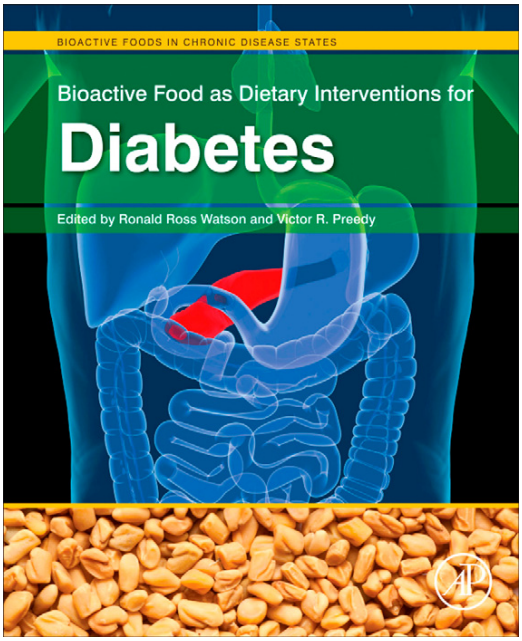

Miranda M., Araiz J., and Romero F.J. (2013) Lutein and Diabetic Cataracts. In: Watson RR and Preedy VR (eds.) *Bioactive Food as Dietary Interventions for Diabetes*, pp. 275-289. San Diego: Academic Press.

CHAPTER 25

Lutein and Diabetic Cataracts

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1. INTRODUCTION

The lens is a transparent and avascular structure whose main function is to focus light on the retina. The lens is composed of a single layer of epithelial cells that throughout life undergo mitosis, migrate to the equatorial region, and differentiate into fiber cells. The newly formed fiber cell develops over the older fibers displacing them to the center of the tissue. The inner region (nucleus) represents the embryonic lens and the periphery (cortex) contains the youngest section which is the metabolically active region. The nucleus, mitochondria, and other cellular organelles are degraded during the differentiation into fiber cells, so that the fully differentiated lens fiber loses its ability to synthesize protein and maintain metabolic processes (Spector, 1995). In humans, during the prenatal and early postnatal periods, the formation of new lens fibers occurs rapidly, but after the first few years, the rate decreases markedly. In this way, the fraction of the lens that is metabolically active is constantly diminishing (Spector, 1995).

A cataract, a common pathological abnormality of the lens, is a cloudy or opaque area in the normally clear lens of the eye. Depending upon its size and location, it can interfere with normal vision. Cataracts become more common with increasing age. Most cataracts develop in people over age 55, but they can also occasionally occur in infants and young children. The population over 55 years is more susceptible to lens opacification, and this population group is expected to increase fourfold worldwide. Cataracts are the leading cause of blindness worldwide, and although great advances have been made in surgical treatment, the incidence of cataracts is still a health problem worldwide with important economic impact, that is even more important in the less-developed world.

Cataracts can be subdivided according to their anatomical location within the lens (e.g., cortical, nuclear, and subcapsular), their appearance (e.g., total and pulverulent), and most commonly by a combination of these two parameters (e.g., nuclear pulverulent). They can also be classified according to their etiology (congenital, disease related, or age related). A nuclear cataract is located in the center of the lens, and it is usually the result of advancing age; a cortical cataract affects the layer of the lens surrounding the nucleus and is usually associated with patients who suffer from diabetes; a subcapsular

Bioactive Food as Dietary Interventions for Diabetes
http://dx.doi.org/10.1016/B978-0-12-397153-1.00027-5

Bioactive Food as Dietary Interventions for Diabetes, (2013), pp. 275-289

cataract is found in the back outer layer of the lens and is usually associated with people working with microwave radiation, patients who take steroids or diabetic patients. While the incidence of posterior subcapsular cataract is lower than that of nuclear and cortical cataract, posterior subcapsular cataract has a greater deleterious effect on visual function.

2. OXIDATIVE STRESS AND CATARACTS

Oxidative stress was originally defined as an imbalance between the production of reactive species and antioxidant defenses, which may lead to tissue injury; free radicals can be overproduced or the natural antioxidant system defenses weakened. Oxygen-derived free radicals and reactive nitrogen species have received considerable attention in research, and virtually all diseases examined involved free radicals. In most cases, free radicals are secondary to the disease, but, in some cases, free radicals are its cause. Oxidative stress affects proteins, lipids, and DNA and changes in these three have been observed in cataracts. Moreover, when the cell's ability to repair these components is exceeded, apoptosis occurs, and apoptosis also plays important roles in lens development and pathology. One of the best known toxic effects of reactive oxygen species (ROS) is damage to cellular membranes, which is initiated by a process known as lipid peroxidation. A common target for peroxidation is the presence of unsaturated fatty acids in membrane phospholipids. One of the byproducts of lipid peroxidation is the toxic compound, malondialdehyde, whose involvement in cataractogenesis has been suggested, mainly due to its cross-linking ability.

