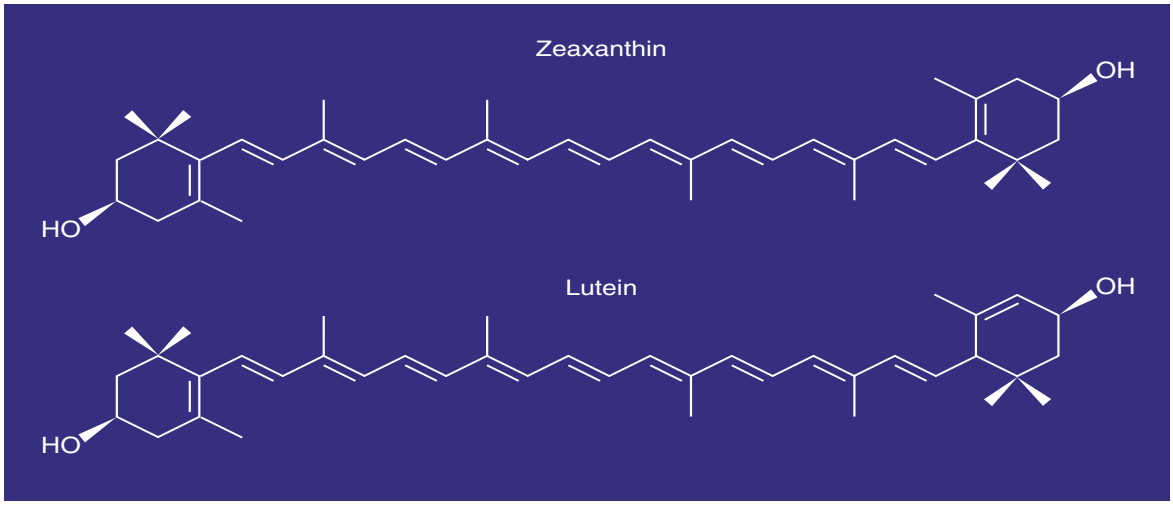

Lutein and Zeaxanthin

Introduction

Lutein and zeaxanthin belong to the xanthophyll family of carotenoids and are the two major components of the macular pigment of the retina. The macula lutea or "yellow spot" in the retina is responsible for central vision and visual acuity. Lutein and zeaxanthin are the only carotenoids found in both the macula and lens of the human eye, and have dual functions in both tissues – to act as powerful antioxidants and to filter high-energy blue light.[1] Lutein is found in high amounts in human serum.[2] In the diet it is found in highest concentrations in dark green, leafy vegetables (spinach, kale, collard greens, and others), corn, and egg yolks.[3] Zeaxanthin is the major carotenoid found in corn, orange peppers, oranges, and tangerines (Table 1).[4] In addition to playing pivotal roles in ocular health, lutein and zeaxanthin are important nutrients for the prevention of cardiovascular disease, stroke, and lung cancer. They may also be protective in skin conditions attributed to excessive ultraviolet (UV) light exposure.

Biochemistry and Pharmacokinetics

Lutein and zeaxanthin differ from other carotenoids in that they each have two hydroxyl groups, one on each side of the molecule. Zeaxanthin is a stereoisomer of lutein, differing only in the location of a double bond in one of the hydroxyl groups. The hydroxyl groups appear to control the biological function of these two xanthophylls.[5] Some dietary lutein appears to be converted to a non-dietary form, meso-zeaxanthin. Infants have more lutein and less meso-zeaxanthin, possibly due to less efficient lutein conversion. Lutein appears to have an affinity for the peripheral retina and rods, while zeaxanthin seems to be preferentially taken up by the cones of the macula.[6] Because xanthophylls are fat-soluble nutrients, bioavailability to tissues is dependent on a number of factors, including nutrient source (whole food or supplement), state of the food (raw, cooked, or processed), extent of disruption of the cellular matrix via mastication and digestive enzymes, and absorption by the enterocytes of the intestinal mucosa (primarily the duodenum). Cooking of lutein/zeaxanthin-containing foods may increase bioavailability by disrupting the cellular matrix and the carotenoid-protein complexes.[7]

