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REPORT

An Eye to the Future

By Dean S. Cunningham, MD, PhD

"I would give anything to read the newspaper again," laments my otherwise healthy 68-year-old patient with recent onset macular degeneration, a condition she had never heard of before. Her physical disability in turn has led to clinical depression, characterized by frequent crying spells, hypersomnia, reclusiveness, and hopelessness. Despite the prevalence of eye disorders in people over the age of 50, relatively few such adults have heard of the major disorders, know what they are or what causes them, understand their paralyzing impact, or know what can be done to prevent them.

I recently surveyed 50 adults between the ages of 35 and 50 and was surprised to learn that while 92% had heard of cataracts, fewer than 15% could describe what one is. Only 4% had heard of diabetic retinopathy and none could describe the condition. While 34% had heard of glaucoma, a mere 4% knew what glaucoma is. Finally, just 8% had heard of macular degeneration and only one person out of 50 knew what it was.

Prevention of disease requires awareness, basic knowledge, and a plan. In this article, I will review the anatomy of the eye, briefly describe how we see, and outline the four major eye diseases for which we all are at risk: cataracts, diabetic retinopathy, glaucoma, and macular degeneration. You will learn what these conditions are, what causes them, and the simple steps you can and should take now to prevent them.



Scope of the Problem

Diseases of the eye that result in loss of vision affect nearly one of two people in the US over the age of 75. Prevalence rates for cataracts, glaucoma, and macular degeneration are seemingly stable, affecting 3-4% of the adult population. Although a risk of 3-4% may seem miniscule and insignificant to the healthy young adult, a prevalence rate of 3-4% for the entire population equates to a 33-50% age-specific prevalence rate as one lives beyond 65 years of age.

The prevalence of diabetic retinopathy is on the rise. Some 8-9% of US adults are diabetic and therefore at risk for diabetic retinopathy. Currently, 2.5% of the US population has permanent visual loss due to diabetic retinopathy. Because of the obesity epidemic, however, it is projected that as many as one-third of today's children will be diabetic as adults. Should this projection hold up, the percentage of the population facing permanent visual loss due to diabetic retinopathy could conceivably triple or quadruple.

Cataracts

Cataracts are the leading cause of blindness worldwide, affecting up to 40% of people over 75. Cataract formation is ubiquitous, beginning in all adults over the age of 30.

A cataract develops when proteins aggregate in the lens of the eye with progressive opacification, thus admitting less light. Cataracts are described according to their location (nuclear, cortical, capsular, or subcapsular) and characterized as congenital, immature, mature, or hypermature. Cataracts are painless and the loss of vision is generally gradual but progressive.

While the etiology leading to the development of cataracts remains unknown, some well-established risk factors predispose one to cataract formation. These include age (being over 30), ocular trauma, concomitant ocular disease, diabetes and/or uncontrolled hyperglycemia, hypertension, hypocalcemia, chronic steroid use, sunlight overexposure, tobacco abuse, alcohol abuse, genetic factors (Native Americans, African-Americans, women, and individuals with dark irises are at higher risk), diets deficient in antioxidants, and increased exposure to oxidative stress.

Oxidative stress occurs as free radicals accumulate as both endogenous by-products (from dietary intake and its breakdown/oxidation) and exogenous by-products (from environmental factors). A free radical has an unpaired electron and is therefore a highly reactive, unstable molecule. Because the free radical is compelled to complete its electron pair, it will in

essence “steal” an electron from a cell membrane or strand of DNA, rendering the donor structurally altered and possibly damaged.

Antioxidants contained in the food we eat and the supplements we take are our bodies’ defense against free radicals. Compared to a cohort of matched individuals without cataracts, individuals with cataracts have been shown to have lower levels of the antioxidants glutathione and superoxide dismutase, and higher levels of thiobarbituric acid reactive substances, a marker for free radical damage.¹

There is wide agreement that diets rich in beta-carotene (a nontoxic, water-soluble precursor of vitamin A) and vitamin C may significantly reduce one’s risk of cataract formation.^{2,3} By contrast, no definitive evidence exists to suggest that vitamin E prevents or slows the progression of cataracts.⁴ This may be due in part to the lipophilic and hydrophobic properties of vitamin E within the vitreous humor.

Application of eye drops containing carnosine or N-acetylcarnosine has a favorable impact on existing cataracts, presumably as both a quencher of oxygen free radical species and an inhibitor of glycation, in which sugars bind to excessive protein to form advanced glycation end-products.⁵⁻⁷ Because N-acetylcarnosine is more lipid soluble than its parent compound, carnosine, its potential is indeed more promising. Alpha lipoic acid, a uniquely fat- and water-soluble antioxidant, also may be beneficial in preventing cataracts. Protective eyewear should always be used to block ultraviolet radiation and prevent traumatic eye injury.

