Chapter 19

Diet and Supplements in the Prevention and Treatment of Eye Diseases

Julie A. Mares[1], Amy E. Millen[2], Thomas P. Lawler[1] and Courtney K. Blomme[1]

[1]*University of Wisconsin-Madison, Madison, WI, United States,* [2]*University at Buffalo, The State University of New York, Buffalo, NY, United States*

I INTRODUCTION

The existence of ocular manifestations of nutrient deficiencies has been well known for more than a century and is well-described. The reader is referred to other texts and reviews that describe the role of nutrition in other aspects of vision that are briefly summarized in the following paragraphs. The role of vitamin A in preventing night blindness and xerophthalmia, which are common problems in developing countries, has been widely discussed [1]. Food shortages, as occurred in Cuba in 1991–94 and among the allied prisoners of World War II, or chronic alcohol use can result in a condition broadly referred to as nutritional amblyopia, which results in blurred vision and reduced visual acuity (recently discussed in Ref. [2]). This may be the result of poor intake and absorption of B vitamins or antioxidants, alcohol and tobacco toxicity, or a combination of these factors.

More recently, it has become apparent that nutrition may be important to some patients with hereditary visual disorders. One of the more common conditions is retinitis pigmentosa, an autosomal dominant condition resulting in progressive visual loss. It begins with the loss of night vision in childhood or adolescence. This is followed by the loss of peripheral vision because of the degeneration of rods, and finally the loss of central vision because of the degeneration of cones (recently reviewed in Ref. [3]). Vitamin A supplements have improved some aspects of retinal function in patients with retinitis pigmentosa, but vitamin E had an adverse effect [4]. Subsequent research indicated that supplementation with lutein [5] or docosahexaenoic acid (DHA) [6] (in addition to vitamin A) slowed the rates of retina degeneration and visual decline, but it may be that adequate intakes through dietary means are effective and may pose less risk over the long term [7].

Nutrition may also be important to the development of the visual system in newborns. Some studies, but not all, have observed better visual development in infants who were breast-fed, as opposed to those who were bottle-fed. This has led to a search for the nutritional differences between breast milk and infant formulas that may explain better vision in breast-fed infants. In two recent studies, breastfeeding was associated with better visual acuity at age 3.5 [8] and 4–6 years [9]. Breast milk contains high levels of DHA, which rapidly accumulates in retinal photoreceptor membranes neonatally. DHA supplementation has been reported in some, but not all, studies to improve visual functions in some preterm and term infants (reviewed in Ref. [10]). Some suggest that improvements may only be transient. One study reported that DHA supplementation for 6 months postnatally did not improve vision in later childhood [9]. This suggests the possibility that other components of breast milk generally missing from infant formulas, such as carotenoids, may be responsible for better vision in breast-fed infants. Considerable evidence in the past two decades indicates a unique role for specific dietary carotenoids in eye health throughout the lifespan. This is discussed in the next section. Overall nutritional intake in infancy, childhood, and adolescence might influence chronic age-related eye diseases that develop in later life. Evidence suggests that childhood diet influences the risk of cardiovascular disease later in life [11], but the influence on age-related eye diseases, which are the focus of this chapter, has not been investigated.

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The impact of nutrition on age-related declines in vision and age-related eye disease has been investigated over only the past 30 years. The deterioration of human vision advances with age. Over 80% of blindness worldwide occurs in people over age 50. This chapter addresses the influence of diet on the most common causes of vision loss in middle-aged and older people: age-related cataract, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR).

The aging public's awareness of the decline in vision with age, and of the possibility that nutrition may influence this decline, has driven the marketing of nutritional supplements, which are sometimes costly and of uncertain benefit. In this chapter, we consider the existing evidence for the benefits of certain diets and supplements in slowing age-related visual problems associated with cataracts, AMD, DR, and glaucoma.

II LUTEIN, ZEAXANTHIN, AND EYE HEALTH THROUGHOUT THE LIFESPAN

There is evidence to suggest that the eye may uniquely require three oxygenated carotenoids for good vision throughout life, as well as to limit degeneration of the retina and lens of the eye, which contributes to AMD and cataracts in later life. These include lutein (L), zeaxanthin (Z), and L metabolite, meso-Z (MZ). These carotenoids cannot be cleaved to vitamin A and have not been considered essential for life, growth, and reproduction (the criteria that typically defines essential nutrients). However, they may be uniquely important to the eye and essential for optimal vision in the young and aging. The reader is referred to recent comprehensive reviews [12–14]. Overall, the evidence is limited, but suggestive and actively under investigation. Below, an overview of these carotenoids is given and their possible role in vision throughout life is described. In Sections II–IV, the evidence that suggests their importance in slowing age-related cataract, macular degeneration, glaucoma, and DR is discussed.

L, Z, and MZ, together, are the most abundant carotenoids in the eye and are selectively concentrated in the macula and most other ocular tissues, to the exclusion of [15–17] other carotenoids which are found common in human blood and tissues. Exceptions are in the retinal pigment epithelium (RPE) of the eye (the blood–retina barrier between the blood vessels that nourish the back of the eye and the rod and cone photoreceptors), and ciliary body (part of the layer of tissue (uvea) that delivers oxygen and nutrients to other areas of the eye) [15]. Monkeys deprived of plant foods do not have these carotenoids L, Z, and MZ in their eyes, demonstrating that obtaining them from the diet is essential [18,19]. In humans, their concentration [15,17] and optically measured density [20,21] in the macular area of the retina is highly variable. The accumulation of these carotenoids is referred to as macular pigment (MP). It is absent in premature human infants [22], is low in autopsy samples of newborn infants, and is higher in samples from older infants and children up to 4 years of age [17]. Thus, the current evidence suggests that L, Z, and MZ accumulate in the retina rapidly during late gestation and infancy, if supplied by the mother's diet or, after birth, by breast milk or infant formulas containing these carotenoids.

Historically, breast milk has been the primary source of L and Z after birth. Consistent with the exclusive accumulation of L and Z in the macula in early life, breast milk appears to selectively concentrate these carotenoids, especially in the first few months of lactation. In fact, L and Z are proportionally more prevalent in breast milk than maternal serum [23,24]. In contrast to the carotenoid content of breast milk, carotenoids are not routinely added to infant formulas. Research is needed to determine immediate and long-term impact of breast feeding on vision, compared with feeding infant formulas which lack these carotenoids and appear to be less bioavailable than breast milk [25] when added to infant formulas. Additionally, more work needs to be done to determine the level of carotenoids that should be included in infant formula for infants who do not receive breast milk. Lastly, the need for these carotenoids might be particularly high in premature infants who do not have the benefit of optimally accumulating carotenoids in utero and are limited in ability to obtain them after birth. Until more is known, it is prudent to provide infants with early life nutrition such as can be provided by breast feeding from mothers with adequate intake of these carotenoids.

L and Z accumulate most markedly in the center of the macula. The timing of their accumulation and the relative proportion of L, Z, and MZ corresponds to the maturation of the macula over the first 4 years of life (recently reviewed in Ref. [26]). The time period of the accumulation of L and Z in the retina also corresponds to the accumulation of long-chain polyunsaturated fatty acid (LC PUFA), arachidonic acids (synthesized from essential fatty acid, linoleic acid) and DHA (synthesized from alpha-linolenic acid), which are also highly concentrated in retinal tissue (like the brain and other neural tissues (reviewed in Ref. [27])). These xanthophyll carotenoids and omega-3 fatty acids appear to be essential for the development and/or maintenance of normal RPE cells [28], the layer of cells that support the nutrient and metabolic needs of the rod and cone photoreceptors.

L, Z, and MZ in the macula (and L and Z in the lens) comprise is commonly referred to as "macular pigment."

These carotenoids absorb short wavelength (about 400−530 nm) light in the blue range of the spectrum that is known to damage photoreceptors and the RPE. In monkeys, depletion of L and Z in early life results in increased susceptibility to blue-light damage [29]. Preterm human infants supplemented with L had greater sensitivity responses of rod photoreceptors [30]. However, the extent to which a lack of carotenoids in early life creates lasting visual advantages or prevents lifelong vision problems is unknown. Vision throughout life might also be modified by the degree to which L and Z have accumulated in utero and by the intake of foods containing these carotenoids in later infancy and childhood. Supplementation of carotenoid-depleted monkeys reduced blue-light damage to the fovea [29].

It has long been proposed and recently demonstrated that these carotenoids enhance vision function. This was recently reviewed in Ref. [12]. Briefly, supplementation with L, Z, and/or MZ for 3 months to 3 years has improved visual acuity and or contrast sensitivity in many, but not all, clinical trials. Visual acuity improvements were noted in individuals with AMD or DR, but not, to date, in individuals with healthy vision. Differently, improvements in contrast sensitivity have been observed in samples of both healthy men and women and in individuals with diabetes or early- and late-stage AMD. Improvements in the time it takes to recover from bright lights (photostress recovery) or enhancement in the ability to see in conditions of glare have been observed in a few studies, but not most. Improvements in visual processing speed and rates of dark adaptation with adequate L and Z intake have been hypothesized and are supported by limited data, but have not been well-studied. Supplementation with L and Z slowed vision loss in adults with retinitis pigmentosa who were also taking vitamin A [5]. The ability to accumulate macular pigment is highly variable, particularly over a few months. The improvement in trials is often the largest in people who have made the most marked improvements of MP optical density levels. Also, improvements in vision outcomes have been more consistently observed when supplements include other antioxidants and/or long-chain polyunsaturated omega-3 fatty acids (LC omega-3 PUFAs).

The density of L and Z in the lens and retina may influence the eye diseases that occur in later life. It has been reasoned [31] that infant eyes are particularly vulnerable to oxidative damage in early life, which may have consequences decades later. Because of the redundancy of the visual system it may be difficult to observe the impact of early life nutrition on vision function in later life in small samples of people.

Sources of L and Z are also important from childhood through adulthood. Food sources of L and Z include a wide variety of fruits and vegetables, grains, and eggs [32]. They are particularly concentrated in green leafy vegetables, but corn products and eggs may comprise significant sources for some people, such as American Hispanics. Mean intake levels estimated in the 2011−12 National Health and Nutrition Examination Survey (NHANES) were 1.7 mg/day in adults over 20 years of age and 0.8 mg/day in children 2−19 years of age [33]. Levels of L and Z intake in some South Pacific study samples are higher [34] and reached 25 mg/day in one study in Fiji [35]. Increasing obesity in the United States might contribute to reductions in carotenoid status, as obesity (and other phenotypes related to metabolic syndrome) is associated with lower levels of L and Z in serum and MP after accounting for dietary intake [20]. It is hypothesized that obesity reflects genetic and lifestyle factors which lower the absorption of these oxygenated carotenoids and their uptake and stabilization in the eye [20,36].

III CATARACT

Cataract is the leading cause of blindness worldwide, accounting for almost half of all blindness [37]. The visual burden of cataract is largest in developing countries, where malnutrition is more common and the relatively simple surgical excision of cataract is less available. However, the economic burden of cataract in developed countries is high. For example, in the United States, the total direct medical cost of cataract was $6.8 billion in 2004, representing 42% of the total direct medical cost of all visual disorders in that year [38]. Seventeen percent of Americans older than 40 years have cataract in either eye, and 5% have had cataracts extracted [39]. The rate of cataract and extraction steeply increases with age. More than half of individuals over age 80 years have had cataract surgery (United States). Lens opacities can make seeing more difficult, especially under dim light and in the presence of glare (such as when driving at night), even before surgery is indicated. Over 30 years ago it was estimated that if preventive measures could delay cataract by only 10 years, the visual and surgical burden would be cut in half [40].

Lens opacities form as a result of protein aggregation or lens fiber disorganization due to either acute metabolic insults or the gradual accumulation of damage with age. The lens must remain clear in order to collect light and focus it on the retina. Lens opacities scatter light, blurring vision. With aging, the lens also slowly becomes brunescent, adding a brown tint to vision. When light transmission is blocked substantially enough to reduce visual acuity, a cataract exists; if opacities become severe, blindness can occur.

Cataracts generally occur in three regions of the lens (recently reviewed in Ref. [41]) (Fig. 19.1). The most common region is opacities in the nucleus, or center, of the lens. This is called a nuclear cataract, and most people develop this with age. Nuclear cataract may reflect cumulative insults that have occurred since early childhood.

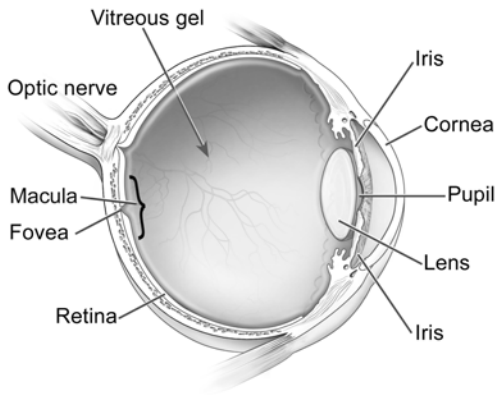

FIGURE 19.1 Anatomical features of the human eye. *Courtesy of National Eye Institute, National Institutes of Health.*

Nuclear lens fibers do not have mitochondria, nuclei, or other cytoplasmic organelles and thus lack the capacity to repair damage over one's lifetime. Less commonly, opacities develop in the region just under the lens capsule that separates the lens from the vitreous humor (posterior subcapsular cataracts, or PSCs), and in the fiber layer between the outside edges of the lens and the nucleus (cortical cataract). Cataracts sometimes occur exclusively in one region However, often opacities occur in multiple regions, particularly as cataracts become more severe.