After lutein and zeaxanthin are absorbed by the enterocytes they are transported across the intestinal lumen and incorporated into the chylomicrons. They reach the circulating blood and are subsequently taken up by hepatocytes, entering the hepatic circulation where they are incorporated into lipoproteins. In humans, low- and high-density lipoproteins transport lutein and zeaxanthin via the systemic circulation to various tissues.[8] Data on xanthophyll

absorption is limited, but studies involving single dietary doses indicate lutein reaches peak concentrations in the chylomicron fraction at approximately two hours post-ingestion,[9] and peaks in serum at about 16 hours post-ingestion.[10] Lutein absorption from a purified crystalline lutein supplement is almost twice that from spinach or other vegetable sources.[7] Non-dietary factors affecting absorption and bioavailability of lutein and zeaxanthin include age, body composition, gender, malabsorption of fats, alcohol consumption, smoking, and liver or kidney disease.[11-14]

Table 1. Lutein and Zeaxanthin Content of Foods

Food	Lutein content	Zeaxanthin content
Kale, cooked	20-33 mg*/1 cup	11-20 mg*/1 cup
Turnip greens, cooked	18.1 mg/1 cup	5.1-12.2 mg*/1 cup
Collard greens, cooked	10.2-17.2 mg*/1 cup	0.37-5.1 mg*/1 cup
Spinach, cooked	12-15 mg*/1 cup	5.9-12.7* mg/1 cup
Spinach, raw	6.6 mg/1 cup	3.6 mg/1 cup
Broccoli, cooked	3.4 mg/1 cup	3.5 mg/1 cup
Brussels sprouts, cooked	3.4 mg/1 cup	2.0 mg/1 cup
Green peas	2.3 mg/1 cup	2.3 mg/1 cup
Corn, cooked	0.6 mg/1 cup	2.8-3.0 mg/1 cup
Persimmons	0.6 mg/1 cup	0.8 mg/1 cup
Egg yolks	0.3 mg/1 yolk	0.25 mg/1 yolk
Tangerines	0.3 mg/1 cup	0.2 mg/1 cup
Orange juice	0.3 mg/1 cup	0.34 mg/1 cup
Orange sweet peppers	–	1.7 mg/1 cup

* Depending on variety

Mechanisms of Action

Lutein and zeaxanthin are powerful antioxidants, and lutein is widely known as the primary nutrient for protecting ocular function. It has long been thought that carotenoid intake also reduces the risk of certain forms of cardiovascular disease,[15-17] stroke,[18-19] and cancer.[20-21] Lutein and zeaxanthin may prevent cellular damage in these conditions by quenching singlet oxygen or neutralizing photosensitizers.

Lutein and zeaxanthin inhibit lipid peroxidation, a likely factor in the etiology of both retinal and cardiovascular disease. The presence of adhesion molecules on endothelial cell surfaces is a marker of atherosclerosis pathogenesis. *In vitro* research has demonstrated lutein incubation with cultured endothelial cells effectively inhibits the expression of these adhesion molecules.[22] Other research has found lutein and zeaxanthin can inhibit thickening of the walls of carotid arteries and LDL-induced migration of monocytes to human artery cell walls.[23] These are potential mechanisms for lutein's protective effect in cardiovascular disease.

In the case of skin health, lutein, zeaxanthin, and other carotenoids appear to be depleted in the skin under conditions of prolonged UV light exposure.[24-25] Skin exposure to UV rays generates reactive oxygen species, inflammation in skin cells, and erythema. Intake of dietary antioxidants, including lutein and zeaxanthin, reduces this inflammatory response, as carotenoids are poor absorbers of UV light.[26]

Clinical Indications

Ocular Conditions

Age-related Macular Degeneration

In older Americans, age-related macular degeneration (AMD) is the leading cause of blindness. It is characterized by atrophy of the macular disk. The retinal pigmented epithelium and photoreceptors (particularly the rods and the blue-light sensitive cones) are the most affected. There are two types of AMD – early or dry and late or wet. Early AMD is characterized by soft drusen accumulation and pigmentary changes in the retinal epithelium and macula**,** while late-stage AMD involves neovascularization of the retina, an exudative mound, and intraretinal hemorrhage and scarring.[27-28]

