Today, more than ever, ophthalmologists are being asked to answer patients’ questions about vitamin supplements and nutrition. The importance of diet and eye health is not new. The need to obtain adequate vitamin A to prevent xerophthalmia and night-blindness, particularly where malnutrition is rampant, has been known for decades (reviewed by Underwood and Arthur1). More recently, interest has been directed at whether nutritional supplements might prevent loss of vision caused by degenerative conditions that become more common as we age, such as cataract and macular degeneration.

The benefits of nutritional supplements may have broad public health importance. Results of the Age-Related Eye Disease Study (AREDS)2 suggest that nutritional supplements may be one of the most promising means discovered, to date, of delaying end-stage age-related macular degeneration (AMD), the most common cause of blindness among older people in developed countries.3 There is some interest in the possibility that supplements might slow the progression of diabetic retinopathy;4 the number 1 cause of blindness among working-age people.5 Moreover, some studies (reviewed herein) suggest that supplements might slow the development of cataract, which affects more than half of us by age 75 years.5,6 In addition, surgery for cataracts is expensive, accounting for more than 12% of the Medicare budget, which was last evaluated in 1992.7 As these age-related conditions become more prevalent in a population that is aging,8 the potential public health benefits of supplements are large. However, scientific evidence to support these benefits is stronger in some cases than others.

The purpose of this review is to provide guidelines for clinical practice on recommending the use of nutritional supplements for reducing the development of eye diseases that are common among older people, based on the current evidence. While supplementation may be considered in treatment of more rare inherited retinal degenerations, this will not be considered in the current review. Benefits of several specific types of supplements that are commonly available for slowing the development of common eye diseases and risks are considered in separate sections that follow. We also discuss issues for clinicians to consider as more scientific evidence becomes available, from the many studies that are expected to emerge during the next few years.

Ultimately, any physician hopes to improve the overall health and well-being of patients, rather than merely focus on eye health. Therefore, we will also briefly consider the evidence that describes the benefits and risks of supplements to overall health. For a thoughtful and more thorough discussion of this larger topic, we refer readers to the recent article by Willett and Stampfer.9

Epidemiologic Studies

Extreme deficiencies of many vitamins and minerals have been shown to cause cataract or retinal dysfunction in experimental animals, particularly under extreme experimental conditions in the laboratory (previously reviewed10,11). In humans, the results of epidemiologic studies are needed to determine whether more modest fluctuations of vitamins and minerals influ-

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ence age-related degenerative conditions under the conditions that are unique to people. Studies of large and diverse populations provide an estimate of the magnitude of impact that changes in vitamins and supplements have on the risk of common eye diseases, relative to other medical or lifestyle changes that can be recommended to patients (such as stopping smoking, controlling hypertension, losing weight, etc.). Results of observational investigations and clinical trials are summarized in the following sections.

MULTIVITAMINS

Benefits to Eyes

Multivitamins usually contain all essential vitamins that one would expect to get from foods at levels that meet the nutrient requirement of nearly all healthy individuals. These nutrient levels are the highest requirement of the recommended dietary allowances (RDAs) for specific age and sex groups. Many, but not all, also contain the essential minerals at levels that we typically get from food. The RDAs are set at levels that are judged by panels of scientists to be those needed to promote health in most groups of healthy people. However, they may not be adequate for individuals with unique needs caused by the presence of disease.

Observational studies in 8 different populations indicate lower rates of cataract or cataract extraction among people who use multivitamin supplements, compared with only 2 studies that observed no association (previously discussed and more recently reported). However, in the absence of randomized controlled clinical trials, there is no proof, at this time, that multivitamins lower the risk of cataract. The possibility exists that other aspects of a healthy lifestyle among supplement users explain the lower rates of cataracts in the observational studies.

Unfortunately, we may never have the guidance of clinical trials to answer the questions of benefits of multiple supplements on cataract in the American population. If multivitamins do lower risk, as the observational studies consistently suggest, then many years may be required to observe a benefit in clinical trials—yet, such trials are generally conducted for less than 10 years.