Oxidative stress is thought to play a major role in the etiology of age-related cataract. The young lens has substantial reserves of antioxidants (vitamins C and E, carotenoids, and glutathione – GSH) and antioxidant enzymes (superoxide dismutase, catalase, and GSH reductase/peroxidase) that may prevent damage but aging is associated with diminished antioxidant reserves and antioxidant enzymatic activities; this decrease can lead to accumulation of ROS and peroxynitrite in the lens (Berthoud and Beyer, 2009). Exposure to ultraviolet (UV) radiation is associated with a variety of harmful effects, ranging from photoaging to skin cancer. UVB (290–320 nm) directly damages the cellular DNA leading to the formation of the 6–4 cyclobutane pyrimidine dimmers, and UVA (320–400 nm) indirectly also damages the DNA via the production of oxygen radical species. Lens function is to focus light on the retina, and UV radiation, under certain conditions, can cause the generation of damaging ROS. The lens fibers do not have the ability to replace damaged proteins, and, therefore, the UV filtering function decreases with age whereas the levels of protein-bound UV filters, which generate peroxides upon UVA illumination, increase with age (Mizdrak et al., 2008).

ROS has also been related to apoptosis. Apoptosis is a form of cell death which has been involved in the initiation and progression of cataracts. There are distinct mechanisms that execute apoptosis according to various different apoptotic stimuli: the mitochondria-dependent pathway (intrinsic pathway) and the death-receptor-dependent

pathway (extrinsic pathway). Cataracts have been related to the mitochondria-dependent pathway. Mitochondrial damage induces the release of cytochrome *c* into the cytoplasm, which contributes to programmed cell death. It has been demonstrated that H_2O_2 induces the activation of caspase-9 and caspase-3 in lens epithelial cells (Yao et al., 2008). Caspases play an important role in regulating cell apoptosis; caspase-3 is activated by caspase-9 and both are involved in the mitochondria-dependent pathway. It has also been demonstrated that the Bcl-2/Bax ratio is significantly decreased in lens cultures by the treatment with H_2O_2 (Yao et al., 2008). Bcl-2 can prevent ROS production and regulate the mitochondrial transitional pore opening by opposing the effect of Bax, thereby blocking cytochrome *c* release and inhibiting caspase activation.

Reactive nitrogen species are also thought to play an important role in cataract development. Many cells have the capacity to synthesize nitric oxide (NO). NO is produced by the action of nitric oxide synthase (NOS) on L-arginine. There are three isoforms of NOS, and two of them, endothelial cell NOS (eNOS) and neuronal NOS (nNOS), are expressed constitutively, while the third, inducible NOS (iNOS), is generally expressed in response to immunological challenges or other pathophysiological stimuli. Normal ocular tissues (retina, ciliary body, iris, conjunctiva, and cornea) express NOS, and NO is normally present at a low concentration in the aqueous humor that bathes the lens. The generation of NO gives rise to several other reactive species, such as NO^+, NO^-, NO_2, N_2O_3, and $ONOO^-$, which are all capable of inflicting tissue damage. Indeed, NO generation is known to be associated with retinal degeneration and glaucoma. Varma and Hedge found that NO is deleterious to the lens and that this damage is associated with a substantial decrease in the contents of ATP and GSH (Varma and Hegde, 2007). It has been observed that induction of iNOS and abnormal production of NO occur in certain animal models of cataract (Inomata et al., 2001), and that the concentration of NO in the aqueous humor is known to be elevated in traumatic cataract (Kao et al., 2002). Moreover, it has been shown that treatment with NOS inhibitors delays the development (or decreases the severity) of cataracts (Nabekura et al., 2003).

Oxidative stress is counteracted by antioxidants, which are substances that, at low concentrations relative to the substrate, inhibit the damage to proteins, lipids, carbohydrates, and DNA. The lens lacks blood vessels to assist in dispersing reactive oxygen and nitrogen species. However, the normal lens is well supplied with primary antioxidants to repair oxidatively damaged cell components; these antioxidants are enzymes, and nonenzymatic substances. The nonenzymatic mechanisms include ascorbate, crystallins and GSH, and UV filters (tryptophan derivatives) (Reddy, 1990). Enzymes include superoxide dismutase, catalase, and peroxidases (GSH peroxidase, peroxiredoxins, and microperoxidases) (Reddy, 1990). Repair of lens proteins after oxidative damage involves the participation of GSH-dependent thioltransferase, reduced nicotine-adenine-dinucleotide phosphate (NADPH)-dependent thioredoxin/thioredoxin reductase system, and methionine sulfoxide reductases (Spector et al., 1987).