Numerous observational studies have examined the correlation between lutein and zeaxanthin concentrations in the macula, dietary intake, and macular degeneration. In the multicenter Eye Disease Case-Control study, Seddon et al evaluated the relationship between dietary intake of carotenoids and the risk of neovascular AMD in 356 subjects. After adjusting for risk factors, they found a 57-percent decreased risk for AMD in individuals with the highest intake of lutein/zeaxanthin (6 mg daily), compared to those who consumed the lowest level (0.5 mg daily).[29]

Other studies have examined the relationship between lutein/zeaxanthin intake, serum lutein/zeaxanthin, and macular pigment density (MPD). In 278 healthy volunteers higher levels of dietary lutein intake correlated with higher serum lutein and zeaxanthin and significantly higher MPD.[30] Bernstein et al also demonstrated lutein supplementation of 4 mg daily resulted in significantly higher MPD levels in AMD patients compared to control subjects not supplementing.[31] These observational studies seem to indicate maintenance of macular pigment density is crucial to maintaining visual acuity and decreasing the risk of developing AMD.

Since 2001, three double-blind, intervention studies have examined the effects of lutein supplementation on vision improvement in AMD patients. In a 12-month trial of 14 AMD patients, Richer demonstrated improvements of up to 92 percent in visual acuity tests after subjects consumed a diet containing five ounces of spinach (approximately 14 mg lutein) 4-7 times weekly.[32]

In 2004, Richer published the results of a follow-up study – the Lutein Antioxidant Supplementation Trial (LAST), a double-blind, randomized, placebo-controlled study. Ninety males with atrophic AMD were supplemented with either 10 mg lutein, 10 mg lutein plus a broad spectrum formula containing antioxidants/vitamins/minerals, or placebo for one year. The subjects were examined for MPD, photo-stress recovery, contrast sensitivity, and visual acuity at baseline, and every four months until the end of the study. The most significant finding was a 36-percent increase in MPD in the lutein group and a 43-percent increase in MPD in the lutein plus antioxidant group, compared to a slight decrease in MPD in the placebo group. Lutein supplementation also resulted in significant improvements in visual acuity, objective visual function parameters, photo-stress recovery, and contrast sensitivity. The LAST confirms lutein plays an important role in ocular health and that AMD appears to respond favorably to lutein supplementation.[33]

In an Italian study, 50 patients with AMD were given daily cocktails containing antioxidants and 15 mg purified lutein or placebo for 18 months. The study was published in Italian so details are not readily available, but the researchers demonstrated a two-fold increase in visual acuity in AMD patients compared to the placebo group.[34]

Cataracts

Cataracts are the leading cause of impaired vision in the United States, with a large percentage of the geriatric population exhibiting some signs of the lesion. Cataracts are developmental or degenerative opacities of the lens that result in a gradual, painless loss of vision. Oxidative insult appears to be a precipitating factor in cataracts, resulting in the development of insoluble, oxidized lens proteins. Higher levels of hydrogen peroxide have been found in cataractous lenses compared to normal lenses, indicating oxidative stress.[35-36]

Studies examining lutein and zeaxanthin levels in extracted cataractous lenses have found up to three-fold higher levels in the newer epithelial tissue of the lens than in the older inner cortex portion. The

epithelial cortex layer comprises 50 percent of the tissue, yet it has been found to contain 74 percent of the total lens lutein and zeaxanthin, supporting the hypothesis that these nutrients are protective against the oxidative damage causing cataract formation.[37]

The Nurses Health Study examined the effect of 12 years of carotenoid consumption on the risk of cataract formation in 77,466 female nurses, ages 45 and over. After controlling for other risk factors, nurses in the highest quintile for lutein and zeaxanthin consumption had a 22-percent decreased risk for cataract extraction, compared with those in the lowest quintile.[38] Numerous other observational studies have found that increased consumption of foods high in lutein/zeaxanthin is associated with a decreased risk for cataracts or cataract extraction in both men and women. These studies provide strong evidence for a protective role for lutein/zeaxanthin against development of cataracts.[39,40]