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Diabetic Retinopathy

Diabetic retinopathy is the third leading cause of blindness in people over the age of 20, and eventually adversely affects at least two of three diabetics.⁸

The progressive degeneration of capillary walls characteristic of diabetic retinopathy results in diffuse and focal weakness (microaneurysms) with leakage (hemorrhage and exudates), thereby culminating in vascular occlusion. As the condition advances, retinal ischemia occurs with compensatory new blood vessel growth (angiogenesis or neovascularization), complicated by further hemorrhage, inflammation, scarring, and eventually retinal detachment. Diabetic retinopathy is classified as background or proliferative. Background diabetic retinopathy is further classified as simple or pre-proliferative. The onset of diabetic retinopathy is characterized by diminished visual acuity, color discrimination, and contrast sensitivity.

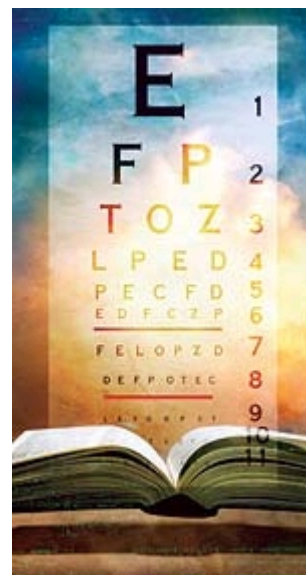
The diagnostic hallmark of diabetic retinopathy is a defect at the level of the retinal capillaries and is the pathological manifestation of the toxic effects of chronic hyperglycemia. Generally, risk for diabetic retinopathy is strongly correlated with the duration of uncontrolled hyperglycemia, but can be accelerated or slowed by genetic constitution. Hispanics, African-Americans, and Native Americans with diabetes have an increased prevalence of diabetic retinopathy for just such reasons.

The microvascular complications accompanying diabetes have a biochemical basis that involves four metabolic pathways: polyol, hexosamine, protein kinase C, and glycation end-products. Understanding these pathways' role in the pathological changes that accompany diabetes may assist in diabetes prevention and treatment. For example, glucose gives rise to oxidative stress and an alteration in the redox potential of cells vis-à-vis oxidative phosphorylation. Knowing that makes it intuitive that antioxidants play a pivotal role in modulating the generation of oxygen free radicals,⁹ as has been demonstrated repeatedly with different supplements.

If you are diabetic, you should check your hemoglobin A1c every three months and strive to maintain it below 7.0. Checking daily blood sugar levels is simply not enough. Furthermore, you should also undergo an ophthalmologic examination yearly.

If you are at risk for diabetes or diagnosed as prediabetic, you should maintain your fasting insulin level in the low normal range through a diet with a reduced glycemic load and the judicious use of supplements that augment the activity of insulin (for example, magnesium,^{10,11} zinc,¹² niacin,¹³ and biotin¹⁴), one's sensitivity to insulin (for example, chromium polynicotinate,¹⁵ alpha lipoic acid,¹⁶ vitamin E,¹⁷ taurine,¹⁸ vitamin C,¹⁹ DHEA,²⁰ and hydroxycitric acid¹³), or glucose homeostasis (for example, gymnema sylvestre,²¹ quercetin,²² biotin,^{14,23} bitter melon,²⁴ conjugated linoleic acid and alpha lipoic acid in combination,²⁵ selenium,²⁶ vitamin E,¹⁷ pyridoxine,²⁷ and vanadyl sulfate^{28,29}).

Maintaining normal insulin levels is essential to longevity.³⁰ N-acetylcysteine, a precursor of glutathione, is protective against pancreatic beta cell damage through inhibition of nuclear factor-kappa beta activation³¹ and maintenance of a euglycemic state.⁹ Aside from strict control of blood glucose levels, keys to slowing the progression of diabetic retinopathy include normalization of blood pressure, treatment of hypercholesterolemia, smoking cessation, regular exercise, and maintaining a body mass index (BMI) of less than 25.





Glaucoma

Glaucoma is the second leading cause of blindness in the US. An increase in intraocular pressure leads to irreversible damage of the optic nerve and concomitant visual field loss. Glaucoma is classified as open-angle, angle-closure, congenital, and secondary. Unfortunately, glaucoma is painless and often is not diagnosed until in its advanced stages when the damage is irreparable.

In most cases, intraocular pressure increases when the vitreous humor reabsorption is reduced or its outflow is blocked. In addition to those with a family history, African-Americans are at increased risk. Glaucoma also can occur secondary to eye injury, as a complication of an ocular surgical procedure, as a co-morbid condition of diabetes, or following the chronic use of steroids or overuse of ocular anti-inflammatories. Those with severe nearsightedness also are at greater risk for glaucoma. Glaucoma is thought to represent one of the many age-related neurodegenerative disorders.