GSH is present in unusually high concentration in the mammalian lens, though GSH levels are much higher in the cortex than in the nucleus of the lens. It is the primary antioxidant in the lens and protects against oxidative stress by scavenging free radicals and other reactive species. GSH is a peptide composed of three amino acids: cysteine, glutamate, and glycine. It has been demonstrated that oxidation of GSH results in the concomitant formation of GSSG. Under normal conditions, the observed ratio of GSH/glutathione disulfide (GSSG) is >100, indicating that the cell is able to maintain a remarkably high reducing environment, quickly recycling the oxidized GSSG back to GSH (Spector et al., 1987). This process requires an active GSSG reductase that utilizes NADPH formed via the hexose monophosphate shunt.

GSH has three roles in cataract formation. First, GSH may be important in maintaining protein thiols in the reduced state, thus preventing the formation of high-molecular-weight protein aggregates, which are the basis for light scattering and lens opacification. A second function may be to protect membrane –SH groups that are important in cation transport and permeability. A third functional role is to detoxify hydrogen peroxide and other organoperoxides. The GSH redox cycle is intimately involved in the detoxification of H_2O_2, which is normally present in the aqueous humor (Reddy, 1990).

In cataracts in older humans, extense protein oxidation has been observed: oxidation of thiol to protein and mixed disulfides, as well as cysteic acid and methionine oxidation to methionine sulfoxide, formation of high-molecular-weight protein aggregates covalently linked by disulfides, and oxidation of membrane lipids (Spector et al., 1987).

Decreased GSH levels have been noticed in human cataract; moreover, these levels are lower in diabetic cataracts than in senile cataracts (Altomare et al., 1995) and administration of buthionine sulfoximine, an effective inhibitor of γ-glutamylcysteine synthetase (the enzyme that catalyzes the first step in GSH biosynthesis), caused cataract in mice (Calvin et al., 1986). Therefore, supplementation of GSH to the lens may help in maintaining its protective ability against oxidative stress and other attacks and lead to delay the onset of cataract. Since GSH by itself is not effectively transported into cells, the decrease in GSH can be prevented by treatment with N-acetylcysteine (NAC) and GSH esters to boost GSH in the cell (Martensson and Meister, 1989). GSH esters are hydrolyzed to release GSH in cells. NAC is hydrolyzed to cysteine in the cell; it is the availability of cysteine that usually limits GSH synthesis. NAC, GSH monoester, and GSH isopropyl ester, injected intraperitoneally, are effective in delaying or preventing cataract formation induced by X-irradiation or buthionine sulfoximine (Martensson and Meister, 1989).

3. MECHANISMS OF DIABETIC CATARACTS

The prevalence of diabetes mellitus worldwide is increasing rapidly in association with the increase in obesity; worldwide, more than 285 million people are affected by diabetes mellitus. This number is expected to increase to 439 million by 2030.

Complications are a major fear of patients with diabetes, and these complications include cataracts, diabetic retinopathy, nephropathy, etc. Actually, it is thought that diabetes mellitus is associated with a fivefold higher prevalence of cataracts. Even though cataract surgery is the most common surgical ophthalmic procedure worldwide, patients with diabetes mellitus have higher complication rates derived from cataract surgery.

Three molecular mechanisms may be involved in the development of diabetic cataract: nonenzymatic glycation of eye lens proteins, oxidative stress, and activated polyol pathway in glucose disposition. All of these changes accelerate generation of ROS and increases in oxidative chemical modification of lipids, DNA, and proteins in the lens of diabetic patients. It can be then concluded that oxidative stress is involved in the pathogenesis of late diabetic cataracts and that these elevated glucose levels present in diabetes and the existence of oxidative stress are inseparable, though it is not definitely demonstrated if this is the cause or the consequence of these complications.

A good example of the above-mentioned interactions is the importance of GSH levels in diabetic lens. As mentioned earlier, lens contains a high concentration of reduced GSH, which maintains the thiol groups in the reduced form. These contribute to lens' complete transparency. Glycation, the nonenzymic reaction between a free amino group in proteins and a reducing sugar, slowly inactivates GSH-related as well as other enzymes. In addition, GSH can be also glycated and, therefore, contributes to the opacification of the lens in these patients.

The increase in the polyol pathway has also been related to oxidative stress in cataracts. The enzyme, aldose reductase, catalyzes the reduction of glucose to sorbitol through the polyol pathway. It has been shown that the intracellular accumulation of sorbitol (sorbitol is produced faster than it is converted to fructose by the enzyme, sorbitol dehydrogenase) leads to osmotic changes in lens fibers that degenerate and form sugar cataracts. Osmotic stress caused by the accumulation of sorbitol induces stress in the endoplasmic reticulum, the principal site of protein synthesis, ultimately leading to the generation of free radicals. In addition, the free radical NO is elevated in the diabetic lens and, as mentioned above, diabetic lenses show an impaired antioxidant capacity, increasing their susceptibility to oxidative stress (Arnal et al., 2009).

