

Retinopathy

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Diabetic retinopathy (DR), the leading cause of visual disability and blindness among adults in the developed world, may affect as many as 20 million people. Early detection and treatment are keys to preventing the vision loss and blindness associated with the disease. Unfortunately, only about half of those with diabetes have proper eye examinations on a yearly basis. It is very important that diabetics have a dilated eye exam each year.

Retinopathy damages the retina by destroying the capillaries (minuscule blood vessels connecting arteries and veins) that provide blood to the retina, the light-sensitive nerve tissue that sends visual images to the brain. With the onset of retinopathy, these vessels weaken or bulge with microaneurysms that may hemorrhage, leaking blood or fluid into surrounding tissue. When new blood vessels grow on the retina (and into the vitreous), they can cause blurred vision and even temporary blindness. The real danger lies in the scar tissue that ultimately forms, detaching the retina from the back of the eye and often causing permanent loss of vision.

Chronically elevated blood insulin and glucose levels induce retinopathy. Fortunately, research shows that even after having long-term diabetes, lowering glucose has a positive effect on slowing the progression of retinopathy. A study took place involving 834 people who were over the age of 30 when they developed diabetes and who were approximately 65 at the start of the study. A glycohemoglobin test was performed at the start of the study, along with two follow-ups, 4 and 10 years later, which included a physical and eye exam. Glycohemoglobin (also known as hemoglobin A1C) is the best measurement of long-term glucose control. A high glycohemoglobin number correlates with uncontrolled diabetes.

In noninsulin treated participants, those that had the highest glycohemoglobin levels at the start of the study had nearly a threefold greater chance of having developed retinopathy after 10 years than those with the lowest levels. In participants who already showed proof of retinopathy at the start of the study, the presence of elevated glycohemoglobin resulted in a fourfold greater risk of retinopathy progression and a fourteenfold greater risk of proliferative retinopathy.

In those people on insulin with the highest levels of glycohemoglobin, there was a 90% increased risk of developing retinopathy than those in the lowest levels. The researchers concluded that controlling hyperglycemia even later on in the course of diabetes will result in a significant decrease in the incidence and progression of retinopathy and in the development of visual loss (Klein et al. 1994). Published studies show that controlling excess serum insulin is also important in preventing retinopathy (Racah et al. 1998; Boehm et al. 2002; Leslie et al. 2002).

There are additional precautions that can be taken to guard against the development of retinopathies. Deficiency of vitamin B6, for instance, is a proven cause of the disease. In order to rule out a nutritional deficiency as the cause of retinopathy, a 10-week program is suggested that incorporates a high-potency B-complex vitamin formula along with other supplements that will be described in this protocol.

AN INTERESTING STUDY IN RATS

A newborn rat model of retinopathy was used to test the hypothesis that a lack of the antioxidant superoxide dismutase (SOD) contributes to retinal damage. The study concluded that delivery of SOD to the retina via long-circulating liposomes was beneficial and suggested the potential value of the restoration or supplementation of antioxidants in retinal tissue as a therapeutic strategy (Niesman et al. 1997). It is difficult to provide SOD directly to the retina, but adequate supplementation with nutrients, such as zinc, copper, and manganese, provide the minerals needed for the formation of SOD in the cells.

ANTIOXIDANT LENS AND VITREOUS ACTIVITY

Another study investigated antioxidant activity in the lens and vitreous of diabetic and nondiabetic subjects. Researchers found significantly decreased glutathione peroxidase activity and lower ascorbic acid levels in the lenses of diabetic patients, especially in the presence of retinal damage. (Ascorbic acid is known to exert important antioxidant functions in the eye compartment.) This study indicated that oxidative damage is involved in the onset of diabetic eye complications, in which the decrease in free radical scavengers was shown to be associated with the oxidation of vitreous and lens proteins (Altomare et al. 1997).

DECREASED RETINAL ANTIOXIDANT ACTIVITY IN DIABETICS

Activities of enzymes that protect the retina from reactive oxygen species were investigated in diabetic rats known to have developed retinopathy. Diabetes significantly decreased the activities of glutathione reductase and glutathione peroxidase in the retina. Activities of two other important antioxidant defense enzymes--superoxide dismutase and catalase--were also decreased (by more than 25%) in the retinas of diabetic rats (Kowluru et al. 1997).