The only randomized, double-blind trial on carotenoid supplementation and age-related cataracts measured visual acuity, glare sensitivity, and serum carotenoid levels in 17 clinically diagnosed patients. Patients received 15 mg lutein three times weekly for two years and were compared to patients receiving 100 mg alpha-tocopherol or placebo for the same period. In patients receiving lutein, statistically significant improvements in visual acuity and glare sensitivity and increased serum concentrations of lutein were observed, compared to the alpha-tocopherol and control patients.[41]

Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a rare, inherited, degenerative disease characterized by atrophy of the light-sensing rods in the retina. The rods are responsible for vision in low-light situations; therefore, early RP (often in childhood) is frequently characterized by poor night vision. A progressive loss of peripheral vision occurs over time, resulting in tunnel vision in late stages of the disease. Although treatment is limited, high-dose vitamin A supplementation has been shown to slow the degeneration.[42] In one study, Dagnelie et al found 40 mg lutein daily for nine weeks significantly improved visual acuity among 16 RP patients. Testing of visual acuity was via computer-simulated self-test by RP patients.[43] Ongoing double-blind, placebo-controlled trials are examining the effects of lutein supplementation in patients with RP.

Skin Health and Ultraviolet Light Exposure

Stahl et al examined the effect of mixed carotenoid and straight beta-carotene supplementation on skin erythema after exposure to UV light. Subjects were divided into two groups: Group 1 received a carotenoid supplement containing 24 mg beta-carotene and Group 2 received 24 mg mixed carotenoids (8 mg each of beta-carotene, lutein, and lycopene) daily for 12 weeks. Group 2 patients demonstrated increased serum levels of all three nutrients and a significant decrease in erythema was observed in both groups after UV exposure compared to pre-supplementation. This study suggests carotenoids deposited in the skin may protect against erythema and inflammation resulting from UV rays.[44] In support of this hypothesis, other researchers have demonstrated the presence of lutein and its oxidative metabolites in human skin.[45,46] Although a direct association between skin levels of lutein and lutein consumption has not been established, higher skin lutein levels are observed in humans who take a regular lutein-containing, multivitamin supplement.[47]

Cardiovascular Disease and Stroke

Epidemiological studies have long suggested an association between carotenoid intake and decreased risk of cardiovascular disease.[16,48] Research has shown oxidized low density lipoprotein (LDL) to be a key factor in the initiation of atherosclerosis, one of the pathological processes involved in cardiovascular and cerebrovascular disease. LDL expresses numerous adhesion molecules that appear to enhance the binding of monocytes to aortic endothelium, where they may become transformed into foam cells and initiate atherosclerosis.[22,49] Consequently, antioxidants, including carotenoids, have been investigated for the ability to scavenge free radicals and inhibit lipid peroxidation in cardiovascular and cerebrovascular disease.

Case-control studies utilizing carotid intima-media thickness (IMT) to measure atherosclerotic progression in asymptomatic men and women

have found a moderate inverse association between lutein and zeaxanthin serum levels and carotid IMT. In a three-year study, 231 asymptomatic age-, sex-, race-, and field center-matched case subjects from the Atherosclerosis Risk in Communities (ARIC) study cohort demonstrated significantly lower serum lutein/zeaxanthin levels and an average IMT two times larger (1.2 ± 0.3 mm) than matched control subjects (0.6 ± 0.1 mm).[50]

More recently, the Los Angeles Atherosclerosis Study examined the association between plasma lutein/zeaxanthin levels, atherosclerotic progression, and carotid IMT. A total of 573 asymptomatic men and women were assessed via plasma lipid levels and carotid artery ultrasound at baseline and after 18 months. After adjustment for age, sex, and smoking status, changes in carotid IMT were significantly inversely associated with lutein and zeaxanthin levels. The researchers concluded higher levels of these carotenoids may be protective against early atherosclerosis.[51]

Two studies have investigated the hypothesis that high lutein/zeaxanthin might exert a protective effect against stroke in men. A prospective observational study of 43,738 men without cardiovascular disease or diabetes found a slightly significant association between xanthophyll intake and ischemic stroke. The relative risk for ischemic stroke for the top quintile of lutein intake compared with the bottom quintile was 0.63. Further studies are warranted.[18] A second cohort study of 26,593 male smokers in Finland investigated the association between carotenoid intake and risk of stroke subtypes. An inverse association between lutein intake and subarachnoid hemorrhage was observed, and subjects in the highest quartile of lutein intake had a risk ratio of 0.47 for subarachnoid hemorrhage compared to those in the lowest quartile (risk ratio of 1.0).[19]