4. ANTIOXIDANTS USED IN CATARACTS

Drugs have been developed which are aimed to interact at the level of altered lens metabolism and lens pathophysiology. The anticataract agents claimed to be effective in cataracts may be classified in the following categories: (1) aldose reductase inhibitors, (2) nonsteroidal anti-inflammatory drugs, and (3) antioxidants.

If oxidation of lens proteins is part of the pathophysiology of cataracts, it is not surprising that a great number of reports studied the possible relationship of different antioxidants with the prevention of cataracts. Studies in animals and observational epidemiological

studies (including the Age-Related Eye Disease Study (AREDS) Research Group) in humans have reported the possible beneficial effect of a great variety of antioxidants, that include vitamin C, vitamin E, vitamin A, beta-carotene, lutein, zeaxanthin, zinc, epigallocatechin, GSH, lycopene, as well as ω-3 fatty acids. The results of these studies are controversial. Some of the observational studies provide only weak support for multivitamins or other vitamin supplements. The problem is that these studies have been realized generally in healthy subjects, but these kinds of compounds and nutrients may help individuals exposed to high oxidative stress, such as heavy smokers, and those with poor nutrition.

Some of the beneficial effects of these antioxidants are due to their stimulatory effect on GSH production or their GSH-sparing effect, as is the case of vitamin E, vitamin C, lipoic acid, or melatonin (Abe et al., 1994; Ayala and Soderberg, 2004). Besides this effect, the potential role of vitamins in preventing cataract is well documented, especially vitamin C or ascorbic acid because they play an important role in lens biology, not only as antioxidants but also as UV filters (Ayala and Soderberg, 2004).

A great amount of herbal drugs has been found to possess potential therapeutic effect in radiation-induced cataract, especially *Ginkgo biloba* or Green tea (*Camellia sinensis*) extracts. The major mechanism in the prevention of cataractogenesis of these drugs is their antioxidative potential.

Among the antioxidants used in preventing or delaying cataract formation, we will pay special attention to lutein.

5. LUTEIN

Lutein and zeaxanthin are xanthophyll carotenoids found particularly in dark-green leafy vegetables and in egg yolks. Their presence in human tissues is entirely of dietary origin. The structures of lutein and zeaxanthin are characterized by the presence of a hydroxyl group attached to each of the two terminal β-ionone rings in the molecule (Figure 25.1). Even the structures are very similar: lutein has 10 conjugated double bonds in the molecule, whereas zeaxanthin has 11 conjugated double bonds, and this means that lutein absorbs at slightly shorter wavelengths than does zeaxanthin.

They are widely distributed in tissues and are uniquely concentrated in the retina and lens, indicating that each has a possible specific function in these two vital ocular tissues.

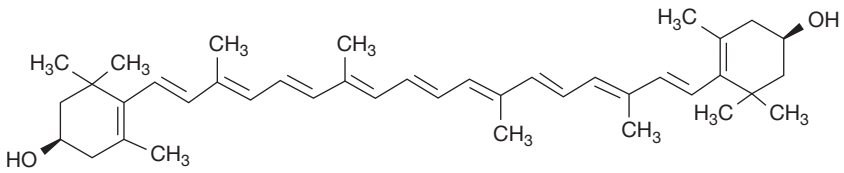

Figure 25.1 Lutein structure.

In the lens, lutein and zeaxanthin along with tocopherols, α-carotene, lycopene, and retinol can be found but very little β-carotene is present (Bernstein et al., 2001). Concentrations of lutein/zeaxanthin, tocopherol, and retinol in lens epithelium/cortex tissue are higher than in the older lens tissue. There is an inverse relationship between macular pigment density and lens density, suggesting that the macular pigment may serve as a marker for xanthophylls in the lens (Bernstein et al., 2001). In the retina, zeaxanthin is the main component in the central macula, while lutein is distributed throughout the retina.

Crystalline lutein is readily absorbed from foods and from dietary supplements whereas, to enter the bloodstream, lutein esters require prior de-esterification by intestinal enzymes. Unlike the hydrocarbon carotenoids which are mainly found in the low-density lipoprotein (LDL) fraction, xanthophylls, like lutein and zeaxanthin, are incorporated into both high-density lipoprotein (HDL) and LDL. Today, lutein can be obtained from diet in several different ways, including supplements, and most recently in functional foods. Animal toxicology studies have been performed to establish lutein's safety as a nutrient. These studies have contributed to the classification of purified crystalline lutein as generally recognized as safe (GRAS). The achievement of GRAS status for purified crystalline lutein allows for the addition of this form into several food and beverage applications.