The study showed that diabetes is associated with significant impairment of the antioxidant defense system and that antioxidant supplementation can help alleviate the subnormal activities of antioxidant defense enzymes. Administration of supplemental vitamins C and E for 2 months prevented the diabetes-induced impairment of the antioxidant defense system in the retina (Kowluru et al. 1997). Another study found no protective effect from antioxidant nutrients for diabetic retinopathy and concluded that further research is necessary to confirm associations of nutrient antioxidant intake and the disease (Mayer-Davis et al. 1998).

RETINOPATHY OF PREMATURITY

A study assessed retinopathy in 60 oxygen-treated, premature infants and their mothers. All 60 infants showed signs of acute oxidative stress. The concentrations of methionine-cysteine in the plasma, as well as blood selenium levels, were significantly lower in the premature infants who had moderate retinopathy than they were in the oxygen-treated premature infants without retinopathy. The mothers of the premature infants with retinopathy showed the same pattern of deficiencies as their babies. Vitamin E treatment of premature infants seemed to have a positive effect against the development of retinopathy of prematurity (Papp et al. 1997).

The close correlation between the antioxidant capacity of the mothers and babies suggests that supplementation with sulfur-containing amino acids (methionine, cysteine) and folic acid during pregnancy might improve the antioxidant capacity of premature infants. An antioxidant cocktail of selenium plus vitamin E given to high-risk mothers (high risk factors include advanced age, smoking, and pregnancy-induced hypertension) before delivery might be useful in the prevention of retinopathy in premature infants (Papp et al. 1997).

THE ROLE OF L-CARNITINE

Other research examined the effect of propionyl-L-carnitine (an analogue of L-carnitine) on retinopathy in rats with laboratory-induced diabetes. Findings pointed to a potential therapeutic value of propionyl-L-carnitine for diabetic retinopathy (Hotta et al. 1996). Until propionyl-L-carnitine becomes commercially available, taking 2000 mg a day of acetyl-L-carnitine should be considered by those with retinopathy. (L-carnitine is a natural substance that is found in meat. It is related to the B vitamins.)

GLYCATION

Glycation of proteins has been shown to play a prominent role in the development of many diseases related to diabetes, including atherosclerosis, cataract formation, and retinopathy. Oxidation induced by glycation can wreak havoc on the eye. Protein glycation occurs when sugar molecules inappropriately bind to protein molecules, forming cross-links that distort the proteins and consequently render them useless. High blood sugar also increases glycation activity, which may also explain the various kinds of tissue damage that characterize advanced diabetes. Diligently controlling blood sugar is a major means of preventing or at least slowing the onset and progression of diabetic retinopathy. Glycation appears to increase oxidative processes, which may explain why both glycation and oxidation simultaneously increase with age.

Strategies for the prevention of diabetic complications should therefore aim to prevent both the effects of glycation and oxidative stress.

A drug called aminoguanidine has been used successfully to protect against glycation (Guillausseau 1994). Compounds produced through metabolism of sugars bind preferentially to aminoguanidine rather than to lysine proteins. Thus, aminoguanidine is able to inhibit advanced glycation end-product (AGE) formation and can help prevent the harmful development of collagen cross-links and changes in the proliferation of mesangial cells.

Aminoguanidine used in the dose of 300 mg a day can specifically inhibit glycation, as can the nutrients keto-glutarate and pyruvate. Studies have shown aminoguanidine to be useful in slowing complications of diabetes, such as retinopathy. (Aminoguanidine can also inhibit the formation of atherosclerotic plaques.)

Carnosine is a naturally occurring antiglycation agent found in red meat. In the lens of the eye, protein cross-linking is part of cataract formation. Carnosine eye drops have been shown to delay vision senescence in humans, being effective in 100% of cases of primary senile cataract and 80% of cases of mature senile cataract (Wang et al. 2000). The most widely used antiglycating therapy is to consume orally 1000 mg a day of supplemental carnosine.