A Causes

The pathogenesis of cataract involves the accumulated stresses caused by physiological and environmental stressors that arise from such things as the photochemical formation of free radicals and osmotic imbalances. Most cataracts are the result of aging, but cataracts can also occur as a result of surgical or other eye trauma, steroid use, or some types of radiation. Smoking is the most common modifiable risk factor for age-related cataract in population studies [42]. Exposure to smoke from combustion of wood or other fuels [43,44] may similarly increase cataract risk. Other nonnutritional risk factors include prolonged exposure to ultraviolet (UV)-B light (particularly in the cortical region of the lens), diabetes (especially for cortical cataract and sometimes nuclear cataract and PSC), obesity, heavy use of alcohol or elevated markers of systemic and local inflammation [45] or arthritis (as a marker of inflammation) [46]. Genetic factors have been most extensively investigated for nuclear cataract, and heritability studies suggest a substantial role of genetic factors in the development of nuclear cataract occurrence and progression, but specific genotypes are not well-studied [47].

Animal studies have indicated that cataract can be induced by high-galactose diets, experimental diabetes, nutrient deficiencies (riboflavin, calcium, zinc, and selenium), or nutrient excesses (selenium) (reviewed previously in Ref. [48]). Genetic mutations or polymorphisms that cause perturbations in calcium [49] or iron metabolism [50] have also been associated with cataracts. Otherwise, in the absence of extreme metabolic insults or deficiencies, lens opacities often develop slowly over many years. A gradual influence of nutrition on the development of cataract over adult life is suspected and is supported by animal studies. In Emory mice, a mouse strain that develops cataracts in adulthood, calorie restriction slows the development of lens opacities [51]. Since the 1980s, a body of evidence has been accumulated to indicate lower rates of cataracts among populations of people who eat micronutrient-rich diets or take multivitamins (summarized in Table 19.1 and discussed later).

B Healthy Diet Patterns

Generally, healthy diets or vegetarian diets have been associated with lower risk of cataract extraction or nuclear cataract in several studies in populations around the world [51–55]. The reduced risk associated with healthy diets in epidemiological studies of generally well-nourished populations [53,54] is about twofold and not explained by single nutrients [56], suggesting additional unknown food components that may lower risk and/or that food components work jointly to lower risk. The following sections consider many specific food components which may be responsible.

1 Carbohydrates

In experimental animals, cataracts are easily developed by feeding monosaccharide-rich diets or agents that promote diabetes (reviewed in Ref. [48]). Two mechanisms for cataract promotion within the lens are proposed. When the metabolic pathways to utilize sugars are overwhelmed, sugar alcohols are formed by aldose reductase, accumulate in the lens, and can cause osmotic cataracts. Another mechanism might involve nonenzymatic glycosylation and the accumulation of advanced glycation end products in the lens [57] or cataracts [58].

Humans with galactosemia, a rare, autosomal recessive disorder leading to an inability to break down dietary galactose, as found in milk, can be treated with a galactose-free diet. However, treated individuals are still at higher risk of developing cataract throughout life [59]. In a meta-analysis of human observational studies, higher dietary carbohydrate quantity and glycemic index were associated with the risk of cortical and nuclear cataracts, respectively [60]. In people with diabetes, poor glycemic control has been associated with higher lens density [61]. The prediabetic state has also been associated with cataract

TABLE 19.1 Summary of Evidence Relating Nutritional Exposures to Cataract

Nutritional Exposure	Strength of Evidence	Comment
Healthy Diet Patterns	*Benefit of following micronutrient-rich diet patterns is likely*: A large body of evidence suggests that healthy diets lower chronic diseases and their risk factors. Four observational studies suggest lower rates of cataract among people reporting the intake of healthy diet patterns.	Two population studies suggest that the benefit of healthy diets on lowering risk of nuclear cataract is stronger than the benefit of high intake of single nutrients. Many studies in animals and humans support the benefit of numerous specific micronutrients and phytochemicals.
Carbohydrate	*Possible increased risk associated with high levels of specific or overall refined carbohydrates:* Animal studies suggest several mechanisms. A meta-analysis of population studies suggests that higher dietary carbohydrate quantity and glycemic index was associated with the risk of cortical and nuclear cataract, respectively.	Results in population studies might reflect an influence of diabetes on cataract, rather than carbohydrates specifically and/or that high-carbohydrate diets are often nutrient-poor.
Antioxidants	*Benefit of food antioxidants is likely; supplemental antioxidants do not consistently lower risk and, there is the possibility that they increase risk in some cases:* Animal studies prove that oxidative stress leads to lens opacities and that antioxidants lower indicators of oxidative stress and/or damage. Population studies in many samples indicate lower risk of cataract with higher intake or blood levels of various antioxidants. The data are most consistent for diets rich in lutein and zeaxanthin.	In population studies, diets rich in specific antioxidant nutrients are likely to be markers for diets rich in plant foods (fruits, vegetables, whole grains) which contribute a wide range of nutritive and nonnutritive antioxidants. Clinical trials of high-dose antioxidants do not generally support the benefit of one or two specific antioxidant nutrients or a combination of high-dose antioxidants. In a meta-analysis of clinical trials, high-dose beta-carotene and/or vitamin E increased mortality.
Lead	*Exposure possibly increases risk:* Two observational studies suggest that intake of antioxidants in supplements increase the risk of cataract. This risk factor and the influence of other heavy metals, particularly when dietary antioxidants are low, require further research.	
B vitamins	*Benefit of dietary riboflavin and niacin in malnourished or healthy populations is possible:* Results of one clinical trial and many observational studies suggest protective relationships with the intake of these B vitamins. *High-dose intake of folate, B6 or B12 may increase risk:* Supplemental intake of a combination of these three increased the risk of cataract extraction in one trial. Dietary folate intake in a well-nourished study sample, in the time period after folate fortification, increased the risk of PSC over 9 years.	Considered together, the evidence for an adverse effect is strongest for folate in supplements or in fortified foods, but additional research is needed to better evaluate this possibility.
Vitamin D	*The benefit of good vitamin D status (from adequate sunlight, foods, and/or supplements) on cataract is unknown.* Animal and cell studies suggest antiinflammatory properties of vitamin D. Results of three observational studies indicate lower prevalence of cataract in persons with high levels of a biomarker of vitamin D status in the blood. Relationships of vitamin D intake from foods and supplements in relation to cataract are limited to four cross-sectional studies and are inconsistent.	
Multivitamin Supplements	*Both benefit and harm are possible:* Benefit may exist for persons at risk for nuclear cataract, but multivitamins might increase the risk of cortical of PSC.	

[62]. However, the specific impact of simple sugar consumption on cataract risk is uncertain. Epidemiological associations might reflect, to some extent, broader nutrient-poor diet patterns that often accompany diets high in carbohydrates or the impact of these diet patterns or diabetes on oxidative stress or inflammation.

Animal studies suggest that other aspects of the diet might modify cataractogenesis that develops as a result of diabetes- or galactosemia-induced cataract. The development of these cataracts has been lessened by intake of plant extracts [63] or a wide variety of nutrients and phytochemicals such as vitamins C and E (previously reviewed in Ref. [64]), soy isoflavones [65], caffeine [66], resveratrol [67], and cumin [68].

2 Antioxidants

It is well known that oxidative stress increases lens damage [41]. Relationships of antioxidant nutrients to cataract development in animals, and to the occurrence of cataract in populations, have been extensively reviewed [44,48,69–71]. Deficiencies of riboflavin, selenium, and zinc—cofactors for enzymes that play important roles in oxidative defense—cause cataracts in some species (previously reviewed in Ref. [48]). Deficiencies of vitamins C or E and major water and lipid-soluble antioxidants have not been reported to cause cataracts independently, but they do protect against oxidative damage in a variety of animal and cell systems. Vitamin C is abundant in human lenses, and its levels in the lens reflect those in the diet [72]. Lipid-soluble antioxidants in lenses include vitamin E and the specific carotenoids L and Z [16], which uniquely accumulate over other blood carotenoids. Both have been demonstrated to protect against UV-light-induced peroxidation in lens cells [73].

High levels of combined antioxidants in diet or serum [74–77], or of single antioxidant nutrient in diet and blood, have been associated with lower prevalence or incidence of cataracts or cataract extraction associations with numerous observational studies [44,71,78]. In contrast, there has been no evidence in randomized clinical trials for up to twelve years, that supplementation with one or more antioxidant nutrients (above recommended dietary allowances) slow the progression of age-related cataract [79]. An exception is in one trial in which they were accompanied by a multivitamin [80]. Moreover, taking vitamin C supplements was associated with an *increased* risk of cataract extraction over 10 years in women [81]. Both high-dose vitamin C and E were associated with higher risk of cataract over about 8 years in Swedish men, across many subgroups and risk increased among long-term users [82]. One explanation for these conflicting pieces of evidence is that both deficiencies and excess of antioxidants could be harmful. In the lens, vitamin C can enhance oxidative stress and contribute to glycation of lens proteins [83,84]. Moreover, there is evidence that oxidation of vitamin C can produce a compound that enhances photosensitivity which could further promote cataracts [85]. In addition, in a meta-analysis of trials, beta-carotene and vitamin E, singly or combined, significantly increased mortality [86]. For these reasons, caution is suggested in the consumption of high-dose antioxidants for the prevention or slowing of cataracts [79].

Supplements containing L and Z have only been available since about 1995, and they are likely to become more common since the addition of L and Z to high-dose antioxidants was recommended as a standard of care in treating intermediate or advanced stages of AMD (see Section III). There is mounting evidence that intake of these carotenoids may explain, in part, the lower cataract risk associated with people who eat diets rich in vegetables. Diets and serum rich in L and Z are consistently related to lower incidence or prevalence of nuclear cataract or cataract extraction in longitudinal studies [75,87–91], except in well-nourished men and women over 60 years of age participating in a clinical trial of high-dose antioxidants [92]. However, foods rich in these carotenoids, such as green vegetables and dark green leafy vegetables, are rich in many micronutrients and antioxidants, so that consistency of this association may simply reflect micronutrient and antioxidant-rich diets in general. In one large 5-year randomized trial in people with AMD, adding L to high-dose antioxidant supplements slowed the progression to cataract surgery among participants in the lowest quintile for levels of these carotenoids in their diets, although there was no protective benefit in the larger group of participants [93]. Relationships between high-dose L and Z supplement use and general health and mortality have not been well-studied.

Thus, the overall body of evidence from animal and population studies suggests that antioxidant components of the diet may contribute to protection against cataract development. However, there is little evidence to suggest that short-term supplementation with one or a few antioxidants is likely to have an important impact on the development of cataracts, which develop over many years and are influenced by a wide variety of dietary, health, and lifestyle factors. Moreover, adverse effects on cataract development or other aspects of health are possible when taken in high doses.

3 Minerals and Heavy Metals

Research on the benefits of antioxidants has not considered the potential larger importance that antioxidant protection might have under conditions of high oxidative stress. Oxidative stress can also result from genotypes

that result in iron overload [50]. Mechanisms for toxicity of heavy metals may include depleting cellular glutathione and/or heavy metals displacing zinc and copper on enzymes involved in protection against free radicals, causing oxidative stress [96].

Only a few epidemiological studies have examined the joint effect of low intake of antioxidant-rich foods and heavy metal exposure. In a sample of fish-eating people living in an area of the Amazon, with among the highest levels of mercury exposure in the world, joint existence of poor plasma selenium and high blood mercury is associated with a dramatically higher (16-fold) prevalence of age-related cataract [95]. In one clinical trial, beta-carotene was protective against cataract only in smokers who were likely to have higher exposure to heavy metals [97]. Thus, a benefit of food antioxidants may be greater in smokers or people who are exposed to industrial pollutants.

4 Other Vitamins

B vitamins: Results of several observational studies [75,92,98–103], and one trial in a malnourished population [104], have suggested protection against the development of lens opacities in individuals with higher dietary or blood levels of the B vitamins riboflavin, thiamin, and/or niacin. Riboflavin and niacin have roles in enzymatic mechanisms to protect against oxidative stress. Supplementation with these in an undernourished population in China protected them against the occurrence of nuclear cataracts [104].

In contrast, supplementation with a combination of B vitamins (vitamin B6, B12, and folate), at doses exceeding the recommended dietary allowances, increased the risk of cataract in U.S. physicians over 7 years [105]. Consistent with this finding, in participants already using multivitamins, high dietary folate was associated with higher risk of mild PSC among participants in the Age-Related Eye Disease Study (AREDS) [92]; cataracts in the PSC region of the lens was increased twofold [106].

Vitamin D: A role for vitamin D in the functioning or health of the lens is suggested by the evidence of the vitamin D receptor (VDR) in human lens epithelium [107]. As previously reviewed, inflammation is implicated in the development of cataract and the antiinflammatory properties of vitamin D [108] have been hypothesized to protect against age-related cataract.

Three investigations have recently described the lower prevalence of cataracts among people with high, compared with low, blood concentrations of 25-hydroxyvitamin D (25(OH)D) and cataract. Serum 25(OH)D reflects intake of vitamin D from foods, supplements, and the endogenous production of vitamin D that occurs upon exposure of skin to UV-B radiation in sunlight [109]. In 1988, results of an exploratory analysis of 112 participants, indicated a decreased odds of any and cortical cataract among those with high compared to low 25(OH)D concentrations [74]. Since then, data from two cross-sectional studies, one in a cohort of postmenopausal women [110] and the other in a population-based survey from Korea [111], have suggested possible protective associations between serum 25(OH)D and cataract, but only in subsets of their samples (e.g., postmenopausal women age <70 years [110] and in men [111]). The conflicting risks of sunlight—which may increase risk of cataract—and dermal production of vitamin D—which may decrease risk for cataract—make observational associations of vitamin D status and cataract exceptionally difficult to disentangle.