Extensive research has focused attention on the potential role of lutein and zeaxanthin in protecting against several chronic diseases, such as cancer, heart disease, and particularly eye diseases such as age-related macular degeneration and cataract. Possible biological mechanisms of the protective role of lutein and zeaxanthin in the eye have been reviewed by Krinsky et al. (2003) and include their ability to: (a) filter harmful shortwave blue light and (b) function as antioxidants.

It is known that lutein supplementation inhibited lipid peroxidation *in vitro* in human lens epithelial (Chitchumroonchokchai et al., 2004) and in lens of streptozotocin diabetic rats (Arnal et al., 2009).

Human intervention studies show that lutein supplementation results in increased macular pigment, and a relationship between macular pigment optical density, a marker of lutein and zeaxanthin concentration in the macula, and lens optical density, an antecedent of cataractous changes, has been suggested (Moeller et al., 2000). However, there is mixed evidence on the association of lutein ingestion or supplementation with cataract from epidemiological studies (Table 25.1).

In the Carotenoids in the Age-Related Eye Disease Study (CAREDS), an ancillary study of the Women's Health Initiative (WHI), Moeller et al. (2008) observed that diets rich in lutein and zeaxanthin are moderately associated with decreased prevalence of nuclear cataract in older women. The CAREDS population consists of women who were enrolled in the observational study of the WHI who had intakes of lutein plus zeaxanthin that were above the 78th and below the 28th percentiles, as assessed at baseline enrollment into the WHI in 1994–98. This study concluded that the prevalence of

Table 25.1 Research Studies About There Association of Lutein Ingestion or Supplementation with Cataract

Type of study	*n*	Characteristics and state of subjects	Time	Country	Main observation	Relation of lutein with cataracts	Reference
Cross-sectional study	1112	People aged ≥50 years		India	Significant inverse associations were found for blood lutein and cataract	Yes	Dherani et al. (2008)
Prospective cohort study	1802	Women aged 50–79 years with intakes of lutein and zeaxanthin above the 78th (high) and below the 28th (low) percentiles in the Women's Health Initiative Observational Study	4 years	United States	Women in the group with high dietary levels of lutein and zeaxanthin had a 23% lower prevalence of nuclear cataract compared with those with low levels	Yes	Moeller et al. (2008)
Prospective study	35 551	Women health professionals	10 years	United States	Higher dietary intakes of lutein/zeaxanthin were associated with significantly decreased risks of cataract	Yes	Christen et al. (2008)
Double-blind study	177	Institutionalized elderly people aged ≥65 years	7 days	Spain	Subjects who consumed >3290 μg day^{-1} of lutein were less likely to have cataracts than those whose consumption was <256 μg day^{-1}	Yes	Rodríguez-Rodríguez et al. (2006)

Population-based epidemiologic study	3271	People aged ≥40 years	5 years	Australia	Cortical and subcapsular cataracts were not associated with lutein intake. For nuclear cataract the odds ratios were 0.67 (0.46–0.96) for every 1-mg increase in crude and energy-adjusted daily lutein	Yes	Vu et al. (2006)
Prospective study	899	899 subjects in the population-based Pathologies Oculaires Liées à l'Age (POLA) Study		France	Subjects with high plasma dehydro-lutein had a significantly (66%) reduced risk of nuclear cataract. Plasma lutein was not significantly associated with any type of cataract	Yes	Delcourt et al. (2006)
Double-blind study	77	Patients with age-related cataracts	2 years	Spain	Visual function in (visual acuity and glare sensitivity) patients with age-related cataracts who received the lutein supplements improved	Yes	Olmedilla et al. (2003)
Cross-sectional design	376	People aged 18–75 years		Netherlands	No associations between lens optical density and lutein concentration in adipose tissue	No	Berendschot et al. (2002)
Case-control study	677	343 cases with cataract and 334 age/sex frequency-matched controls aged 55–74	14 months	Spain	Blood levels of lutein were not associated with reduced odds for cataract	No	Valero et al. (2002)

Continued

Table 25.1 Research Studies About There Association of Lutein Ingestion or Supplementation with Cataract—cont'd

