] It has been suggested that a boost to the body's immune system by antioxidants may in part account for this.[4] It is very important to try to keep the balance of ROS to antioxidants as level as possible by either dietary means or supplementation from as early an age as possible to prolong, if not prevent, the onset of age-related disorders and chronic human diseases such as cardiovascular disease, stroke, cancer and eye disorders and to protect the immune system.

Common antioxidants

- Vitamins C and E
- Lutein and zeaxanthin
- Beta-carotene
- Lycopene
- Selenium
- Quercetin (flavanoid)

Vitamin E

Vitamin E (tocopherol) performs an important role as an antioxidant in protecting lipids (e.g. in cell membranes) and vitamin A from oxidation by aggressive oxygen radicals. In this function, it is supported by non-enzymatic substances such as vitamin C and beta-carotene, as well as by enzymatic substances such as glutathione peroxidase, which contains selenium. Tocopherol also influences the synthesis of prostacyclin and the metabolism of eicosanoids and, therefore, also indirectly prevents thrombotic disease and inflammation reactions. Vitamin E also appears to protect low density lipoprotein (LDL)-cholesterol from oxidation and thus counters atherosclerotic changes. Vitamin E has been recognised as having many potentially beneficial effects in human health and disease prevention.

Many human studies have considered the effect of vitamin E on various biochemical and physiological parameters. These include large and small scale intervention studies designed to assess the effects of vitamin E on conditions such as heart disease, cancer, degenerative diseases and the immune system. Evidence suggests that a high intake of vitamin E may prevent atherogenesis through LDL oxidation, platelet reactivity and cytokine release.[5] It has recently been established as a useful marker for identifying patients with coronary heart disease.[6] There are insufficient data available to recommend vitamin E for the prevention of heart disease in the general public.[7,8] However, there are many ongoing studies investigating the effect of vitamin E on cardiovascular disease, including a study in Texas entitled 'Effect of High Dose Vitamin E on Carotid Atherosclerosis'.

Beta-carotene

Beta-carotene has a dual role as a source of vitamin A and as an antioxidant. It can be converted to retinol on demand and the body's antioxidant defence system may not function optimally without adequate beta-carotene. A large number of epidemiological and observational studies indicate that an inadequate supply of beta-carotene (and other carotenoids) is associated with an increased risk of cancer, particularly lung cancer, atherosclerosis and coronary heart disease. However, it is not known whether beta-carotene intake is acting as a marker for other components of fruits and vegetables or another lifestyle factor, rather than having an effect in its own right. As an antioxidant, beta-carotene has the ability to quench singlet oxygen and neutralise free radicals which both cause oxidative damage (oxidant stress) to cells in the body.

Studies such as the US Physicians' Health Study and the Heart Protection Study (UK) have shown no adverse effects of beta-carotene. The Heart Protection Study is ongoing in the UK with 20,000 volunteers and is due to be completed in 2007. This study is investigating the effects of vitamins A, C and E along with simvastatin on cardiovascular disease. Beta-carotene supplements have been indicated to improve immune function, protect against cardiovascular disease, some cancers and stroke, and may play a role in protecting the skin against damage from the sun. Beta-carotene supplementation has been shown to reduce lipid peroxidation in smokers,[9] which is known to increase oxidative stress, which increases the risk of cardiovascular disease, stroke and lung disease.

In view of the possible preventive effect of beta-carotene against the development of atherosclerosis, coronary heart disease, hyperlipidaemia and cancer, a balanced supply of antioxidants (including an adequate supply of beta-carotene) would appear to be beneficial.

Vitamin C

In its function as a water-soluble antioxidant, ascorbic acid supports the anti-oxidative protective mechanisms of the cells against highly reactive oxygen free radicals. In conjunction with vitamins A, E and beta-carotene (provitamin A), it scavenges free radicals, deactivating and detoxifying them. Vitamins C and E act synergistically, in that vitamin E is regenerated by ascorbic acid after it has reacted with lipid peroxide radicals, so that it can again take part in the detoxification process.

Vitamin C appears to have a positive effect on the prevention of a large number of other chronic diseases, e.g. ischaemic heart disease, atherosclerosis, stroke and diabetes. Vitamin C, especially along with tocopherol, inhibits LDL oxidation, which is believed to be involved in the formation of plaques.[10] Also, in several studies, plasma ascorbate levels were inversely associated with coronary vascular disease and stroke.[11,12] Beneficial effects have been observed with high doses of ascorbic acid on endothelial-dependent vasodilation.[13,14] Research is ongoing and, in the UK, the Women's Antioxidant Cardiovascular Study (WACS) is currently investigating (completion 2006) the effect of vitamins C, E and beta-carotene on cardiovascular health in women.

Lycopene

Lycopene is a non-provitamin A, fat-soluble carotenoid and like many other carotenoids is considered to be an antioxidant. There are no specific deficiency disorders associated with lycopene, as there are no ideal intake values available. There has been much research into the beneficial effects of lycopene, and some results have shown a decrease in the risk of cancer and heart disease when people have been given large doses of this carotenoid. Most people do not consume this suggested amount, due to their low fruit and vegetable consumption, and therefore supplements may be beneficial.

Lycopene has been associated with decreased risk of degenerative diseases and it may provide protection against cancer and cardiovascular disease; it is thought to do this via its antioxidant function. Lycopene is associated with decreased risk of cardiovascular disease (atherosclerosis, coronary heart disease etc),[15] although studies have been limited. One study concluded that circulating levels of lycopene may play a role in early stages of atherogenesis and may have clinical and public health relevance.[16]

There is a need for much investigation into the biology of lycopene (absorption, metabolism, excretion and biological function) and long-term studies into the effects of lycopene in relation to disease risk factors. Until additional evidence is available, public health recommendations should still emphasise the consumption of a diet rich in fresh fruit and vegetables.