There have been a small number of studies examining relationships between the intake of vitamin D from foods and or supplements and the evidence is conflicting and does not take into account intraindividual differences in the level of vitamin D synthesized in the skin on exposure to sunlight or the competing risk of sunlight. Food sources of vitamin D include naturally occurring sources like fatty fish, fish liver oil, mushrooms, and egg yolk as well as fortified food sources such as milk, orange juice, breakfast cereals, and margarine [109]. A protective association of prevalent nuclear cataract with retrospectively recalled milk consumption [75] may reflect, in part, vitamin D intake or it could reflect a protective association of riboflavin, also associated with lower odds for nuclear cataract, or it could reflect an overall dietary pattern. Studies examining associations between cataract and estimated intake of vitamin D from all foods consumed reported null associations [52,101]. The evidence to describe relationships between the intake of vitamin D in supplements and cataract is limited to one retrospective study in which the intake of vitamin D from supplements was associated with increased odds of nuclear and cortical cataracts [112]. However, the confounding effects of other supplemental nutrients and lifestyle factors could not be accounted for.

In summary, study of the association between vitamin D status and cataract needs additional research in order for any conclusions to be drawn. Ideally, future studies will concurrently evaluate vitamin D intake from all sources and the competing risk of excess ocular sunlight exposure which may accompany higher rates of vitamin D synthesis in the skin. The role of vitamin D status in the eye is likely to vary by anatomical site and the extent to which vitamin D may influence the health of the cornea, lens, or retina differently is still under study.

5 Multivitamin Supplements

In contrast to the evidence for high-dose antioxidants and cataract, a large body of evidence from observational

studies [80,113–116] and clinical trials [104,106,114] indicate a protective effect of multivitamin use on nuclear cataract. However, evidence does not consistently support a benefit for cortical or PSC opacities. In one 9-year trial, the benefit of multivitamins was not observed for cortical opacities and the risk of cataracts in the PSC region of the lens was increased twofold [106].

IV AGE-RELATED MACULAR DEGENERATION

A Overview

AMD is a result of deterioration of the macula (see Fig. 19.1), the cone photoreceptor-rich part of the retina responsible for central vision and reading fine detail. AMD is the leading cause of blindness in developed countries and the third leading cause worldwide [37]. By the age of 65, roughly 8% of people in the United States have an intermediate form of AMD, which has a high risk of progressing to advanced AMD [117], and 2% of Americans over 80 years have advanced AMD [117]. There is no cure for this condition, and medical and surgical treatments are limited to people with one type of advanced AMD (wet AMD) with limited long-term effectiveness. Because of the steep increase in AMD with age, prevention is likely to have a large impact on the social and economic burden of this condition.

The early stages of AMD are signaled by yellowish white deposits, or drusen (Fig. 19.2), in the subretinal space and in the posterior part of the photoreceptor layer. Drusen can vary in size and area; more extensive drusen development is predictive of greater eventual progression to advanced stages. In intermediate stages, there are sometimes areas of hyper- or hypopigmentation (retinal pigment abnormalities) in the retina pigment epithelial (RPE) cells, a single layer of cells that support the rod and cone photoreceptors, caused by disturbances in the distribution of melanin pigments. Extensive drusen and retinal pigment abnormalities are thought to signal the existence of pathological processes associated with a distressed central retina. These changes are thought to compromise the ability of nutrients and oxygen to flow from the choroidal blood supply, through Bruch's membrane, to the RPE cells and the photoreceptors they support. Drusen may also reflect the existence of inflammatory processes that contribute to degradation of this area.

When deterioration of the macula proceeds to the extent that the RPE cells and the rod and cone photoreceptors they support die, advanced AMD occurs. It is sometimes referred to as "dry" AMD when it is limited to atrophy of the RPE and photoreceptors. If growth of new blood vessels occurs, then the advanced AMD is referred to as "wet" AMD. Impairment in visual acuity (after correction for glasses) is common with advanced AMD, progresses with the severity of disease, and can cause legal blindness. Bleeding or leaking of these vessels can also cause acute limits in vision. Advanced AMD of both types interfere with vision in the center of the visual field (such as that needed to view a person's face straight on) and the ability to read fine detail needed, for example, to read newspapers.

Rod-photoreceptor-related vision loss also occurs with advanced AMD, and often even before the loss of visual acuity associated with advanced AMD. There is impairment in rod-mediated dark adaptation, characterized by a slow recovery of visual sensitivity in low light conditions, such as when moving from areas of bright to dim illumination. This is thought to be caused by deposition of hydrophobic lipids in the RPE/Bruch's membrane complex with AMD and aging. This could slow the rate of delivery of vitamin A to rod photoreceptors, creating a transient local deficiency of vitamin A for rod photoreceptors

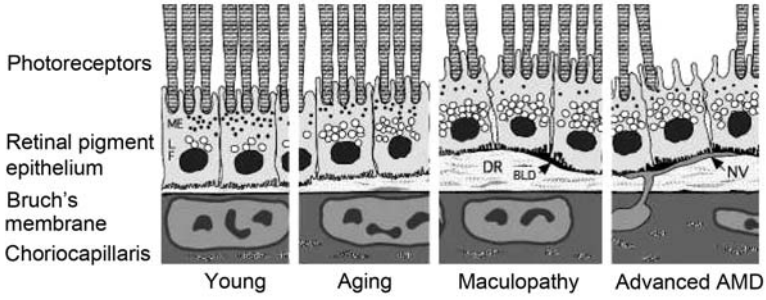

FIGURE 19.2 Changes to layers of retina in the macular region during aging, and progression of AMD in early and advanced stages. With age, there is an accumulation of lipofuscin (*LF*), a decline in melanin (*ME*) in the RPE, and a thickening and lipid enrichment of Bruch's membrane. Basal laminar deposits (*BLD*) are seen in early maculopathy but may also reflect aging. Drusen (*DR*) accumulation also characterizes early maculopathy. In intermediate AMD, *DR* becomes more extensive, and there are areas of the RPE that are hypopigmented or hyperpigmented (because of *ME* clumping). In more advanced AMD, there is atrophy of the photoreceptors and there may be neovascularization (*NV*)—the growth of new blood vessels and narrowing of the choriocapillaris. *Courtesy of Francois Delori, Schepens Eye Research Institute/Harvard Medical School, Boston, MA.*

(rods), slowing the recovery of light sensitivity by rod photoreceptors [118]. This localized vitamin A deficiency reduces the amount of vitamin A metabolite, 11-cis-retinal, available to combine with the protein, opsin, to form the visual pigment rhodopsin and the rate of phototransduction (converting light energy into neural impulses) [119]. This idea is consistent with the observation that short-term, high-dose retinol supplementation increased the rate of rod-mediated dark adaptation in people with early AMD or signs of retinal aging [120].

A significant proportion (22%) of adults over 60 years of age, in otherwise normal retinal health, have been also observed to have dark adaptation abnormalities [121], and were observed to increase the risk of developing AMD three years later [122]. This might explain common reports of problems seeing in low light conditions in people with early stages of AMD, even in persons with good visual acuity, tested at high illumination [123,124].

B Causes

AMD appears to develop as a result of a complex interplay of multiple dietary, environmental, and genetic factors that influence oxidative stress [125], inflammation [126,127], and light damage [128]. Smoking is the most commonly reported risk factor [129] for AMD in epidemiological studies. It is also commonly thought that damage by light, especially in the blue range, promotes AMD, although epidemiological studies have not consistently observed higher rates of AMD among people with high levels of sunlight exposure. This might be due to the difficulty in assessing the amount, type, and timing of sun exposure [130]. Some studies indicate high risk for AMD among people with cardiovascular disease [131,132] or risk factors such as obesity, diabetes, and hypertension [133,134].

Next to smoking, the most consistent, strong risk factor for AMD is family history [134]. People with AMD more commonly have certain variants within genes related to complement activation in the inflammatory response. While multiple complement related genes have been identified in AMD risk, the complement factor H (*CFH*) and age-related maculopathy susceptibility-2 (*ARMS2*) genes carry the greatest amount of risk. The *Y402H* variant A within *CFH* explains more than half of the population risk of AMD and is associated with 2.5−6.0 times greater AMD risk than individuals without the risk variant [135]. A variant with independent, yet similarly strong effects is the A69S variant (rs10490924) within *ARMS2* [136]. The genetic predisposition to AMD may involve a propensity for inflammation or exacerbation of an inflammatory response [126]. Some studies observe a higher prevalence of AMD among people with elevated C-reactive protein [137,138], an indicator of systemic inflammation, or among people with inflammatory diseases, such as gout [139], or who have used antiinflammatory medicines, which may signal the presence of inflammatory disease [140]. The evidence that diet and supplements may prevent or slow AMD is discussed later and summarized in Table 19.2.

C Healthy Diets

A wide body of evidence from a variety of study types supports the idea that food choices influence the development and progression of AMD, as discussed in subsequent sections. Healthy diet patterns that are rich in a wide variety of nutrients are consistently associated with lower AMD risk. Various healthy diet patterns have been related to a lower prevalence of early [141−143] and advanced AMD [142−145] and lower incidence of early AMD [146] and progression to advanced AMD [143,147].

Studies have looked at how healthy lifestyle factors, genetics, and/or diet patterns interact to contribute to AMD risk. It is unclear whether the impact of healthy diets and lifestyles is greater in people with high or low genetic risk. In one study, the reduction in the chance of having AMD was large (threefold lower) when healthy diets are jointly accompanied by moderate to high levels of physical activity and avoidance of smoking [141]. Moreover, women with a genetic predisposition for developing AMD (indicated by possessing two high-risk alleles for the *CFH Y420H* gene) significantly increased their odds of having AMD 6 years later if they had a history of heavy smoking, low scores on a healthy diet index and low levels of exercise. Results of another study in a separate sample found that higher adherence to a Mediterranean-style diet was protective in individuals who possessed at least one *nonrisk CFH Y420H* allele, but conferred no benefit in individuals with two high-risk *CFH* alleles [147]. Having high levels of body fat, which likely reflects a combination of genetic factors, diet, and physical activity, has been associated with a 12-fold higher risk for incidence of early or advanced AMD [148] and, together with smoking, has been observed to lower risk for progression of AMD 8- to 19-fold among people who had one to two copies of two common risk alleles [149]. The stronger associations observed when healthy diets, physical activity, not smoking, and genetic factors are considered jointly may be explained by the fact that they all contribute in lowering oxidative stress, inflammation, blood pressure and improving blood lipids, all of which are thought to promote AMD.

Moving forward, it might be possible to gain a better understanding of optimizing specific aspects of diet, by combining data from several large epidemiological studies and examining relationships with specific foods *within* groups of people who have similar overall diet quality.

TABLE 19.2 Summary of Evidence Relating Diet to AMD

Nutritional Exposure	Strength of Evidence	Comment
Healthy Diet Patterns	*Benefit of following micronutrient-rich diet patterns is likely:* A large body of evidence from results of studies in animals and humans support the benefit of numerous specific micronutrients and phytochemicals. Three studies suggest that scores on overall healthy diet patterns lower risk. (One study suggests risk lowering is particularly marked when combined with physical activity and not smoking.)	
High Glycemic Foods	Diets with low glycemic index scores might reduce the risk of developing AMD. Hyperglycemia in known to contribute to oxidative stress and inflammation, known to promote AMD. Results of a few observational studies suggest lower rates of AMD are associated with diets with low glycemic index scores.	A low glycemic index score is likely to be a marker for a plant- and nutrient-rich diet that contains many food components likely to lower AMD risk.
Antioxidants	*Benefit of foods or supplements rich in many antioxidants is likely*; Oxidative stress in the retina is high and known to contribute to AMD. In clinical trials, supplementing with individual antioxidants does not slow the progression of AMD. However, the benefits of a specific combination antioxidant supplement in slowing progression has been demonstrated in one large study sample (AREDS); benefits persisted over longer follow-up of the cohort for about 10 years. Benefit is also suggested by the results of several smaller studies. While observational studies suggest that antioxidant-rich diet patterns are likely to prevent AMD, antioxidant supplements have not been shown to *prevent* AMD.	*Caveats regarding AREDS-tested supplements:* – The longer-term risks and benefits are unknown. – Whether lower doses or different combinations of nutrients may have more benefit or lower long-term risk is unknown. Trials of one or two high-dose antioxidants have not shown benefit.
L and Z	*Benefit in slowing AMD and/or improving vision is likely:* The biological plausibility that L and Z can protect against oxidative stress, inflammation, and/or reduction of damage due to light exposure is strong and supported by studies in both animals and humans. In population studies, diets high in foods that contain L and Z are consistently related to lower risk for advanced AMD (although inconsistently related to lower risk for earlier stages). Several small and short-term clinical trials provide preliminary evidence to suggest that L and Z supplementation may improve vision in people with AMD. Benefit in slowing advanced AMD in individuals with low dietary intake is suggested by secondary analyses in a large clinical trial (AREDS2).	Diets rich in L and Z may reflect the overall benefit of high intakes of many micronutrient-rich foods. The ability to accumulate L and Z (and therefore, the potential benefit) varies across people. Differences in accumulation in the macula, genetic risk factors for AMD, and survival bias may make it difficult to observe consistent relationships between L and Z intake and AMD incidence and progression.
Zinc	*Benefit in slowing progression is proven:* High-dose zinc supplements slowed the progression of intermediate to advanced AMD in a large, multicenter, placebo-controlled clinical trial over 6 years; benefit was sustained over about 10 years of follow-up. In combination with antioxidant supplements, this supplement also reduced moderate visual acuity loss,	The safest dose with benefit is unknown. The long-term benefits and risks of consuming high levels of zinc in supplements are not well-studied. Inconsistency across observational studies might be explained by differences in the degree to which other components of foods rich in zinc (milk, beans, meats, and shellfish) or correlated nutrients or lifestyles have been accounted for. The benefit of zinc may depend on