Type of study	*n*	Characteristics and state of subjects	Time	Country	Main observation	Relation of lutein with cataracts	Reference
Cross-sectional survey	372	Men and women, aged 66–75 years		England	Risk of posterior subcapsular cataract was lowest in people with higher plasma concentrations of lutein	Yes	Gale et al. (2001)
Cohort study	478	Nondiabetic women aged 53–73 years sampled from the Nurses' Health Study cohort	13–15 years	United States	Prevalence of nuclear opacification was significantly lower in the highest nutrient intake quintile category for vitamin C, vitamin E, riboflavin, folate, beta-carotene, and lutein/zeaxanthin. After adjustment for other nutrients, only vitamin C intake remained significantly associated	No	Jacques et al. (2001)
Prospective cohort study	36644	Male health professionals aged 45–75 years	8 years	United States	Men in the highest fifth of lutein and zeaxanthin intake had 19% lower risk of cataract than men in the lowest fifth	Yes	Brown et al. (1999)
Cohort study	1354	Adults participating in the Eye Disease Study of Beaver Dam	5 years	United States	Persons in the highest quintile of lutein intake in the distant past were half as likely to have an incident cataract as persons in the lowest quintile of intake	Yes	Lyle et al. (1999a,b)

Cohort study	400	Adults aged 50–86 years participating in the Eye Disease Study of Beaver Dam	5 years	United States	Serum carotenoids were not significantly associated with nuclear cataract, marginal inverse associations with lutein were suggested in people $\leq$65 years	Yes?	Lyle et al. (1999a,b)
Cohort study	400	Adults aged 50–84 years participating in the Beaver Dam Study and in the Nutritional Factors in Eye Disease Study	1 year	United States	Higher levels of lutein in serum were significantly related to lower odds for nuclear lens sclerosis only in men who smoked	Yes, only in some persons	Mares-Perlman et al. (1995)

nuclear cataract was lower among women in the high, compared to low, lutein intake groups after adjusting for age. A 32% lower prevalence odd of nuclear cataract was observed for women in the highest quintile category of serum lutein + zeaxanthin compared to those in the lowest category. Intake of total dietary fat (% kcal) significantly attenuated the associations between dietary lutein + zeaxanthin and nuclear cataract. The associations with serum lutein + zeaxanthin were less strongly attenuated.

In the Melbourne visual impairment project (Vu et al., 2006), 3271 residents aged ≥40 years were recruited in 1992–99, 2594 attended the follow-up examination. The authors reported that cortical and posterior subcapsule cataracts were not significantly associated with lutein and zeaxanthin intake. For nuclear cataract, the odds ratios were 0.67 and 0.60 for every 1-mg increase in crude and energy-adjusted daily lutein and zeaxanthin intake, respectively.

However, in a small trial of people (17 patients) with age-related cataract, lutein supplementation (15 mg administered three times per week for 2 years) has been shown to improve visual acuity and glare sensitivity (Olmedilla et al., 2003). In a cross-sectional study of 372 older adults in England, Gale et al. (2001) found that the risk of posterior subcapsular cataract was lowest in those with higher concentrations of plasma lutein (OR: 0.5; 95% CI: 0.2–1.0, p for trend 0.012). In a similar way, Brown et al. studied 36 644 US male health professionals and found that men in the highest fifth of lutein and zeaxanthin intake had a 19% lower risk of cataract relative to men in the lowest fifth (relative risk: 0.81; 95% CI: 0.65, 1.01; p for trend = 0.03) (Brown et al., 1999).

In the Beaver Dam Eye Study, it was found that persons in the highest quintile of lutein intake in the distant past were half as likely to have an incident cataract as persons in the lowest quintile of intake (95% CI: 0.3–0.8) (Lyle et al., 1999a); however, serum carotenoids were not significantly associated with nuclear cataract, marginal inverse associations with lutein (OR: 0.3; 95% CI: 0.1, 1.2; $p = 0.13$ for linear trend) and cryptoxanthin (OR: 0.3; 95% CI: 0.1, 1.3; $p = 0.11$ for linear trend) were suggested in people ≤65 years of age (Lyle et al., 1999b). In a more detailed study, Mares-Perlman et al. (1995) reported that levels of carotenoids are not consistently associated with less severe opacities in the general population, but higher levels of lutein in serum were significantly related to lower odds for nuclear sclerosis in men who smoked.

Jacques et al. (2001) studied the relationship between usual nutrient intake and subsequently diagnosed age-related nuclear lens opacities in 478 nondiabetic women, aged 53–73 years, and reported that the prevalence of early age-related nuclear lens opacities was significantly lower in those in the highest compared to lowest quintile category of lutein plus zeaxanthin intake; however, after adjustment for other nutrients, the inverse association was no longer significant.

Also, lutein supplementation has provided both null and positive results on different biomarkers of oxidative stress. Collins et al. (1998) treated volunteers with a variety of carotenoids, including lutein, and concluded that carotenoid supplementation did not

have a significant effect on endogenous oxidative damage. However, one of the limiting factors in demonstrating the effects of lutein on oxidation lies in the difficulty of measuring the oxidative stress *in vivo* because the oxidation products of lutein are unstable.