Cancer

In a 10-year study following 120,000 U.S. men and women, a significant reduction in lung cancer was observed in those with the highest intake of total carotenoids, including lutein and zeaxanthin.[52] A second 14-year study assessed the same relationship in 27,000 Finnish male smokers via a food-item questionnaire. Consumption of carotenoid-containing fruits and vegetables was associated with decreased risk of lung cancer. A decreased risk was also observed in those in the highest quintiles of lutein/zeaxanthin intake versus the lowest quintiles.[20] A population-based survey of 20 South Pacific Island populations examined the association between lutein consumption and lung cancer rates. Researchers found an inverse association between lutein and lung cancer and a markedly lower incidence rate for lung cancer among Fijians, compared to other South Pacific populations. Fijians consume an average of 200 g dark greens (25 mg lutein) daily; whereas, inhabitants of other South Pacific countries consume diets in which colorful fruits and vegetables are less plentiful.[53]

Nutrient-Nutrient Interactions

Although inconclusive, some studies have demonstrated a competitive inhibition for absorption among carotenoids. The two carotenoids most often examined have been beta-carotene and lutein. Competition for absorption seemed only to be a factor in short-term studies (less than two years), while longer studies have not demonstrated this effect. Simultaneous feeding of lutein as the predominant carotenoid with beta-carotene appears to inhibit absorption of beta-carotene.[54] Conversely, beta-carotene also appears to slightly inhibit lutein absorption in single-feeding studies.[10,11]

Drug-Nutrient Interactions

Certain drugs, nutritional supplements, and foods have been reported to decrease the absorption of lutein/zeaxanthin. Cholesterol-lowering medications, including cholestyramine (Questran®) and colestipol (Colestid®), and Xenocal®, a drug used to treat obesity, may reduce the absorption of fat-soluble carotenoids.[55,56] Proton-pump inhibitors such as Prilosec®, Losec®, Prevacid®, Aciphex®, Protonix®, and Pantoloc® increase gastric pH and have been shown to decrease the absorption of a single dose of beta-carotene. Whether or not these drugs have the same effect on lutein/zeaxanthin absorption has not been determined. Mineral oil, corn oil, medium chain triglycerides, olestra, and pectin may also inhibit the absorption of lutein and zeaxanthin.[56]

Side Effects and Toxicity

No toxicities or adverse reactions have been reported in the scientific literature for lutein/zeaxanthin at doses of up to 40 mg daily for two months.[43] Fijians consume an average of 25 mg lutein daily throughout a lifetime without any toxic effects.[53] High doses of beta-carotene supplements (>30 mg daily) have been associated with carotenodermia,[57] and the same may occur with high doses of lutein and zeaxanthin. Studies of lutein and zeaxanthin in pregnant and nursing women have not been conducted, so pregnant and nursing women should obtain lutein/zeaxanthin from daily servings of fruits, vegetables, and egg yolks. Ames testing has demonstrated an absence of any mutagenic effect for purified lutein.[58]

Dosage

Average daily intake for lutein and zeaxanthin in the United States is 2.0-2.3 mg daily for men and 1.7-2.0 mg daily for women,[59] although dietary intakes of approximately 6-20 mg lutein daily appear to be necessary to decrease risk of macular degeneration.[32-34] If taken in supplement form, lutein and zeaxanthin are available in either the free or esterified forms, which appear to have comparable bioavailability.[60] Although commercially available lutein/zeaxanthin supplements often contain significantly more lutein than zeaxanthin, new products are being developed with higher amounts of zeaxanthin. Typically, lutein supplements are available in either 6- or 20-mg tablets or capsules. While the 6-mg dose is based on early studies, the 20-mg dose is more typical and is usually taken once daily. Carotenoids are best absorbed in the presence of fat, but as little as 3-5 g in a meal appear to ensure carotenoid absorption.[61]

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