(*Continued*)

TABLE 19.2 (Continued)

Nutritional Exposure	Strength of Evidence	Comment
	consistent with some other smaller studies that observed improvements if vision function with supplementation. *Benefit of adequate zinc intake from foods in slowing development of AMD is likely:* Zinc deficiency impairs retinal function in animals and humans. Diets high in zinc have been related to lower AMD in some but not all epidemiological studies.	the exposure to toxic metals from cigarette smoke and pollution.
Dietary Fat	*High intake of total fat might encourage the development of AMD:* High fat intake in mice with a genetic propensity to lipid disorder results in AMD-like lesions. Overall fat intake is associated with lower prevalence or progression of AMD in most population studies (although not always statistically significant). *Benefit of foods rich in LC omega-3 fatty acids is likely*: The retina is high LC omega-3 PUFAs which require a high rate of renewal. Diets high in omega-3 fatty acids are associated with lower inflammatory markers in the blood. Deficiency of omega-3 fatty acids in nonhuman primates increases sensitivity to blue-light damage. High intake of LC omega-3 fatty acids or fish is associated with lower risk for AMD in 7 of 8 study samples. In two randomized controlled trials of DHA and EPA supplements, added to high-dose antioxidants did not slow progression of persons with AMD over about 5 years.	Higher risk for AMD among people with diets high in fat might reflect lower overall nutrient density of high-fat diets or other aspects of lifestyle associated with the intake of high-fat diets. Diets high in LC omega-3 fats or fish may be related to lower AMD risk due to unmeasured and controlled for aspects of diet (intake of vitamin D and/or selenium) or lifestyle. Benefits should be considered in conjunction with the possibility that fish and some fish oils may contain mercury or other contaminants. Inconsistencies in protective associations in observational studies or across populations who vary in intake of omega-3 fatty acids or clinical trials might reflect modifying effects of genetic risk for AMD or the metabolism of omega-3 fatty acids.
B vitamins	Benefit is possible: Benefit is suggested by only one randomized clinical trial and two observational studies. More research is needed.	The evidence is insufficient to indicate which B vitamin(s) might be protective and whether folic acid supplements might be harmful over the long-term in some people.
Vitamin D	*Benefit of good vitamin D status (from adequate sunlight, foods, and/or supplements) is possible.* Animal and cell studies suggest antiinflammatory properties of vitamin D. In cohort studies and studies of population-based survey data, associations between 25(OH)D concentrations, as an indicator of vitamin D status, and early AMD are inconsistent. Only one study is of a prospective design, but data on vitamin D status was derived from a retrospective review of Medicare claim files and AMD diagnosis. Data from one national survey and two case-control studies suggest that an association between 25 (OH)D and late-staged AMD may exist but few robust studies have investigated this association.	Higher blood levels of vitamin D could be related to other aspects of diet or lifestyle that could protect against AMD.
Multivitamin Supplements	*Benefit is unknown:* The use of multivitamin supplements has not been associated with lower risk for AMD in population studies (except in Americans who did not report drinking milk daily). Multivitamins did not lower the incidence of AMD over 11 years in a large cohort of physicians.	The impact of multivitamins on the onset or worsening of AMD has not been tested in clinical trials.

Combining data will also allow for more statistical power to examine aspects of diet by levels of genetic risk, levels of physical activity, and other lifestyle factors.

D Glycemic Index

The glycemic index of foods was introduced to be another possible aspect of diet that could influence the development of AMD [150]. Although advanced glycation end products have been found in drusen, it is not yet known whether they are a cause or consequence of degenerative changes. Degeneration of the retinal vasculature is a well-known complication of diabetes mellitus; yet the presence of diabetes has sometimes, but not always, been related to AMD in epidemiological studies. The biological plausibility that elevation in blood sugar promotes AMD, particularly in the absence of diabetes, remains untested. Nevertheless, diets with a low glycemic index often include few refined grains and sugars and plenty of fruits, vegetables, whole grains, legumes, and milk, which have numerous components that could protect against AMD. Thus, high glycemic index diets, like high-fat diets, may be related to higher rates of AMD, in part or in whole, because they lack a wide variety of protective nutrients and other diet components.

E Antioxidants

Oxidative damage to proteins, lipids, and DNA, by free radicals within the photoreceptor outer segments (POS) or RPE, can be the result of photooxidation of lipids from light exposure. They can also be the by-product of metabolic events, such as oxidative metabolism or enzyme reactions that use oxygen (such as xanthine oxidase). The retina is particularly susceptible to oxidative stress, because of its high rates of oxidative metabolism and light exposure, and its high concentration of long-chain polyunsaturated fatty acids, whose double bonds are vulnerable. Free radicals that propagate oxidative damage may also be produced directly as a mechanism for biological defense, as is the case when white blood cells respond immunologically to pathogens with an oxidant boost.

In epidemiological studies, when associations with antioxidant nutrients are considered one at a time, low levels of one or more antioxidants in the blood or diet have often, but not always, been related to higher prevalence or incidence of certain age-related changes in the macula. Dietary antioxidant nutrients related to lower occurrence of AMD include vitamin E [146,151,152] or one or more carotenoids (reviewed in Ref. [153] and subsequently reported in Refs. [154–157]) or zinc [146,151,154–158]. In the Rotterdam Eye Study [146], a 35% lower risk of incident AMD was observed among the 10% of participants who were consuming antioxidant-rich diets (i.e., diets with above the median intake of all four antioxidants in AREDS supplements) compared with above median intake for only one. In this sample, high dietary intake of antioxidants particularly lowered the risk of developing AMD associated with high genetic risk [159].

Although the level of antioxidant vitamins in foods is usually lower than in high-dose antioxidant supplements, the number of different known and unknown antioxidants in foods is likely to exceed those in supplements. Foods high in antioxidants, such as vegetables, might lower oxidative stress to a greater degree than supplements. In a recent randomized, crossover trial, eating two or more cups of brassica vegetables (such as broccoli) lowered a urinary marker of oxidative stress, whereas moderate levels of supplementation with antioxidants in multivitamins did not [160]. A number of the flavonoids have been documented to have antioxidant or antiinflammatory activity or increase ocular blood flow (reviewed in Ref. [161]). The polyphenol, resveratrol, found in foods like grapes, peanuts, wine, raisins, and some berries, was found to inhibit damage to human retinal pigment epithelial cells due to substances in cigarette smoke [162]. However, the evidence regarding the effectiveness of these compounds in limiting AMD-related pathology is limited and conflicting. The impact of decades of consuming dietary nutrient and nonnutrient antioxidants on AMD may be substantial [163] and has not been adequately studied.

High-dose antioxidant supplements are considered a standard of care in the United States for individuals who have intermediate AMD or advanced stages of AMD [164]. This is based on results of AREDS, a 6.2-year randomized, placebo-controlled clinical trial, in which high doses of a combination of antioxidants (500 mg of vitamin C, 400 IU of vitamin E, 15 mg of beta-carotene, and 80 mg of zinc along with 2 mg of copper) slowed the progression of AMD from intermediate to more advanced stages by 28% [165]. The beneficial effects of the AREDS formulation persisted over 10 years, at which time there was a 27% reduction in risk of developing advanced AMD [166]. There is also evidence that this treatment reduces the age-related oxidation of cysteine in the blood, which supports the possibility that the benefit is due to a reduction in oxidative stress [167]. There was additional efficacy of the AREDS formulation when beta-carotene was replaced with L and Z (12 mg), particularly in those with low dietary intake of L and Z [168].

Genetics might modify the benefit of AREDS supplements on the rate of progression to advanced AMD, but the evidence is inconsistent. The inconsistent evidence was recently discussed by Seddon and colleagues [169] who observed a protective effect of these antioxidants and zinc only among persons with the nonrisk genotype for

CFH or *risk* genotype for *ARMS2*; whereas no modification be genotype was observed by others [170]. Whether the differential effects would be observed in other study samples or among persons taking these supplements over longer periods of time is unclear.

There is no evidence that people who have early AMD or who are at risk for AMD because of a family history will benefit from such high-dose antioxidant supplements. The levels of antioxidants that are safe and effective and efficacy of other supplement formulations over the long term is not well-studied. Results of a large meta-analysis suggest that vitamin A, beta-carotene, and vitamin E at high doses may increase mortality [171].

F Lutein and Zeaxanthin

L and its structural isomers Z and MZ are selectively concentrated in the retina where they are thought to protect against damage due to light and oxidative stress which would otherwise promote AMD (recently reviewed in Ref. [12]). They may also lower AMD risk by lowering inflammation in the retina, as a result of light damage in the retina (discussed later) or in other areas of the body [30,172] by suppressing an inflammatory response, which could indirectly promote AMD.

The highest density of these carotenoids in the central macula is found in the inner retina, in the Henle fiber and inner plexiform layers [173], where they comprise a yellow pigment referred to as MP. At these locations, they are likely to function as an optical filter that absorbs short-wavelength visible (blue) light [174]. This might protect against AMD or simply enhance vision (as discussed in Section II) They are also present in the lipid-rich POS where evidence suggests that they are likely to act as antioxidants in specific membrane domains which are rich in unsaturated lipids that are vulnerable to oxidation [175].

In the central macula, Z isomers predominate and include both Z and the L metabolite, MZ. The MP density reduces about twofold between the central macula and the periphery of the fovea, where the L isomer predominates [17]. The total concentration reduces 100-fold from the center of the cone-dominated fovea to the rod-dominated peripheral retina [176].

One mechanism by which the absorption of blue light by MP could protect against the development and progression of AMD is by blocking light-induced formation of a toxic di-retinal conjugate, A2E. Drusen deposits, characteristic of early AMD, which may be promoted by inflammatory processes [177], contain lipofuscin, the principal component of which is the toxic compound, A2E, which forms as a consequence of light-related vitamin A cycling in the retina. A2E accumulates in the RPE during phagocytosis of the rods and cones, and it is taken up by the lysosomes. A2E, in excess levels, has a variety of potential toxic effects, one of which is sensitivity to blue-light damage [178]. When a critical intracellular level of this compound has been reached, cell damage to DNA occurs, induced by blue-light irradiation [179]. Because MP could absorb 40−90% of incident blue light [174], it could reduce A2E toxicity.

There is evidence in animals that L and Z protect areas of the retina which are influenced by AMD in humans. Primates and some birds which selectively accumulate L and Z in their eyes are best to study the impact of MP on AMD or related photoreceptor health. Primates fed diets deficient in these xanthophylls [18,28] suffer a loss of RPE cells and increased photoreceptor cell death [180]. Subsequent supplementation with L protected the fovea of the retina against blue-light damage [181]. Retinal Z has also been demonstrated to prevent light-induced photoreceptor death in quail [182]. In mice, dietary L supplementation has been reported to inhibit inflammatory and angiogenic molecules related to neovascularization, similar to the inhibition of inflammatory and angiogenic processes in human retinal cell cultures [183,184].

The evidence for protection in humans comes mostly from epidemiological studies and clinical trials. In observational studies, lower rates of advanced stages of AMD have been associated with higher dietary levels of these carotenoids [185−190]. Associations between the intake or serum levels of L and Z and earlier stages of AMD are inconsistent [146,151,156,185,187,188,190]. However, results from the Carotenoids in Age-Related Eye Disease Study indicate that a protective association between dietary L and AMD is observed after excluding people who have made marked dietary changes and in women <75 years of age, in whom, the association is less likely to be influenced by survivor bias [156].

The relationships between dietary L, Z, and AMD may depend on a person's ability to accumulate carotenoids from the diet or supplements. A substantial amount of evidence (recently reviewed in Refs. [12,191]) suggests that many individual characteristics and aspects of individuals' diets modify the uptake of L and Z into the body and eye. Briefly, having indicators of metabolic stress (such as high levels of body fat, diabetes, or high levels of triglycerides) [20,192] or certain genetic variants [36,193−195] are related to lower MP density and/or the ability to increase MP with L and Z supplements [196].

A variable ability to accumulate carotenoids from supplements over the short term (2 months to 2 years) has been observed (recently reviewed in Ref. [12]). Variable accumulation in these studies might also reflect differences in supplement composition (with respect to the three xanthophyll carotenoids L, Z, and MZ) or doses, or other ingredients present in the supplement (such as omega-3 fatty acids or other antioxidants) or diets of individuals. The results of some small studies indicate

that the presence of lipids [197,198] or egg in foods [199,200] or omega-3 fats in supplements [201] might enhance bioavailability and the macular accumulation of these carotenoids.

Synergistic relationships between dietary L and genetic predisposition for AMD are possible and may explain some inconsistencies in relationships of dietary L to AMD. The presence of the common genetic risk variant in the *CFH* gene (*Y402H*), which increases risk for AMD, was less predictive of AMD in people whose diets were rich in L and Z [159,202].