Other studies have not observed any correlation between lutein and incidence of cataracts (Delcourt et al., 2006; Valero et al., 2002). In the population-based Pathologies Oculaires Liées à l'Age (POLA) Study, Delcourt et al. (2006), after examining 815 subjects, found that plasma lutein was not significantly associated with any type of cataract, though globally, total lutein and zeaxanthin showed a trend toward an inverse association with nuclear, mixed, and any cataract that did not reach statistical significance.

The FDA recently reviewed intervention and observational studies that evaluated the role of lutein and zeaxanthin in reducing the risk of cataracts and concluded that no credible evidence exists for a health claim about the intake of lutein or zeaxanthin (or both) and the risk of cataracts.

It is clear that there is a great variability in results regarding effects of dietary supplementation. This variability may be related to limitations of long-term observational or interventional studies or may also be related to diet- and lifestyle-related factors that are capable of influencing the risks for cataracts. The problem, again, is that lutein may not reduce the risk of cataracts in the general population but may help individuals exposed to high oxidative stress, such as heavy smokers, and those with poor nutrition.

REFERENCES

Abe, M., Reiter, R.J., Orhii, P.B., Hara, M., Poeggeler, B., 1994. Inhibitory effect of melatonin on cataract formation in newborn rats: evidence for an antioxidative role for melatonin. Journal of Pineal Research 17, 94–100.

Altomare, E., Vendemiale, G., Grattagliano, I., Angelini, P., Micelli-Ferrari, T., Cardia, L., 1995. Human diabetic cataract: role of lipid peroxidation. Diabetes & Metabolism 21, 173–179.

Arnal, E., Miranda, M., Almansa, I., et al., 2009. Lutein prevents cataract development and progression in diabetic rats. Graefe's Archive for Clinical and Experimental Ophthalmology 247, 115–120.

Ayala, M.N., Soderberg, P.G., 2004. Vitamin C can protect against ultraviolet radiation induced cataract in albino rats. Ophthalmic Research 36, 264–269.

Berendschot, T.T., Broekmans, W.M., Klöpping-Ketelaars, I.A., Kardinaal, A.F., Van Poppel, G., Van Norren, D., 2002. Lens aging in relation to nutritional determinants and possible risk factors for age-related cataract. Archives of Ophthalmology 120, 1732–1737.

Bernstein, P.S., Khachik, F., Carvalho, L.S., Muir, G.J., Zhao, D.Y., Katz, N.B., 2001. Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye. Experimental Eye Research 72, 215–223.

Berthoud, V.M., Beyer, E.C., 2009. Oxidative stress, lens gap junctions, and cataracts. Antioxidants & Redox Signaling 11, 339–353.

Brown, L., Rimm, E.B., Seddon, J.M., et al., 1999. A prospective study of carotenoid intake and risk of cataract extraction in US men. American Journal of Clinical Nutrition 70, 517–524.

Calvin, H.I., Medvedovsky, C., Worgul, B.V., 1986. Near-total glutathione depletion and age specific cataract induced by buthionine sulphoximine in mice. Science 233, 553–555.

Chitchumroonchokchai, C., Bomser, J.A., Glamm, J.E., Failla, M.L., 2004. Xanthophylls and alpha-tocopherol decrease UVB-induced lipid peroxidation and stress signaling in human lens epithelial cells. Journal of Nutrition 134, 3225–3232.