A DRUG THAT MAY REVERSE GLYCATION

One promising advanced glycation end product (AGE) breaker is ALT-711 (3-phenacyl-4,5-dimethylthiazolium chloride). ALT-711 is being developed by the Alteon Corporation to reverse the degenerative effects on soft tissues from diseases, such as diabetes and cardiovascular disease. It is currently in Phase II trials. ALT-711 inserts itself into AGE cross-links, separates and cleaves the linked molecules, and releases the proteins. The safety of ALT-711 and its efficacy in reversing age-related cardiovascular damage has been confirmed in animals and in Phase I and Phase IIa clinical trials. Alteon is planning a Phase IIb clinical trial. The randomized, double-blind, placebo-controlled, clinical study will test the effects of multiple doses of ALT-711 in improving isolated systolic hypertension. The trial will be set up in 42 clinical sites and involve several hundred patients.

CAROTENOIDS AND THE RETINA

Countless studies demonstrate an association between consumption of carotenoids with lowered risk of cancer and cardiovascular disease. Carotenoids, especially lutein and zeaxanthin, have also been found to help preserve eye health. Lutein is a pigment found in dark, green, leafy vegetables, including spinach, kale, broccoli, collard greens, etc. Zeaxanthin is found in fruits and vegetables with yellow hues, such as corn, peaches, persimmons, mangoes, etc. They are often lumped together when discussed or studied because they are structurally very similar, found in many of the same foods, and both are present in the retina. Lutein and zeaxanthin have been found to positively affect macular pigment density and to help prevent age-related macular degeneration (AMD).

Although there are several hundred carotenoids to be found in fruits and vegetables, only lutein and zeaxanthin are found in the retina (Schalch 1992; Yeum et al. 1999). Compared to other antioxidant concentrations found in the eye, German researchers found that lutein and zeaxanthin did not break down nearly as fast as lycopene and beta-carotene when exposed to free radical or UV light induced oxidative stress (Siems et al. 1999). The authors suggest that perhaps the slow degradation of lutein and zeaxanthin may explain the strong presence of these carotenoids in the retina. Also, the quick breakdown of lycopene and beta-carotene may suggest why these carotenoids are lacking in the same retinal tissues.

Researchers have also found that lutein and zeaxanthin are more highly concentrated in the center of the macula. There, the amounts of lutein and zeaxanthin are much greater than their concentrations in the peripheral region. At the Baylor College of Medicine in Houston, scientific investigators demonstrated, using retinas from human donor eyes, that the concentration of lutein and zeaxanthin was 70% higher in rod outer segment (ROS) membranes where the concentration of long-chain polyunsaturated fatty acids and susceptibility to oxidation is highest, than in residual membranes (Rapp et al. 2000). The fact that lutein and zeaxanthin are particularly concentrated in these parts of the eye suggests that they may act as a shield or filter that helps to absorb harmful UVB light and dangerous free-radical molecules, both of which threaten the retinal tissue (Moeller et al. 2000; Bernstein et al. 2001).

THE IMPORTANCE OF ADEQUATE VITAMIN STATUS

- Vitamin B12
- Vitamin E
- Green Tea
- Silibinin

Vitamin B12

(Cyanocobalamin, or hydroxycobalamin, a naturally occurring form) is critical for several functions, such as folate metabolism, myelin synthesis, and the normal development of red blood cells. A lack of this vitamin may leave the optic nerve more susceptible to damage. Studies have suggested that marginal vitamin deficiency plays an indirect but important role in the development of diabetic complications (Anon. 1990).

Vitamin E

One study showed that reducing lipid peroxidation stress of the erythrocyte membrane using vitamin E (alpha-tocopherol nicotinate) therapy may be useful in slowing deterioration of microangiopathy in Type II diabetes mellitus. The dose used in the study was 300 mg 3 times a day, after meals, for 3 months (Chung et al. 1998). In the August 1999 issue of the journal *Diabetes Care*, Dr. George L. King and his colleagues reported that vitamin E supplements normalized bloodflow to the retina and kidneys. Following a 4-month clinical trial in which subjects were given doses of vitamin E that were 60 times the recommended daily allowance, kidney function improved and blood flow to the retina was increased almost to the normal rate. Dr. King is recommending a large follow-up clinical trial (Bursell et al. 1999).