The strong biological plausibility that MP protects against degeneration is supported by the observation of lower levels of L and Z in autopsy specimens of donor eyes with AMD, compared with donor eyes in people without AMD [176]. However, to date, relationships of AMD to MP density, measured noninvasively in living persons, have not been detected in cross-sectional studies [203–207]. This may be due, in part, to bias as a result of recent L supplement use in people who have been diagnosed with or have a family history for macular degeneration or survivor bias common in epidemiological studies of older people. Significant [207] or marginally significant [204] trends for a protective association have been observed when such people are excluded from analyses. A trend in the direction of protection of MP on AMD progression was observed in the only longitudinal study [208], but it was not statistically significant, nor well powered (only 27 people developed AMD over 10 years). Larger longitudinal studies that evaluate the magnitude of protection that higher MP density may have on lowering risk for AMD incidence and progression are underway, with results expected in 2018.

Even if MP density is found to be related to lower risk for developing or worsening AMD in future studies, it will remain to be determined whether this is due to dietary intake of L and Z, or the many other components in fruits and vegetables or healthy lifestyles in people with L-rich diets that may slow the development of AMD. Women who had a combination of healthy lifestyles (fruit and vegetable-rich diet, not smoking and high levels of physical activity) had higher MP density than women who did not, despite having only slightly greater intake of L and Z [141]. This suggests that many possible lifestyle factors may influence accumulation of MP and these factors may be other means of enhancing MP density.

Dietary or supplemental L, Z, and/or MZ could improve several aspects of vision in individuals with early or advanced AMD (summarized in Section 1A). However, whether this substantially improves the daily life of persons with AMD is unclear. Despite the possibility that vegetables, particularly green vegetables and dark leafy greens, may lower risk for AMD (and cataract as discussed previously), some older people limit their intake because they contain high levels of vitamin K, which could interfere with warfarin that has been prescribed to prevent blood clotting. A sudden increase in vitamin K intake from these foods can reduce the effectiveness of the drug. However, patients can consult with their health care team to have their warfarin dose titrated to the highest daily green vegetable intake that the patient can consistently eat.

G Zinc and Other Metals

Zinc may be particularly important to the retina because concentrations of zinc in the retina exceed those elsewhere in the body, with the exception of the prostate [209]. Deficiency of zinc in both animals and people impairs retinal functioning, as previously reviewed [210]. There is evidence for numerous mechanisms (catalytic, regulatory, and structural) [211] by which zinc could influence retinal integrity. Zinc catalyzes enzymatic reactions and is a cofactor of more than 100 enzymes, some of which are involved in oxidant defense. Zinc depletion in RPE cells has reduced levels of catalase, glutathione peroxidase, and metallothionein and has reduced ability to phagocytize POS [212]. Zinc performs structural roles; it facilitates protein folding to produce biologically active molecules (zinc fingers). Zinc is also involved in immune responses [213,214]. Both zinc deficiency and excesses impair immunity [214]. Zinc binds to and inhibits the activity of factor H protein in the complement system and has been proposed to contribute to deposit formation and inflammation associated with AMD [215]. Zinc depletion may also trigger apoptosis of RPE cells or increase the vulnerability of RPE cells to photic injury [216]. However, zinc supplementation can also enhance stress-induced effects in RPE cells [217]. Both lower and higher [218] levels of zinc in the choroid and RPE were observed in autopsy specimens from patients with AMD compared with those without the condition [219].

The long-term benefit of zinc on risk for AMD is suggested by the results of several but not all observational studies (reviewed in Ref. [220]). The use of high-dose zinc supplements (80 mg as zinc oxide, along with 2 mg of cupric oxide) for 6 years with or without antioxidants was associated with modestly lower progression from intermediate to advanced AMD in the AREDS [165]. Benefits persisted over 10 years of follow-up [166]. One smaller zinc supplementation trial had previously reported a benefit of zinc supplementation on vision loss in patients with AMD [221], whereas another did not [222]. In two short (6 months to 2 years) small randomized controlled studies in patients with early AMD, zinc supplementation modestly improved visual acuity, contrast sensitivity, and photostress recovery [221]. No serious safety issues

with zinc supplementation were identified in the 6-year AREDS study (aside from more frequent hospitalization for genitourinary problems in men and more frequent reports of anemia, unsupported by differences in hematocrit), and zinc supplementation was related to lower mortality in this sample [223]. This effect persisted for over 10 years of follow-up [166]. However, the long-term benefits and risks of zinc supplementation at the high levels tested in AREDS are unknown. A differential effect of zinc supplementation, based on the presence of AMD-risk alleles, has been reported in some studies [224–226], but these results were not confirmed in a larger sample of the same study population [170,224,227].

That a protective association of zinc on AMD is observed in most, but not all observational studies and clinical trials may reflect the possibility that protection is limited to individuals who are exposed to high levels of heavy metals through cigarette smoke, diet, or other environmental contaminants. Such high-risk individuals may comprise different proportions of the study samples in observational studies and trials. Two metals have been suggested to place persons at high risk for AMD, cadmium and lead [228]. These divalent cations often compete for the same binding sites as copper and zinc and have the capacity to displace these essential metals [229]. In one recent cross-sectional study in the Korean population, blood levels of lead, cadmium, and mercury were associated with a high odds for having late AMD, whereas, high blood levels of zinc and manganese (another divalent cation) were associated with lower risk.

Cadmium, a naturally occurring metal which is dispersed in the environment as a by-product of industrial activities, smoking, and fertilizers, is a potent inflammatory agent and increases oxidative stress [230]. Cadmium levels in the retinal tissues were approximately double in smokers compared to nonsmokers [231] and may explain, in part, the higher risk of AMD in smokers. Higher urinary cadmium levels were found in smokers who had AMD compared to smokers who did not have AMD [232]. Lead is also a naturally occurring metal which accumulates in our bodies with age as a function of smoking, drinking water, and other types of environmental contamination. Like cadmium, lead can contribute to the production of inflammatory cytokines and oxidative stress. Lead in the neural retina has been associated with the presence of AMD [228].

Iron, another divalent cation, is essential for retinal function, but in excess can also be toxic to the retina by catalyzing the production of reactive oxygen species, causing oxidative damage. A recent review summarizes the evidence for the beneficial and toxic effects of iron [233]. The current body of evidence suggests that iron excess, rather than deficiency, is related to AMD risk. Accumulation of iron has been observed in the retinas of persons with AMD, but it is unclear whether iron accumulation is a cause or consequence of AMD. Higher levels of serum ferritin were weakly associated with higher odds for AMD in one study in the Korean population [234]. Observations of common variants in a gene that encodes a soluble transferrin receptor are related to the odds of having AMD [235] and medical approaches to chelate excess iron are being considered as a strategy which might lower the progression of AMD [233].

In summary adequate levels of zinc from foods (dairy, meat, or beans) is associated with lower risk for AMD in observational studies, but results are limited and not consistent. Supplementation with zinc lowered the risk of progression of AMD and improved visual acuity in some studies. The benefit of zinc intake from diet or supplements on AMD risk may depend on exposure to toxic metals which compete with zinc, but has been understudied.

H B Vitamins

The importance of B vitamins to eye health has been illustrated by their ability to resolve nutritional amblyopias occurring as a result of B vitamin deficiencies and exacerbated by conditions which interfere with the absorption and metabolism of B vitamins, such as chronic alcohol overuse (reviewed in Ref. [2,236]). However, an increasing body of evidence from observational studies [237,238] and one randomized clinical trial [239] suggest that improved status of B vitamins also lowers risk for the development and progression of AMD.

There are several mechanisms by which B vitamins may play a role in AMD. The most widely considered mechanism is through prevention of hyperhomocysteinemia, which was associated with increased risk for late AMD in several past studies [237,240]; a similar, but nonsignificant, trend was observed among non-Hispanic White Americans, in a third study [241]. Folate (B9), cobalamin (B12), pyridoxine (B6), and riboflavin (B2) deficiencies either singly, or in combination, can elevate homocysteine. In two of these studies, high folate levels were associated with lower risk of one or both types of late AMD [237,238]. In one small study, low plasma vitamin B12 levels were associated with having exudative AMD, compared to patients with geographic atrophy [242]. The fortification of foods with folaic acid might lead to a substantial increase in folate status which is thought to exacerbate manifestations of vitamin B12 deficiency in blood [243] and the central nervous system [244,245,246]. Trends for the increasing intake of folic acid-fortified foods and vitamin supplements has the potential to influence AMD risk in the future.

Vitamin B6 appears to play a role in inflammation and oxidative stress; both mechanisms are known to

contribute to AMD risk. High blood levels of the active form of vitamin B6 (pyridoxal 5-phosphate) are associated with low markers of inflammation and oxidative stress [247]. Flavins, derived from riboflavin, are highly concentrated in the retina, in the space between the RPE and the rod and cone photoreceptors and are needed for photoreceptor energy metabolism and function [248]; energy metabolism is particularly high in the outer retina containing photoreceptors because of a high rate of daily renewal of the outer segments and energy is needed in phototransduction.

In summary, a benefit of supplementation of B-vitamins is suggested by evidence from one clinical trial and two observational studies. However, it is not possible to discern which B vitamin(s) were responsible and supplementation with folic acid might be harmful to some people. Additional long-term prospective cohort studies are needed.

I Vitamin D

Vitamin D is hypothesized to suppress localized inflammatory responses that occur in the retina and are implicated in the pathology of AMD [246]. The VDR is found on cells of the immune system [108,250,251] and vitamin D has been shown to alter the proliferation and differentiation of immune cells, decrease immunoglobulin production [252–256], and promote a Th1 over a Th2 cell response [108,250–252]. Evidence of the VDR on human retinal cells [107,257,258] and evidence of decreased retinal inflammation in studies of vitamin D_3 supplemented mice [259] support this hypothesis. Vitamin D is also hypothesized to prevent development of late-stage, neovascular AMD. Endothelial cells express the VDR [260] and studies in cell culture [261,262] and animal models of retinal disease [263,264] show that vitamin D has antiangiogenic properties.

The first report of a protective association between vitamin D status, assessed with 25(OH)D concentrations, and AMD was observed in a sample of participants from a nationally representative survey of the U.S. population [265]. A statistically significant protective association was found with prevalent early, but not late, AMD. Analysis of a different nationally representative survey in Korea was unable to replicate these findings with early AMD, but did observe a protective association with late AMD, but only in men [266]. Analyses in cohort studies have observed conflicting results. A protective association between serum 25(OH)D and early, but not late, AMD was observed in a cohort of postmenopausal women <75 years of age [267], but not in population-based cohorts in France [268] or the United States [269]. Further, a large cross-sectional study of members of Health Maintenance Organization found no association between medical chart-derived vitamin D status and AMD status determined from medical diagnosis codes [270]. Null results for the association between vitamin D status and nonneovascular or neovascular AMD were observed in a retrospective chart review of Medicare beneficiaries' claim files [271].

Results of case-control studies support a protective association of vitamin D on AMD. Graffe et al. observed that cases, as compared to controls, were more likely to have 25(OH)D <50 nmol/L. A total of 24 of the 31 cases of AMD had late-staged disease [272]. Itty et al. found significantly lower concentrations of serum 25(OH)D among 146 patients with neovascular AMD than in patients with either nonneovascular AMD ($n = 146$) or controls ($n = 100$) [273], but Morrison et al. reported no statistically significant differences in 25(OH)D between 50 extremely discordant AMD sibling pairs [274].

One study has reported an association between AMD and polymorphisms in the *CYP24A1* gene (which encodes the enzyme that catabolizes the active vitamin D hormone, $1,25(OH)_2D$) [274]. A different study was unable to replicate this finding [267] but did observe that associations between 25(OH)D and AMD were modified by the presence of high-risk AMD genes.

Observations of a protective effect of blood measures of vitamin D on AMD are supported by the observation that high compared to low intake of milk [265], vitamin D from foods [275,276], and vitamin D from food and supplements combined [267] have been associated with a decreased odds of AMD. One study did not find a statistically significant association with dietary vitamin D intake [277]. Interestingly, previously reported dietary associations between AMD and fish, omega-3 fatty acids (found in fish), and zinc (for which milk is an important source) (*see previous sections in this chapter*) might reflect, in part, a protective effect from dietary vitamin D.

Collectively, the existing data suggest that vitamin D might be another nutrient that protects the aging retina. Studies to date are limited by cross-sectional designs, with only Day et al. [271] investigating associations between vitamin D status and incident disease (assessed from a Medicare claims review). Many existing studies are limited because they primarily have cases of early, not late, disease. For example, the existing studies conducted in national surveys or cohorts have not had adequate cases to investigate associations with late-staged disease [265–269]. Studies of vitamin D and AMD are also difficult to assess because of potential residual confounding or overadjustment from lifestyle factors highly associated with vitamin D status [278] or from genetic risk factors for AMD. Observed associations between AMD and food and supplement sources of vitamin D should be examined with caution as total intake of vitamin D from foods and supplements may not reflect an individual's true vitamin D status [278] as vitamin D can

also be obtained from sunlight exposure. Potential confounding from the detrimental effects of sun exposure, as sun exposure is needed to endogenously synthesize vitamin D [109], adds to the complexity of interpreting epidemiologic studies of vitamin D and AMD. Sun exposure may also increase risk for AMD (reviewed in Ref. [279]). The avoidance of excessive sunlight to minimize risk for skin cancers, cataract, and AMD might jeopardize systemic vitamin D status in older people leading to potentially increased risk of AMD if adequate vitamin D status is shown to be protective. If confirmed, vitamin D status could have an impact on risk for AMD, given that portions of the U.S. population are at risk for poor vitamin D status [280,281]. Continued investigation of this potential association is warranted, especially in cohort studies powered to examine the progression of disease from early to late stages. Since AMD has such a strong genetic influence, it is also important to continue to understand the role of vitamin D status and diet in those with differing genetic risk.