Other antioxidants

Selenium is an essential trace mineral in the human body and is an antioxidant that may help limit the oxidation of LDL cholesterol and thereby help to prevent coronary artery disease. Too low an intake of this mineral has been linked to heart disease and cardiovascular problems. A study in Finland found that cardiovascular deaths were significantly associated with low serum selenium concentrations.[17] Currently there is insufficient evidence available to recommend selenium supplements for the prevention of coronary heart disease but a supplement may be beneficial.

Flavanoids are natural chemicals found abundantly in plants. They are present in fruit and vegetables, red wine, beer, ale, stout and tea. Chemically they are known as polyphenols. Recent research has shown that flavanoids have potent antioxidant properties and this may reduce oxidation of LDLs. Flavanoids also prevent blood platelets sticking together and thereby reduce the risk of a clot.

Lutein and zeaxanthin are carotenoids similar in structure to beta-carotene and they function as antioxidants in the same manner as beta-carotene. They have already been shown to prevent age-related macular degeneration but recent evidence suggests that they may prevent narrowing and hardening of the arteries, which can lead to stroke and heart attack.

Conclusion

Many experts have recommended that sensible nutritional supplementation can be beneficial for most adults, and may be very important to meet specific nutrient requirements. Many articles have been reviewed concerning vitamins, their relationship to disease and preventive healthcare in adults. These report that: low concentrations of vitamins B_6, B_{12} and folic acid are a risk factor for heart disease, some cancers and neural tube defects; low levels of the antioxidant vitamins E, A and C and selenium may increase the risk of heart disease and cancer; and low levels of vitamin D contribute to osteoporosis.

Research suggests that regular use of a multivitamin makes sense for most adults. Due to the increased consumption of fast food, alcohol or nicotine abuse, hectic lifestyles and the low consumption of fruit and vegetables, it is clear that most diets will not be nutritionally complete, and supplements — in most cases a multivitamin with minerals — can fill this gap. All the same, public health recommendations should still emphasise the consumption of a diet rich in fresh fruit and vegetables.

References

1. Blanche D, Gesquiere L, Loreau N, Durard P. Oxidant stress: the role of nutrient in cell-lipoprotein interactions *Proc Nutrition Soc* 1999; 58: 559-63.
2. Halliwell B, Aruoma OI. DNA damage by oxygen-derived species: its mechanisms and measurement in mammalian systems. *FEBS Letters* 1991; 281: 9-19.
3. Ford ES, Will JC, Bowman BA, Venkat Narayan KM. Diabetes mellitus and serum carotenoids: findings from the third national health and nutrition examination survey. *Am J Epidemio* 1999; 149: 168-76.
4. Hughes DA. Effects of dietary antioxidants on the immune function of middle-aged adults. *Proc Nutrition Soc* 1999; 58: 79-84.
5. Meyandi M. Effect of functional food ingredients: vitamin E modulation of cardiovascular diseases and immune status in the elderly. *Am J Clin* Nutr 2000; 71 (suppl): 1665s-8s.
6. Holvoet P, Mertens A, Verhamme P et al. Circulating oxidized LDL is a useful marker for identifying patients with coronary heart disease. *Arterioscler Thromb Vasc Biol* 2001; 21: 844-8.
7. Food and Nutrition Board. A report of the Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary References Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: Institute of Medicine. National Academy Press; 2001; pp 186-283.
8. Gay R, Meyandi SN. The effects of vitamin E, vitamin B6 and vitamin B12 on immune function. *Nutr Clin Care* 2001; 4: 188-98.
9. Allard JP, Royall D, Kurian R, Muggli R, Jeejeebhoy KN. Effects of B-carotene supplementation on lipid peroxidation in humans. *Am J Clin Nutr* 1994; 59: 884-90.
10. Harris JR (ed). Ascorbic acid: biochemistry and Biomedical cell biology. In: *Subcellular Biochemistry*. New York, NY: Plenum Press; vol. 25, 1996.
11. Levine M, Rumsey S, Wang Y. Vitamin C. In: Ziegler EE, Filer LJ (eds). *Present Knowledge in Nutrition*. 7th ed. Washington, DC: ILSI Press; pp 146-59, 1996.
12. Levine M, Rumsey SC, Daruwala S, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. *JAMA* 1999; 281: 1415-23.
13. Carr AC, Frei B. Toward a new recommended daily allowance for vitamin C based on antioxidant and health effects in humans. *Am J Clin Nutr* 1999; 69: 1086-107.
14. May JM. How does ascorbic acid prevent endothelial dysfunction? *Free Radic Biol Med* 2000; 28: 1424-9.
15. Rao AV. Lycopene, tomatoes and the prevention of coronary heart disease. *Exp Biol Med* 227: 908-13.
16. Rissanen T, Voutilainen S, Nyyssonen K, Salonen JT. Lycopene, atherosclerosis, and coronary heart disease. *Exp Biol Med* 2002; 227: 900-7.
17. Virtamo J, Valkeila E, Alfthan G et al. Serum selenium and the risk of coronary heart disease and stroke. *Am J Epidemiol* 1985; 122 (2): 276-82.

Dr Victoria Jewell, nutritional biochemist, Northern Ireland Centre for Food and Health (NICHE), University of Ulster, Coleraine, Northern Ireland.