Christen, W.G., Liu, S., Glynn, R.J., Gaziano, J.M., Buring, J.E., 2008. Dietary carotenoids, vitamins C and E, and risk of cataract in women: a prospective study. Archives of Ophthalmology 126, 102–109.
Collins, A.R., Olmedilla, B., Southon, S., Granado, F., Duthie, S.J., 1998. Serum carotenoids and oxidative DNA damage in human lymphocytes. Carcinogenesis 19, 2159–2162.
Delcourt, C., Carrière, I., Delage, M., Barberger-Gateau, P., Schalch, W., 2006. Plasma lutein and zeaxanthin and other carotenoids as modifiable risk factors for age-related maculopathy and cataract: the POLA Study. Investigative Ophthalmology and Visual Science 47, 2329–2335.
Dherani, M., Murthy, G.V., Gupta, S.K., et al., 2008. Blood levels of vitamin C, carotenoids and retinol are inversely associated with cataract in a North Indian population. Investigative Ophthalmology and Visual Science 49, 3328–3335.
Gale, C.R., Hall, N.F., Phillips, D.I., Martyn, C.N., 2001. Plasma antioxidant vitamins and carotenoids and age-related cataract. Ophthalmology 108, 1992–1998.
Inomata, M., Hayashi, M., Shumiya, S., Kawashima, S., Ito, Y., 2001. Involvement of inducible nitric oxide synthase in cataract formation in Shumiya cataract rat (SCR). Current Eye Research 23, 307–311.
Jacques, P.F., Chylack Jr., L.T., Hankinson, S.E., et al., 2001. Long-term nutrient intake and early age-related nuclear lens opacities. Archives of Ophthalmology 119, 1009–1019.
Kao, C.L., Chou, C.K., Tsai, D.C., et al., 2002. Nitric oxide levels in the aqueous humor in cataract patients. Journal of Cataract and Refractive Surgery 28, 507–512.
Krinsky, N.I., Landrum, J.T., Bone, R.A., 2003. Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. Annual Review of Nutrition 23, 171–201.
Lyle, B.J., Mares-Perlman, J.A., Klein, B.E., Klein, R., Greger, J.L., 1999a. Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study. American Journal of Epidemiology 149, 801–809.
Lyle, B.J., Mares-Perlman, J.A., Klein, B.E., et al., 1999b. Serum carotenoids and tocopherols and incidence of age-related nuclear cataract. American Journal of Clinical Nutrition 69, 272–277.
Mares-Perlman, J.A., Brady, W.E., Klein, B.E., et al., 1995. Serum carotenoids and tocopherols and severity of nuclear and cortical opacities. Investigative Ophthalmology and Visual Science 36, 276–288.
Martensson, J., Meister, A., 1989. Mitochondrial damage in muscle occurs after marked depletion of glutathione and is prevented by giving glutathione monoester. Proceedings of the National Academy of Sciences of the United States of America 86, 471–475.
Mizdrak, J., Hains, P.G., Truscott, R.J.W., Jaime, J.F., Davies, M.J., 2008. Tryptophan-derived ultraviolet filter compounds covalently bound to lens proteins are photosensitizers of oxidative damage. Free Radical Biology & Medicine 44, 1108–1119.
Moeller, S.M., Jacques, P.F., Blumberg, J.B., 2000. The potential role of dietary xanthophylls in cataract and age-related macular degeneration. Journal of the American College of Nutrition 19, 522S–527S.
Moeller, S.M., Voland, R., Tinker, L., et al., 2008. Associations between age-related nuclear cataract and lutein and zeaxanthin in the diet and serum in the Carotenoids in the Age-Related Eye Disease Study, an Ancillary Study of the Women's Health Initiative. Archives of Ophthalmology 126, 354–364.
Nabekura, T., Koizumi, Y., Nakao, M., Tomohiro, M., Inomata, M., Ito, Y., 2003. Delay of cataract development in hereditary cataract UPL rats by disulfiram and aminoguanidine. Experimental Eye Research 76, 169–174.
Olmedilla, B., Granado, F., Blanco, I., Vaquero, M., 2003. Lutein, but not alpha-tocopherol, supplementation improves visual function in patients with age-related cataracts: a 2-y double-blind, placebo-controlled pilot study. Nutrition 19, 21–24.
Reddy, V.N., 1990. Glutathione and its function in the lens – an overview. Experimental Eye Research 50, 771–778.
Rodriguez-Rodriguez, E., Ortega, R.M., López-Sobaler, A.M., Aparicio, A., Bermejo, L.M., Marín-Arias, L.I., 2006. The relationship between antioxidant nutrient intake and cataracts in older people. International Journal of Vitamins and Nutrition Research 76, 359–366.
Spector, A., 1995. Oxidative stress-induced cataract: mechanism of action. The FASEB Journal 9, 1173–1182.
Spector, A., Huang, R.-R.C., Wang, G.-M., Schmidt, C., Yan, C.-Z., Chifflet, S., 1987. Does elevated glutathione protect the cell from insult? Experimental Eye Research 45, 453–465.

Valero, M.P., Fletcher, A.E., De Stavola, B.L., Vioque, J., Alepuz, V.C., 2002. Vitamin C is associated with reduced risk of cataract in a Mediterranean population. Journal of Nutrition 132, 1299–1306.

Varma, S.D., Hegde, K.R., 2007. Susceptibility of the ocular lens to nitric oxide: implications in cataractogenesis. Journal of Ocular Pharmacology and Therapeutics 23, 188–195.

Vu, H.T., Robman, L., Hodge, A., McCarty, C.A., Taylor, H.R., 2006. Lutein and zeaxanthin and the risk of cataract: the Melbourne visual impairment project. Investigative Ophthalmology and Visual Science 47, 3783–3786.

Yao, K., Ye, P., Zhang, L., Tan, J., Tang, X., Zhang, Y., 2008. Epigallocatechin gallate protects against oxidative stress-induced mitochondria-dependent apoptosis in human lens epithelial cells. Molecular Vision 14, 217–223.