J Dietary Fat

There are at least three broad mechanisms by which dietary fats might either enhance or slow AMD. First, because of the high caloric density of fats, eating high-fat foods can displace other nutrient-dense foods that may have otherwise protected against AMD. Second, eating high-fat and low nutrient density foods may contribute to high body mass, which is sometimes reported to be a risk factor for AMD [282–284]. Third, fatty acids themselves have numerous biological effects as components of biological membranes and regulators of biochemical pathways. Some dietary fats increase risk for atherosclerosis, which is related to AMD risk in some studies [131,132] and in a mouse model of atherogenesis [285]. Certain fatty acids can also have direct human physiological effects on the retina by modulating oxidative stress or by the inflammatory response, which can promote AMD pathogenesis (discussed later).

In mouse models of atherosclerosis, feeding high-fat diets resulted in the accumulation of lipid-like droplets in the retina and degenerative changes in RPE cells and Bruch's membrane [286–289]. In epidemiological studies, high dietary fat levels have been generally associated with increased risk for early and late AMD [282–284,286–294], even though these associations have not always been statistically significant. Some exceptions to this trend include prevalence or short-term incidence studies with low power to evaluate associations with either early AMD [295] or advanced AMD [290,291,293].

However, there is inconsistency across studies in the type of fat that was most related to AMD. The presence of AMD was more strongly related to high intake of saturated fats in some studies [291–294,296] and to high intake of PUFAs [297] or monounsaturated fatty acids in other studies [284,292,296]. High intake of monounsaturated fatty acids, nuts, or olive oil were associated with *lower* risk in other studies [297–299]. The intake of *trans*-fatty acids, provided in diets by margarines and other processed foods, was related to higher risk for AMD in three studies [283,284,299]. Because fat intake often changes due to alterations in food formulation and diet patterns, and particularly in relation to the common diagnosis for cardiovascular diseases which can be related to AMD, these relationships are difficult to interpret.

In addition, there is limited knowledge about the joint effects of other risk factors which might influence the associations observed. For example, chronic light exposure reduces the loss of DHA from photoreceptors in rats [300]. This suggests that light exposure may modify the impact of dietary fats on AMD. The protective association of nuts on the incidence of early AMD was greater in people without other risk factors (smoking, low dietary carotenoids and low ratio of total to HDL cholesterol in one study) [298]. However, joint effects are highly inconsistent across single studies. Larger pooled studies are needed to evaluate such joint effects in human epidemiological studies. Moreover, there is limited ability in such studies to adjust for the numerous other protective aspects of diet that accompany a more moderate, as compared to high, intake of fat.

LC omega-3 PUFAs, such as DHA or eicosapentaenoic acid (EPA), may be particularly important to the health of the retina. DHA is the most abundant LC omega-3 PUFA in rod outer segment membranes [301,302] at a concentration that exceeds levels found elsewhere in the body (reviewed in Ref. [303]). Its presence in membranes affects their biophysical properties and may influence membrane-bound enzymes, receptors, and transport. This is important in visual transduction [304], but it may also influence the pathogenesis of AMD. LC omega-3 PUFAs may protect against AMD by direct influence on retinal cell survival [305]. DHA has also been demonstrated to protect RPE cells from oxidative stress [305,306]. Deficiency of omega-3 PUFAs in nonhuman primates increases sensitivity to blue-light damage [181].

DHA might also lower risk for AMD because of its anti-inflammatory properties [307]. Numerous cell culture studies provide clues for possible mechanisms by which LC omega-3 PUFAs could enhance the integrity of vascular and basement membranes and prevent neovascularization (recently reviewed in Ref. [308]).

A mostly consistent body of evidence from observational studies indicates lower risk for early or late AMD among people with higher intake of fish, fatty fish, or LC omega-3 PUFAs [292,294–296,298,299,309,310]. Two studies found no such associations [291,297]. However, curiously, the rates of intermediate and advanced AMD

(characterized by pigmentary abnormalities and geography atrophy) in a sample of older adults from Iceland are markedly higher than rates in three other populations of European ancestry [311], despite having the highest per capita fish intake among Europeans and the fact that 56% report to use cod liver oil, a rich source of LC PUFAs.

Clinical trials have not provided strong support for the benefit of omega-3 supplements. The addition of 350 mg/day of DHA and 650 mg/day of EPA to high-dose antioxidants in the AREDS2 trial did not lower the progression to late AMD in persons who already had intermediate AMD or late AMD in one eye [312]. A lack of effect of omega-3 supplementation (840 mg/day DHA and 270 mg/day EPA) was also observed in a trial of omega-3 supplements alone [313]. A lack of effect in clinical trials or inconsistencies in protective associations in observational studies or across populations, who vary in intake of omega-3 PUFAs, could result from modifying effects of genetic risk for AMD, from the presence of genotypes which influence the synthesis or metabolism of LC omega-3 PUFAs, or the dietary content of other fatty acids. In one clinical trial, a beneficial effect of LC PUFAs was observed only in persons lacking AMD risk alleles for the *ARMS2* genotype [314]. Consistent with this modifying influence of *ARMS2* genotype, lower risk for one form of late AMD (geographic atrophy) in one observational study [315] and early AMD in a Dutch study [159] was observed in persons who had *ARMS2* risk alleles. Weekly fish intake in persons who had two *CFH* risk alleles in an Australian cohort reduced the risk for late AMD [316].

A protective influence of omega-3 PUFAs could also be dependent on the omega-6 content of the diet. A higher ratio of omega-3 to omega-6 PUFAs could increase formation of anti-inflammatory eicosanoids from omega-3 PUFAs, because the omega-6 PUFAs compete for the desaturase enzyme that creates them or replace the omega-6 PUFA content of membranes. A high ratio of omega-6 to omega-3 PUFAs also upregulates genes involved in lipid trafficking in the neuroretina [317]. In the past three studies, the risk reduction associated with a high intake of LC omega-3 PUFAs was stronger among subjects who had low intake of omega-6 PUFAs [283,284,296].

K Herbal Supplements

The use of herbal supplements has increased in the United States. Several herbal supplements, such as those containing ginkgo biloba and bilberry, have been promoted to benefit the health of the retina. However, there are no scientific studies that support their benefit except one very small (20 persons) study of ginkgo biloba in patients with AMD, in which improvement in visual acuity was indicated in a preliminary report (previously reviewed in Ref. [318]).

V DIABETIC RETINOPATHY

A Overview

DR is a complication of diabetes that is considered to be the result of damage to the microvasculature of the retina. It is the leading cause of new cases of blindness in working aged U.S. adults (20–74 years) [319]. Approximately 12.3% of Americans aged 20 years and older have diabetes, and this is estimated to increase to 14.0% by 2030 [320]. Diabetes is especially burdensome in minority populations, such as African Americans, Mexican Americans [321], and Native Americans [322], in whom the prevalence and incidence are higher than the national average. The burden of associated complications like DR will likely also increase in the coming years.

Previous work has described the natural history of the disease (reviewed in Refs. [319,324]). In brief, preclinical stages of DR include changes in retinal blood flow. Nonproliferative diabetic retinopathy (NPDR) consists of the formation of clinical lesions (microaneurysms and intraretinal hemorrhages), the appearance of retinal exudates (lipid deposits from leaky blood vessels) and cotton wool spots (resulting from localized ischemia), and the appearance of venous bleeding and loops. Blindness can result at these stages if macular edema occurs. In the later proliferative stage, proliferative diabetic retinopathy (PDR), new vessels and fibrous tissue can originate from the optic disc or elsewhere in the retina. Problems arise if the vessels grow through the inner limiting membrane into the vitreous humor of the eye, which is constantly contracting and condensing. Often this movement can lead to vessel tear, hemorrhage, and blindness.

Limited treatment options exist that include invasive injections of antiangiogenic agents into the vitreous for PDR [325] and laser photocoagulation [323], to cauterize leaking, newly developed blood vessels. Both injections of antiangiogenic agents and laser photocoagulation involve investing time in treatment and may cause discomfort. Photocoagulation does not necessarily prevent vision loss in all individuals, and can result in peripheral vision loss or decreased dark adaptation [326].

B Causes

Randomized controlled trials have demonstrated that maintenance of tight blood glucose control via intensive insulin therapy is associated with lower incidence and progression of DR in individuals with type 1 and 2

diabetes [327−330]. Even so, intensive insulin therapy did not prevent the occurrence of DR in all individuals and was often associated with increased bouts of hypoglycemia [327] Other well-established risk factors for DR are duration of diabetes [324], hypertension [332], and elevated blood lipids [333].

Various types of diets, foods, or nutrients may influence risk for DR either by affecting (1) blood glucose control, (2) blood pressure, (3) serum lipid levels, or (3) via other mechanisms (e.g., those related to the antioxidant or antiinflammatory activity of differing diets, foods, and nutrients) (summarized in Table 19.3). Nutrition therapy for patients with diabetes could be targeted at preventing DR or its progression and may be less costly than current treatment. This section will highlight areas believed to be the most robust with respect to research on nutrition and DR.

C Healthy Diet Patterns

An accumulating body of work supports a protective association between DR and consumption of a healthy diet, one high in fiber and low in saturated fat (and most likely rich in certain micronutrients). To date, most work on diet patterns has involved examining the association between DR and numerous foods and nutrients individually rather than examining index-derived dietary patterns in relation to DR, as done in other studies of diet and chronic disease [53,141,334,328]. Previous studies have observed protective associations between DR and intake of fruits and vegetables [329−339]. Fruit and vegetable-rich diet patterns, like the Dietary Approaches to Stopping Hypertension diet, might lower DR risk by lowering blood pressure or other risk factors for DR [340]. Roy et al., in a study of African American participants [341], observed an increased risk of progression to macular edema with high, compared to low, sodium intake. However, two recently published, robust analyses have not corroborated these findings [329,342]. These studies considered sodium intake alone, not as a component of a more complex dietary pattern. Recently, findings from a post hoc analysis of a randomized dietary modification trial in individuals with type 2 diabetes observed a protective effect of a Mediterranean Diet (MedDiet) plus extra virgin olive oil, as compared to a low-fat dietary pattern, on the risk of sight-threatening DR over 6 years of follow-up [343]. A MedDiet likely improves DR by reducing blood pressure and improving blood glucose control and lipid profiles; as well as through other mechanisms involving its influence on oxidative stress, inflammation, and promotion of a healthy endothelial function (reviewed in Refs. [344,345]). More work on associations between dietary patterns would be beneficial in understanding the complex role of diet in DR incidence and progression.

D Alcohol Consumption

Research has shown a protective association between moderate alcohol consumption and risk of coronary heart disease and mortality in individuals with type 2 diabetes [346]. These finding have led to recent interest in investigating the association between alcohol consumption and diabetic microvascular disease, such as DR [347,348]. Moderate alcohol consumption is hypothesized to be protective due to a number of different mechanisms related to cardiovascular health and DR risk factors (e.g., inflammation, dyslipidemia and insulin resistance, platelet aggregation), reviewed in more detail elsewhere [349,350].

Alcohol consumption in relation to DR has been studied in a number of observational studies, many of which have found no association between alcohol consumption and DR [351−357]. In 1984, Young et al. reported that heavy alcohol consumption was associated with the development of DR, primarily exudative and PDR, in a sample of 296 men [358]. Since then, a handful of studies have observed protective associations between alcohol consumption and DR, primarily moderate consumption. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, average alcohol consumption was associated with the decreased odds of prevalent PDR among individuals with diabetes onset before age 30 [359]. Analyses examining alcohol's association with the incidence and progression of DR in the same sample, albeit a smaller subset, did not observe the same association [355]. Beulens et al. observed that moderate alcohol consumption was associated with the reduced odds of prevalent PDR among 1857 participants with type 1 diabetes [360]. Two recently published cross-sectional studies [347,361] support a protective association with moderate [347] or light [361] alcohol consumption and reduced odds of any DR or severe DR, respectively. These studies [347,361] also suggest associations may vary by beverage type. Further, a 5-year prospective study observed a protective association of moderate alcohol consumption on the incidence of microvascular disease among 11,140 individuals with type 2 diabetes [348].