To date, there are results of only one clinical trial of multivitamin supplements. This trial, in a malnourished population in China, tested the influence of using multivitamins for 5 years on the prevalence of cataract. A lower prevalence of cataract was observed in users than nonusers of multivitamins, among persons 65 to 74 years of age (but not among persons 45 to 64 years of age). The results of this 5-year study suggest that short-term effects may be possible. Considered in conjunction with observational studies in which only long-term supplementation was associated with lower risk, these results suggest that short-term effects might be limited to malnourished populations. This result will not likely be duplicated in the United States, because people with poor diets are not usually subjects in clinical trials. If the influence of multivitamins on cataract is gradual, over many years, or limited to people with very poor diets, then the possible benefits of multivitamins on cataract are not likely to be experimentally proved.

A 9-year, randomized, placebo-controlled clinical trial of the influence of multivitamin supplementation on cataract development and progression is currently under way in Italy in about 1000 people. This study is likely to provide new insights. Also, in the next 5 to 10 years, the results from many long-term prospective observational studies that are currently under way will provide future insights about whether multivitamins themselves or other associated lifestyles are responsible for lower cataract risk among people who use supplements. If people who take multivitamin supplements consistently have a lower risk of cataract across many different segments of a population, then there is a lower possibility that the apparent beneficial effect is caused by other unrevealed factors.

In contrast, there is no evidence that use of multivitamins slows the onset or progression of AMD, although it has been investigated in several populations (previously discussed and more recently reported). This may be because people who begin to show signs of developing macular degeneration may decide or be advised to start taking nutritional supplements. This change in supplement use (depending on having signs of the conditions) may confound relationships of long-term supplement use to age-related maculopathy. This would make it difficult to observe a protective association if one existed. Such uncontrolled confounding or noise, inherent in any epidemiologic study, may overwhelm any small beneficial effect. It remains conceivable that multivitamins may ensure adequacy of intake of several nutrients that are important to the health of the retina and retinal pigment epithelium. However, evidence of beneficial effect may be hard to generate because supplementation is common, particularly in people who have a family history of early signs of macular degeneration.

Benefits to Overall Health

Considering the evidence that multivitamins might help delay cataract, even if there is a lack of evidence that multivitamins influence macular degeneration, why not recommend a general multivitamin for health “just in case”? The idea that multivitamins are good for general health remains controversial. There is currently some evidence that suggests multivitamins result in fewer days of illness due to infection. However, evidence in observational studies that multivitamin users have lower rates of common chronic diseases such as coronary disease and/or colon cancer is scarce. Evidence of effectiveness of multivitamins in clinical trials is lacking. Fletcher and Fairfield recently argued that subclinical deficiencies of some nutrients such as folate, vitamin D, and vitamin B are common in older people and may increase risk of cardiovascular disease, cancer, and osteoporosis; they recommend the use of multivitamins despite the lack of strong evidence of effectiveness.
Risks

There is no direct evidence to support the notion that multivitamin-mineral supplements (those that meet 100% of RDA) pose a health risk. However, special cautions may apply in certain circumstances; for example, there may be a risk of people getting high levels of vitamin A in the diet (found in meat, liver, and milk sources) or in breakfast cereals or meal replacement beverages. Evidence suggests that excessive dietary intake of preformed vitamin A (retinol) is associated with increase risk of osteoporosis and hip fractures. The safe upper limit for intake of vitamin A is 3000 µg retinal equivalents. This is roughly 4 times the RDA of 700 µg/d for women and 800 µg/d for men. Multivitamin preparations of vitamin A typically provide 800 µg/d, well below the safe upper limit. The average intake of vitamin A from foods in a nationally representative population in the last decade was about 1000 µg/d. Thus, for average Americans, taking a multivitamin supplement still results in a level of intake only 2 times the RDA. However, many people have levels in their diets that are higher. For example, among women in the Nurses' Health Study, the average vitamin A (retinol) intake from foods in women in the upper 20 percentiles for intake of vitamin A was 2500 µg/d. Using a multivitamin that contains the RDA for vitamin A along with a diet rich in vitamin A may result in a total level of intake above the safe upper limit.