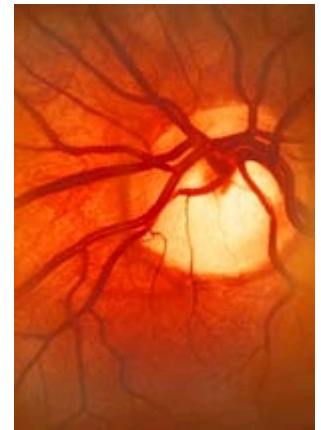
An annual ophthalmologic examination with tonometry is recommended for all adults over the age of 40 years. Preventive measures are aimed at maintaining normal intraocular pressures. A topical nitric oxide synthase inhibitor reduces intraocular pressure,³² as does a diluted solution of forskolin applied topically.³³ Forskolin is thought to decrease intraocular pressure by activating adenylate cyclase, the enzyme which increases cyclic adenosine monophosphate in cells. The topical

application of carnosine also has been shown to reduce intraocular pressure by increasing the vitreous humor outflow.³⁴

Macular Degeneration

Macular degeneration affects one-third of adults over the age of 75, and is the principal cause of visual disability in people over 65 years of age. Because the macula alone is affected, central vision is lost (though total blindness is avoided).

The “dry” form of macular degeneration occurs as the vascular and support cells of the retina atrophy, whereas the “wet” form of macular degeneration occurs as a result of leakage and scarring of the new growth of blood vessels beneath the macula. Aside from aging and the accumulating effect of oxidative stress with concomitant alteration in protein conformation,³⁵ a positive family history of macular degeneration, cigarette smoking, uncontrolled high blood pressure, hypercholesterolemia,³⁶ high-fat diets, and Caucasian descent are relative risk factors for macular degeneration.



Antioxidants (vitamins C and E), beta-carotene, and zinc have no effect on the development of macular degeneration but are thought to slow its progression.³⁷⁻³⁹ Lutein and zeaxanthin, however, may actually prevent macular degeneration.⁴⁰⁻⁴⁴ Ginkgo biloba has a possible protective effect. Ginkgo biloba increases blood flow, antagonizes platelet activating factor, and scavenges oxygen free radicals, all of which may play a role in the development of macular degeneration.⁴⁵ Glutathione and N-acetylcysteine protect against the atrophy of retinal support cells that occurs in dry macular degeneration.⁶

Diets rich in monounsaturated fats and omega-3 fatty acids, and low in saturated and polyunsaturated fats, retard the progression of established macular degeneration.⁴⁶ Routine annual eye examinations are important. According to recent studies, measurement of C-reactive protein, a nonspecific marker for cardiac disease, is predictive for macular degeneration as well.⁴³ Normalization of weight and regular physical exercise also have been shown to offset the risk of macular degeneration.



Interpreting the Science

The conventional gold standard for human research is the randomized, prospective, double-blind, placebo-controlled study. Not surprisingly, such studies are costly and require considerable time to design, execute, and analyze. Furthermore, although human studies control for gender, age, and a limited number of germane exclusion criteria, can one be sure that the outcome reported is not influenced by some unsuspected factor? Of course not—it is impossible to control for all variables in humans.

Conducting such controlled experiments requires syngeneic (genetically identical) animals in a controlled environment. Even then, one must extrapolate the animal model to the human condition under study. While considered clumsy by academic scientists, descriptive studies—such as those that are often the source of information about dietary supplements—can be useful, especially if scientific knowledge forms the rationale for the application. For example, since degenerative diseases in general result from increasing oxidative stress, it follows that an antioxidant like vitamin C reduces oxidative stress and decelerates or stops the degenerative process.

Of course, one must determine the difference between a dose that prevents disease and one that optimizes health. In the case of

anecdotal studies, observations can be useful, too. The British Royal Air Force pilots attributed their improved night vision to eating bread with bilberry jam before flying missions. This “common knowledge” led to the science and later delineation of the role anthocyanosides play in improving the microcirculation and enzymatic activity of the retina.⁴⁷

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Summary

For many age-related degenerative conditions, I believe an ounce of prevention is actually worth more than a pound of cure. This is not a novel idea. As Thomas Edison once wrote, "the doctor of the future will interest his patient in the care of the human frame, in diet and in the cause and prevention of disease."

When deciding which proactive measures to institute in your own health plan, something is certainly better than nothing. The rewards of nutritional supplementation are delayed. For age-related diseases, you may not know whether what you do at age 40 has helped you until age 65, when you are on the golf course while some of your contemporaries are in a nursing home.

Given the collective body of literature pertaining to the prevention of age-related eye disease and the recurring emphasis on oxidative stress, it would be prudent to consider the following as a starting point or basic regimen for the four ocular conditions discussed in this article, despite their disparities in cause and pathology. The supplements you choose should emphasize diverse antioxidant activity, as exemplified by vitamins C and E, alpha lipoic acid, glutathione, lutein, zeaxanthin, and selenium. A topical compound containing N-acetylcarnosine would offer the benefit of superior, direct delivery to the tissues at risk. You can then modify and refine your individual ocular prevention program based on your own needs and preferences.



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taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.