Many of these studies are limited by their cross-sectional designs as well as limited data on alcohol consumption quantity and patterns. Further, if alcohol consumption is mostly influential on the development of PDR, smaller studies limited in the number of advanced cases of disease might not have the power to observe an association if it existed. The findings to date are intriguing and deserve further study. Continued work in the area of dietary

TABLE 19.3 Summary of Evidence Relating Diet to DR

Nutritional Exposure	Strength of Evidence	Comment
Healthy Diet Patterns	*A diet rich in fruits and vegetables, micronutrients, and high in fiber is likely beneficial.* Observational studies support a protective association between high fruit and vegetable consumption and high fiber intake with the reduced odds or risk of DR. A post hoc analysis of a dietary modification trial comparing those randomized to a MedDiet with extra virgin olive oil to a low-fat dietary pattern showed reduced risk of incident sight-threatening DR. Such a diet may be beneficial by helping maintain blood glucose control and by lowering blood lipids and hypertension.	Diets rich in fruits and vegetables are likely high in fiber and rich in other micronutrients.
Alcohol Consumption	*Benefit of light to moderate alcohol consumption on reduced risk of DR is suggested.* Protective associations between moderate alcohol consumption and coronary heart disease led to research on the role of alcohol and DR. Four cross-sectional studies and one prospective study support a protective association between light to moderate alcohol consumption on risk of DR or microvascular disease. Three of these studies show an association with severe or PDR.	Light to moderate alcohol consumption could reflect an overall dietary pattern or lifestyle that protects against DR. The role of alcohol consumption as a risk factor for DR should be continued to be studied, but with consideration of alcohol as part of an overall dietary pattern. Many previous studies are limited by the lack of detail collected on alcohol intake, including the quantity of alcohol consumed, the frequency of consumption, beverage type usually consumed, and duration of consumption.
Dietary Fat and Fiber	*Diets low in saturated fat but high in omega-3 fatty PUFAs are likely beneficial.* A few epidemiologic studies show associations between high saturated fat intake and an increased odds of DR, although results are not consistent. A recent large prospective analysis showed a decreased risk of sight-threatening incident DR among participants consuming >500 mg/day of omega-3 fatty acids. *Benefit of high fiber diets are likely:* There is consistent evidence from observational studies supporting a protective role of dietary fiber intake and high fiber food intake (with an emphasis on soluble fiber) and reduced risk of DR. High fiber intake may be beneficial in helping maintain blood glucose control.	To our knowledge, only one study has specifically studied the influence of LC omega-3 PUFA intake on DR. More research is needed.
Antioxidants	*Benefit of foods rich in antioxidants is likely but inadequately studied.* Studies from diabetes-induced animal models strongly support a protective effect of antioxidant intake and maintenance of a healthy retina. Findings from both small patient and population-based samples are inconclusive. Findings from larger epidemiologic studies examining associations between dietary intake or serum concentrations of antioxidants do not conclusively support a protective effect of antioxidants on DR. Some studies suggest that antioxidant exposure could be potentially detrimental; however some of these findings may be explained by bias inherent in cross-sectional study designs. One clinical trial, in a post hoc analysis, found no association between vitamin E supplementation and history of DR laser therapy.	Observational studies are limited in number and mostly are cross-sectional in design. Results may be biased by changes in diet and supplementation practices upon development of diabetic complications. Long-term observational prospective studies are needed.

(*Continued*)

TABLE 19.3 (Continued)

Nutritional Exposure	Strength of Evidence	Comment
	One observational study suggested that long-term intake of antioxidant supplements or multivitamins may protect against DR.	
Vitamin D	*Benefit of good vitamin D status (from adequate sunlight, foods, and/or supplements) is possible.* In the last 5 years, research on the possible protective association of vitamin D status with DR has led to over a dozen published studies on this topic. Many are limited by their cross-sectional designs. Data from prospective studies are not consistently supportive of a protective association.	Continued examination of this association in prospective studies is needed. Studies should be powered to examine progression of DR, especially progression to PDR. Studies able to adjust for pertinent confounding variables are needed as higher blood levels of vitamin D could be related to other aspects of diet or lifestyle that could protect against DR.

patterns may provide insight into the influence of alcohol, as a part of an overall dietary pattern, on DR.

E Dietary Fat and Fiber

Previous studies have also observed that high calorie and fat (% kcals), both total and saturated, intake may increase risk for DR. A small case-control study in India observed that diets high in energy, animal proteins, and animal fats were more common among persons with PDR than among controls [339]. Data from one ecological study showed a greater prevalence of DR in persons with type 1 diabetes in European regions with higher, compared to lower, mean intakes of cholesterol, total fat, and saturated fat (% kcals) [362]. Further, the Diabetes Control and Complications Trial (DCCT) reported that conventionally treated participants who followed the American Diabetes Association dietary recommendations with respect to fat and total calorie intake were less likely to experience DR progression [363]. Sasaki et al. also observed an increased odds of DR among those consuming high compared to low intake of energy-adjusted, saturated fatty acids, but only in those with good glycemic control; no associations were found for total or monounsaturated fatty acid intake [364]. A prospective study in 649 African Americans with type 1 diabetes observed that total kilocalories along with age, glycosylated hemoglobin (Ghb), and hypertension were found to be significant predictors of vision-threatening DR and severe hard exudates [341]. The authors suggest that increasing kilocalories increases hyperglycemia and dyslipidemia and thus oxidative stress, a proposed etiologic mechanism for DR [365]. Differently, two cross-sectional studies [366,367] observed no statistically significant differences in total calories, total fat (% kcals) [366,367], or saturated fat (% kcals) [367] consumption between persons with and without prevalent DR.

Some of the original investigations of the associations between dietary intake and DR were conducted in the 1980s and involved small intervention studies of linoleic acid, an omega-6 PUFA, among individuals with type 2 diabetes [368,369]. These studies suggested that intake of diets enriched with linoleic acid decreased development and progression of DR, especially among those with poor glycemic control. The authors hypothesized that linoleic acid enrichment of cell membranes would increase the sensitivity of the insulin receptor and thus improve blood glucose control [368]. However, these earlier intervention studies' effects could have been due to linoleic acid consumption displacing consumption of other more harmful fatty acids, such as saturated fat. A recent finding in a sample of 379 patients with diabetes supports a protective association with DR among those consuming high compared to low intake of PUFAs but only in those with good glycemic control [364]. This study did not differentiate between omega-3 and omega-6 PUFAs. A recent prospective analysis of 3482 participants with type 2 diabetes observed a 48% decreased risk of sight-threatening DR with self-reported consumption of 500 mg/day or more of LC omega-3 PUFAs [370]. The observed protectiveness of omega-3 intake on DR was hypothesized to be due to the antiinflammatory properties [371] of omega-3 oxylipins or via their proposed antiangiogenic properties [372] as shown by research in animal studies.

Diets rich in fiber, especially soluble fiber, have been shown to improve glycemic control and insulin sensitivity [373], and thus likely reduce risk for DR. This hypothesis is supported by previous findings of protective associations between consumption of high-fiber containing foods (e.g., fruits and vegetables) and DR, as previously noted [337–339,374]. The DCCT observed that intake of dietary

fiber (% kcals) was inversely correlated with progression of DR [363]. One of two studies [366,367] observed lower intake of fiber in persons with compared to without DR. More recently, a population-based, cross-sectional study of 1261 individuals with type 2 diabetes [375] observed a 41% and 24% increased odds, respectively, of overall and sight-threatening DR among persons with low compared to high consumption of fiber-rich foods with adjustment for confounding factors. However, total quantity or type of dietary fiber was not determined.

In summary, more research is needed to assess the effects of long-term calorie, dietary fat, and fiber intake with respect to incidence and progression of DR. The published studies of calories, dietary fat, and fiber have a number of limitations including the use of ecologic, case-control, or cross-sectional designs, dietary assessment methods, which do not adequately assess long-term dietary intake, lack of adjustment for confounding factors, and small sample sizes.

F Antioxidants

Hyperglycemia is thought to increase oxidative stress through a number of proposed mechanisms which include damage to DNA, lipids, proteins, and carbohydrates as well as functional alterations of a number of other metabolic pathways that promote oxidative stress (previously reviewed in detail elsewhere [376]). Increased oxidative stress is hypothesized to promote diabetic vascular complications such as DR [365,376]. The retina is especially susceptible to damage from reactive oxygen species due to the PUFA-rich endothelial cells of the retinal microvasculature [365,377].

Further, some studies have shown that individuals with diabetes compared to individuals without diabetes have lower blood levels of antioxidants [378,379], as well as lower carotenoids in the retina [20], perhaps as a result of increased oxidative stress. Antioxidant intake has been proposed to help alleviate the observed increased state of oxidative stress in individuals with diabetes and help prevent development of microvascular complications such as DR [380]. Supplementation of streptozotocin-induced diabetic rats for 12 months with antioxidant micronutrients resulted in less degeneration of the retinal microvasculature (indicating early signs of DR) [381] and better retinal function, mitochondrial homeostasis and less elevation in inflammatory biomarkers within the retina [382] than in nonsupplemented animals. However, numerous studies investigating associations between antioxidant micronutrients (primarily vitamins C and E) and DR in small patient or population-based samples have yielded conflicting results [383–385].

To date, insufficient data from robust epidemiologic studies exist to conclude that diets or supplements high in antioxidants prevent or slow DR. In a population-based cohort study no statistically significant associations were observed between dietary intake of vitamin C or vitamin E (assessed 6 years earlier) and prevalent DR [386,387]. In a population-based survey, serum vitamin C concentrations were unrelated to prevalent DR, but serum vitamin E concentrations were positively associated with increased odds of DR [388]. This relationship was attenuated when current supplement users were removed from the analysis. Mayer-Davis et al., in a different cross-sectional study, observed that the severity of prevalent DR was higher in subjects who had high intakes of vitamin C, in insulin users who had high intakes of beta-carotene, and in noninsulin users who had high intakes of vitamin E [389]. A recently published prospective study did observe protective associations between incident DR and vitamin C and carotenoid intake, but not with vitamin E [374]. Data from a clinical trial of vitamin E supplementation also did not observe differences in history of DR laser therapy between supplementation and placebo arms [390]; however, DR was not the primary endpoint for the trial. Associations of prevalent DR to short-term diet and blood nutrient levels in cross-sectional studies may be biased by the recent use of popular antioxidant supplements, particularly in people who may be experiencing more severe symptoms or complications of diabetes.

Most previous studies of antioxidants and DR have not been able to capture the measure of long-term exposure to these nutrients. In one study, participants who reported using multivitamins, vitamin C, or vitamin E supplements for 3 or more years before DR were assessed to have lower odds of DR [386]. It is possible that long-term use of antioxidant supplements may protect against DR. Only one smaller ($n = 97$) randomized clinical trial of patients with type 2 diabetes has reported the effect of antioxidant therapy with the primary outcome of DR [391]; however, the study failed to compare the change in DR stage over time between trial arms. Moreover, there exists only one [374] prospective study reporting data on the influence of dietary antioxidants on the onset or worsening of DR. Given the strong evidence for protection by antioxidants in animal studies, and the suggestion of benefit from long-term antioxidant use in one large observational study, additional prospectively designed studies are needed to better assess these relationships.

G Vitamin D

Over the last 5 years, there has been a rapid increase in the number of papers studying the association between vitamin D status and DR. For example, vitamin D has been shown to reduce the damage in cultured endothelial cells from

advanced glycation end products [392] formed in states of hyperglycemia and thought to propagate oxidative stress and inflammation. [393] The etiology of DR is hypothesized to involve hyperglycemia-induced chronic low grade inflammation [394] and advanced DR involves angiogenesis.

The majority of the work has been in cross-sectional [395–407] and case-control [408–412] studies with around half supporting a protective effect of vitamin D on DR [398,400,401,394,405,407,408,410,411]. Studies, other than those conducted in nationally representative surveys [398,392] and population-based cohorts [397,401], recruited participants from clinic settings. The degree to which this affects the generalizability of study findings is unknown. Other study limitations include small sample sizes ($n \leq 300$ for samples of individuals with diabetes) [395,399,403,394,404,407–410] and assessment of DR status from ophthalmologist examination rather than from standardized grading of retinal fundus photographs [395,396,393,403,405–412]. Only three studies to date have examined prospective associations between vitamin D status and risk of DR [413–415] with only one observing a protective association [414]. However, further adjustment of their multivariable model for Ghb, physical activity, or seasonal removed the statistical significance of the observed association. Studies of associations between polymorphisms in the VDR and DR have been inconclusive with some supporting [416–418] and others not supporting [419,420] possible associations.

Additional work in prospective epidemiologic studies are needed that can account for pertinent confounding variables as well as provide adequate cases to investigate associations between vitamin D status and PDR. Continued work in minority populations with the greatest burden of diabetes and the greatest risk for vitamin D deficiency (e.g., African Americans) [280] should be conducted.

H Summary

The last 20 years has provided a significant body of data suggesting that dietary intake and vitamin D status may be risk factors for DR with mechanisms affecting disease etiology that could extend beyond diet's influence on blood glucose control. Evidence from a large dietary modification trial has provided new evidence that fruit and vegetable-rich dietary patterns such as the MedDiet may protect against DR. Associations between DR and alcohol consumption, macronutrient intake, sodium intake, antioxidants, and vitamin D status still remain inconclusive. Prospectively designed studies are needed to evaluate the importance of these dietary components, as well as other healthy diet patterns, on the incidence and progression of DR in the general population. Given the broad aspects of diet that could protect against DR such data will particularly assist in making public health recommendations.

VI GLAUCOMA

A Introduction

Glaucoma is the leading cause of *irreversible* blindness worldwide, and is predicted to affect nearly 80 million individuals by 2020 [421]. Glaucoma is an umbrella term for a group of diseases that damage the optic nerve, the bundle of nerve fibers that connect the retina to the brain, causing loss of vision starting in the peripheral field of view. The most common form of glaucoma is primary open-angle glaucoma (POAG). In POAG, the "angle" where the cornea and iris meet is restricted. As a result, the flow of ocular fluid to nourish nearby tissues passes too slowly through the trabecular meshwork, increasing eye pressure and leading to progressive deterioration of the retinal ganglion cells that form the optic nerve. The impairment of vascular supply to the optic nerve head is an additional pathological process that is thought to contribute to the development of POAG [422].

Clinically, the focus of glaucoma treatment has been on management of intraocular pressure (IOP). Elevated IOP (reflecting either excessive aqueous humor production or inhibition of aqueous humor outflow) contributes to ganglion cell damage and progressive loss of vision, starting in the periphery of the field of vision. IOP can be modified surgically or through the application of topical medications [423]. However, glaucoma may develop in those who have normal IOP [424], suggesting that other factors may contribute to its pathology.

Age and family history of glaucoma increase risk for POAG. Globally, this condition is about two to three times more common among people of African than of European, Hispanic, or Asian ancestry. Risk has been higher in people who are obese and/or have diabetes and hypertension [436,437]. Diet could influence the occurrence of glaucoma, indirectly, by its influence on these chronic conditions. Diet can also influence IOP. The role of nutrition in both IOP and glaucoma development is still an emerging field. The current state of evidence linking diet directly and indirectly to glaucoma is summarized later.