Another study evaluated the use of antioxidants as a prophylactic for eye disorders, such as macular degeneration, cataracts, retinopathy of prematurity, and cystic macular edema. The study points to the positive role of antioxidants in both experimental research and clinical observations (KaLuzny 1996).

Green Tea

Green tea is another potent antioxidant that could be of use in the treatment of retinopathy. The active compounds in green tea are chiefly catechins. Powerful polyphenolic antioxidants, catechins are astringent, water-soluble compounds that can be easily oxidized. They are a subgroup of flavonoids, weak phytoestrogenic compounds widely available in vegetables, fruit, tea, coffee, chocolate, and wine. The antioxidant potential of both green and black teas, as measured by the Phenol Antioxidant Index, was found to be significantly higher than that of grape juice and red wines. Green tea also has anti-angiogenic properties, indicating that it could be used for the prevention and possibly even the treatment of degenerative eye disorders, such as diabetic retinopathy, that also depend on the development of new blood vessels (Zigman et al. 1999; Thiagarajan et al. 2001).

Silibinin

An in vitro study showed that silibinin (milk thistle extract) can normalize the degree of ribosylation and the sodium pump activity even in the presence of abnormally high glucose levels (Di Giulio et al. 1999). A similar protective effect of silibinin against ribosylation was found in the retina (Gorio et al. 1997). Thus silibinin may be able to decrease the extent of diabetic neuropathy and retinopathy, two extremely serious complications of diabetes. Considering that silibinin has also been shown to protect the kidneys, another organ seriously damaged by glycation (kidney failure is a frequent cause of death in diabetics), silibinin should be seriously explored as an adjunct treatment in diabetes.

CONCLUSION

Retinopathy is a major cause of blindness among adults in the developed world. Risk factors are diabetes (especially with elevated blood glucose levels), vitamin deficiency, and old age. In retinopathy, the retina of the eye is damaged when retinal capillaries bulge or burst, leaking blood or fluid into the surrounding tissue. New capillaries that grow on the retina (and into the vitreous) cause blurred vision or blindness. Permanent blindness can result from retinal detachment caused by scar tissue. Prevention requires annual dilated eye exams and proper vitamin and nutrient intake. Researchers conclude that improved levels of antioxidants in pregnant women could help prevent retinopathy in their premature infants.

SUMMARY

- Long-term antioxidant protection of the eyes can be provided by taking 3 tablets 3 times a day, of Life Extension Mix and 1 capsule a day of the Life Extension Booster formula. These two supplements provide the alpha and gamma forms of vitamin E, lutein, minerals for the formation of superoxide dismutase (SOD), such as zinc, manganese, and copper along with potent B complex vitamins. Some people may also want to take additional vitamin B6 (up to an additional 250 mg).
- Carnosine is an antiglycating agent that helps protect against the damaging effects of glycation. As an oral supplement, two 500-mg capsules daily are recommended. As an eyedrop, carno-sine may help prevent protein cross-linking in the retina. One to two drops daily of carnosine eyedrops are recommended. Those with any kind of eye problem may want to apply 1-2 drops several times a day.
- Zeaxanthin and lutein may help filter harmful UVB light and quench free radicals that harm the retina. Suggested dose from diet or supplements is 5 mg a day of zeaxanthin and 15-20 mg a day of lutein.

- Silibinin may help slow the extent of diabetic retinopathy; 250-500 mg a day is suggested.
- Green tea extract is a powerful antioxidant that has shown promise in the treatment of degenerative eye disease; 600-700 mg of a 95% polyphenol extract is suggested.
- Taking 2000 mg a day of acetyl-L-carnitine should be considered by those who have retinopathy, particularly if on a vegetarian diet.

FOR MORE INFORMATION

Contact the National Eye Health Education Program of the National Institutes of Health, (301) 496-5248.

PRODUCT AVAILABILITY

Life Extension Mix, Life Extension Booster, Super Carnosine, Brite Eyes II (carnosine drops), Super Zeaxanthin with Lutein, vitamin E, green tea extract, Gamma E Tocopherol/Tocotrienols, Silibinin Plus, vitamin B6, or ornithine alpha-ketoglutarate, calcium pyruvate and acetyl-L-carnitine can be ordered by calling (800) 544-4440 or by ordering online. Ask for a list of European suppliers of aminoguanidine.

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