B Obesity

A body of evidence indicates that a higher body mass index (BMI) is linked to higher IOP, the principle modifiable risk factor for glaucoma [427–430]. Change in BMI over 5 years was found to be associated with change in IOP during that time [431]. Increases in BMI, body fat percentage, and waist circumference were

prospectively linked to increases in IOP in a large cohort of Korean adults. A number of mechanisms have been put forth to explain the relationship between obesity and IOP, including high blood pressure, elevated blood glucose, increased blood viscosity, insulin resistance (and diabetes or metabolic syndrome), and oxidative stress. Hyperglycemia, which is common in individuals with high BMI, might reduce outflow of aqueous humor through the trabecular meshwork via glycosylation of extracellular matrix proteins [432] or by increasing oxidative stress (discussed later). Weight loss through diet and exercise may serve to lower IOP in glaucoma patients who are obese and/or have diabetes, but this hypothesis has not been tested in clinical trials. While there is convincing evidence that high BMI and diabetes mellitus are related to higher IOP, BMI has not been consistently related to the incidence of glaucoma [433].

C Antioxidants

A role for oxidative stress in the pathophysiology of glaucoma has emerged in recent years [434]. It has been suggested that chronic oxidative stress may contribute to death of retinal ganglion cells and to remodeling of the trabecular meshwork [435,436], an effect that may prevent proper draining of aqueous humor and increase IOP. High levels of reactive oxygen species can also contribute to signaling pathways that lead to cellular apoptosis. Therefore, dietary antioxidants could alter glaucoma risk. This includes sufficient levels of vitamins and minerals (iron, B vitamins, zinc, and selenium) that are cofactors for antioxidant enzymes (catalase, glutathione peroxidase, superoxide dismutase), glutathione, and food components that are direct antioxidants (vitamins C and E, carotenoids, and numerous other plant components).

Cross-sectional observational studies support a relationship between the status of antioxidants in the blood and the presence of glaucoma [426–439]. Likewise, similar studies have demonstrated that glaucoma patients have lower total antioxidant status of the aqueous humor [439–441], suggesting that a state of oxidative stress is present in the eye as well. Although total antioxidant status may be compromised, numerous studies have demonstrated that levels of antioxidant enzymes (e.g., glutathione peroxidase, superoxide dismutase) are *higher* in the aqueous humor of glaucoma patients [442,443], suggesting that the expression of these enzymes is upregulated in response to oxidative stress. Moreover, markers of oxidative DNA damage have been found to be elevated in the trabecular meshwork of glaucoma patients [444], suggesting that the tissue responsible for aqueous humor drainage is affected by oxidative stress. The trabecular meshwork may be particularly susceptible to oxidative stress, as it has poorly developed antioxidant defense systems relative to other ocular tissues [445].

Despite the evidence demonstrating a connection between oxidative stress and risk of glaucoma, little evidence from prospective cohort studies exist to support the idea that consuming dietary antioxidants can reduce glaucoma risk or progression. Although fruit and vegetable-rich diet patterns [338] and consuming a high number of fruits and vegetables [446] were associated with a lower likelihood of having glaucoma in cross-sectional studies, large prospective studies have observed no relationship between antioxidant-nutrient consumption and risk of developing glaucoma [447]. In addition, consumption of supplements containing vitamin A or vitamin E was not associated with glaucoma risk, although consumption of vitamin C supplements was associated with mildly decreased risk in the NHANES [448].

The inconsistency in relationships between the intake of fruit and vegetable-rich diets might reflect the possibility that only some fruits and vegetables lower risk more than others. This is suggested by a recent study in which total dietary nitrate intake (high in leafy greens and to lesser extents in certain fruits and vegetables) was associated with lower POAG risk (particularly with early visual field loss in the paracentral field of vision for which dysregulation of the ocular vascular system has been implicated) [449]. This finding contributes to a substantial body of evidence that suggests a key role of the nitrous oxide system in POAG pathogenesis, which may both elevate IOP and dysregulate ocular blood flow [450].

Leafy greens that are rich in L and Z might be protective against the development of glaucoma, as with other forms of age-related eye diseases. These carotenoids are known to have antioxidant effects (See Section II). Results of two small studies suggest that MP is lower in people with glaucoma. In one case-control study the density of L and Z in macular pigment (MP) were lower in glaucoma cases than controls [451] In another study, MP levels were lower in glaucoma patients who had a loss of the foveal ganglion cell complex, compared to glaucoma patients in whom this complex was intact [452]. MP level also correlated with retinal nerve fiber layer thickness and cup to disc ratio, both considered important indicators of glaucomatous optic neuropathy. However, higher dietary levels of L and Z have not been related to the prevalence or incidence or progression of glaucoma in the few studies which have examined these associations [446,447]. Variable abilities to absorb carotenoids and transport them into the eye (Section II) might explain the inconsistencies in these findings. Additional prospective studies of levels of L and Z in the diet or MP to the incidence and progression of glaucoma are needed.

There is generally a lack of randomized clinical trials that have directly examined the effect of antioxidants on

glaucoma incidence and progression. One 2-year supplementation trial in patients with preexisting glaucoma observed no effect of antioxidants (containing L and Z) with or without omega-3 fatty acids on visual field measures or ganglion cell thickness [453]. This may be too short of a period of time to observe a protective effect if there is one.

Ginkgo biloba extract, derived from a plant commonly used in traditional Chinese medicine, has received attention as a potent antioxidant that may be useful in the treatment of glaucoma [454]. Ginkgo biloba extract improved measures of visual field in patients with preexisting normal-tension glaucoma [455,456] and slowed the loss of the visual field in this subgroup of glaucoma patients [457]. These apparent benefits of ginkgo biloba for glaucoma patients may be related to its role as an antioxidant, or to improvements in the microcirculation feeding the retina, or to the inhibition of apoptosis in retinal ganglion cells [454]. Ginkgo biloba has gained some mainstream acceptance as a useful treatment for glaucoma, but only in normal-tension glaucoma patients, or in patients whose glaucoma has progressed despite successful lowering of IOP [458].

In summary, although there is considerable evidence to suggest a link between oxidative stress and glaucoma risk, there is less evidence to demonstrate that specific antioxidants can reduce this risk. There is also evidence that other components of certain fruit and vegetables (such as nitrates, or those rich in L and Z) might lower risk by mechanisms other than lowering oxidative stress, or in addition to it. At the current stage of knowledge, it is advisable that glaucoma patients, or those at high risk of glaucoma, get their antioxidants through a healthy diet rich in fruits and vegetables, as there is little evidence that high-dose antioxidant supplementation is either effective or safe in the long term.

D Omega-3 Fatty Acids

Animal research suggests that supplementation with omega-3 fatty acids may reduce IOP by increasing aqueous outflow [459], an effect expected to slow progression of optic nerve degeneration. Furthermore, omega-3 deficiency increased ganglion cell dysfunction when IOP is elevated [460]. Consistent with the idea that LC omega-3 PUFAs might play a role in the etiology of glaucoma, POAG patients were observed to have lower levels of EPA and DHA in several fatty acid fractions derived from red blood cells [461]. The authors speculate that omega-3 PUFAs may reduce risk of POAG by improving microcirculation around the optic disc, consistent with the role of n-3 fatty acids as inhibitors of platelet aggregation.

However, results of investigations in two large cohorts, followed prospectively do *not* support a protective role of omega-3 fats and POAG. In the Nurse's Health Study and the Health Professionals Follow-Up Study cohorts [462], and in the SUN cohort [463], a higher ratio of dietary omega-3 to omega-6 fatty acids were related to *higher* risk for POAG. One possible explanation suggested is that higher omega-6 consumption leads to greater availability of prostaglandin F_{2a}, an omega-6 derivative that is believed to reduce IOP [462]. Given the larger body of evidence suggesting that a higher dietary omega-3 intake may be beneficial for cardiovascular health and lowering AMD risk, lowering omega-3 fat intake is not recommended for the general population. Furthermore, other lines of evidence suggest a protective role for omega-3 fatty acids.

E Alcohol

Acute consumption of alcohol can transiently reduce IOP [464,465], raising the possibility that consistent, moderate consumption of alcohol over time would reduce the risk for glaucoma. It has been suggested that alcohol may reduce aqueous humor formation by the ciliary body, primarily through the inhibition of antidiuretic hormone [466]. In observational studies, which reflect the impact of alcohol over a longer term, relationships of alcohol to IOP are conflicting. Alcohol use was associated with lower IOP in one cross-sectional study [467], but with *higher* IOP in another [468]. Most often, alcohol intake has not been related to IOP [356,429,469–471]. In one large prospective study, there was a trend toward lower IOP in individuals consuming >30 g alcohol (approximately two drinks) per day [470]. The inconsistent relationships of alcohol to glaucoma risk might be explained by limited statistical power and variable adjustment for other lifestyle factors associated with alcohol. Furthermore, the range of habitual alcohol intakes is fairly narrow, making it difficult to study the effect of chronic binge drinking.

F Caffeine

Caffeine is a central nervous stimulant commonly consumed by most age groups and is found abundantly in coffee, dark colas, energy drinks, and certain teas. Caffeine has diverse effects throughout the body, raising the distinct possibility that caffeine influences eye health. Data from clinical trials suggest that consumption of caffeine can raise IOP [472,473,474], but other trials have not shown any effect [475,476]. A meta-analysis of randomized clinical trials revealed that acute consumption of caffeine can transiently increase IOP, but only in patients with preexisting glaucoma or ocular hypertension [477].

The increased IOP with caffeine consumption may be attributable to increased aqueous humor production or

inhibition of aqueous humor drainage. Caffeine raised IOP in dogs by increasing aqueous humor production without affecting drainage [478]. The same group demonstrated that caffeine- induced structural changes in the ciliary epithelium that would support transportation of aqueous humor [479]. Acute caffeine consumption increases systemic blood pressure [474] and this may also contribute to aqueous humor production via increased filtration through the ciliary body.

Results from the Blue Mountains Eye Study corroborate this finding, as regular coffee drinking was cross-sectionally linked to higher IOP in glaucoma patients only [480]. These findings from cross-sectional research and randomized clinical trials support the recommendation that glaucoma patients limit caffeine consumption. Although research has not yet linked caffeine to visual field loss in glaucoma patients, it is plausible that higher IOP with caffeine use would contribute to the onset of blindness.

While there may be a connection between caffeine intake and IOP in patients with pre-existing glaucoma, little data suggests that regular caffeine consumption increases risk for glaucoma. Data from the Nurses' Health Study and the Health Professionals Follow-up Study revealed that caffeine consumption was not prospectively linked to higher rates of POAG [481]. However, a significant relationship was found for those with a family history of glaucoma, suggesting that the effect of caffeine on glaucoma risk has a genetic component. It is plausible that the transient effect of caffeine on IOP is not sufficient to damage the retina, or that the IOP response is attenuated when caffeine is consumed habitually. More longitudinal research is needed to firmly establish the relationship between caffeine dose, IOP, and glaucoma risk, and to discern whether this relationship varies according to glaucoma diagnosis.

G Summary

There is considerable emerging evidence to suggest a link between pathological processes of glaucoma (oxidative stress, elevation of IOP) and diet components. Diet might also lower risk for the development of obesity and chronic diseases that are more common in people with glaucoma. The current body of scientific evidence on relationships of diet to glaucoma suggests that fruit and vegetable-rich diets may lower glaucoma risk through either or both means. However, the data are limited and insufficient to support the possibility that the intake of specific foods or dietary supplements is likely to lower glaucoma risk. At the current stage of knowledge, it is advisable that glaucoma patients, or those at high risk of glaucoma, eat healthy diets rich in fruits and vegetables.

VII CHAPTER SUMMARY

Scientific evidence suggests that *nutrition matters* in maintaining eye health, as with other parts of the body. That is, there is mounting evidence for substances in food which exert effects that are likely to promote or delay the development of the most common and costly causes of vision loss: age-related cataract and macular degeneration and DR. An emerging, but limited, body of evidence suggests that several specific aspects of healthy diets and lifestyles might lower glaucoma risk, as well. It is possible that healthy diets and lifestyles matter more (or less) in people genetically prone to these processes. Healthy diets, other healthy lifestyles, and genetic risk might work synergistically to lower risk for age-related eye diseases. However, the evidence is insufficient to make separate recommendations for individuals based on genetic risk.

Despite the evidence that *nutrition* matters, evidence that supplements of single or combination of nutrients slow age-related cataract, macular degeneration, glaucoma or DR is more limited. An exception is for the intake of high-dose antioxidant supplements and zinc in people with AMD, which is considered a standard of care for slowing the progression of AMD. There is no strong evidence that these or other supplements *prevent* this disease, or other age-related eye diseases. In most cases, nutrient-dense foods provide a larger array of potentially protective substances than pills. Increasing evidence suggests a larger impact of foods than supplements. An exception may be for vitamin D, which is sometimes hard to obtain from natural food sources. Vitamin D status might be most important in extreme northern and southern hemispheres which provide inadequate UV light in winter to permit the synthesis of this vitamin in skin.

Optimal ocular health may begin with gestation and infancy and continue into old age. Recent evidence has emerged to suggest a possible role of L and Z in gestation and infancy; a role in lifelong health has been proposed, but not studied. The most sustainable means of promoting eye health through nutritional means in populations over the long term may be to foster the ability to breast feed and assure access to a variety of foods, a large proportion of which are plant foods.

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