A final concern is giving patients the impression that multivitamins will provide adequate micronutrients, reducing the effort to obtain them in foods. Micronutrients in foods may be more bioavailable. This may be the case for zinc, which is better absorbed from animal sources.

An advantage of consuming the nutrients we need from foods instead of supplements is that food provides different chemical forms of a nutrient that may be important. For example, supplements contain only the vitamin E compound α-tocopherol, which is thought to have the highest vitamin E activity, even though γ-tocopherol constitutes the majority of vitamin E in the diet. There is mounting evidence for unique or more potent properties of γ- and δ-tocopherols in a variety of mechanisms that may be involved in preventing the pathogenesis of chronic diseases (reviewed previously). Moreover, supplementation with α-tocopherol reduces serum and tissue levels (previously reviewed) of γ- and δ-tocopherols that we get from foods. Therefore, the nutrient form found in supplements may not be sufficient and may actually reduce the bioavailability of other nutrients, although there is currently little evidence of specific health risks.

A third advantage to relying on the foods we eat, rather than supplements, is that foods contain other chemicals that have health benefits. Currently, evidence is building to support the benefits of many food components not contained in supplements. For example, the plant pigments lutein and zeaxanthin may be important for eye health and general health (discussed in a later section). There are likely to be many other important food chemicals of which we are currently unaware. Thus, multivitamins may give patients a false sense of security about their nutritional status that will reduce the intake of potentially important food components.

HIGH-DOSE ANTIOXIDANT SUPPLEMENTS

Benefits to Eyes

There is substantial evidence that the potential for oxidative stress in the retina and lens is high and that oxidative stress contributes to the development of cataract and degenerative changes in the retina. Many supplements are marketed to prevent age-related eye diseases that contain antioxidants such as vitamin C (given as ascorbic acid) and vitamin E, carotenoids, and zinc at high levels. Levels of other nutrients in these supplements are generally 2 to 10 times the RDA. Selenium, which, at high doses, has been shown to cause cataract, is contained in lower levels.

There are some data to support a beneficial effect of high-dose antioxidant supplements in delaying or preventing cataracts, but overall the body of evidence is weak. In 2 large clinical trials, high-dose antioxidants did not delay cataract over approximately 6 years. However, in a smaller trial (158 persons who completed the 3-year study), antioxidant supplements did delay early lens opacification. In the latter trial, blood levels of antioxidants were higher in the supplemented group, and lower in the control groups, than in the AREDS, which might explain the differing results. However, confirmation of this smaller trial is important to rule out the possibility that chance or some features of the study design, implementation, or population explain the positive results that differ with the results of other clinical trials. Also, while this trial and results of several observational studies have reported lower occurrence of lens opacities among people taking antioxidant supplements, they did not demonstrate benefits beyond those that would be possible from general multivitamins.

In contrast to cataract, there is evidence from a large, randomized clinical trial that antioxidant supplements may benefit people with AMD. In the AREDS, patients taking a specific high-dose antioxidant supplement containing ascorbic acid (500 mg), vitamin E (400 IU), and beta carotene (15 mg) along with high-dose zinc (80 mg as zinc oxide together with 2 mg of copper as cupric oxide) had a 28% lower rate of clinical progression to end-stage AMD (either neovascular macular degenerative or geographic atrophy) if they already had intermediate or advanced stages of this condition. No benefit was observed among patients with earlier stages of age-related maculopathy (drusen <125 µm or pigmentary abnormalities without large drusen). However, the power to detect a long-term benefit in patients with early-stage AMD, considering the low rate of progression to end-stage disease in this group (1.3% during 6 years) was low. The AREDS was not long enough or large enough to rule out potential benefit to people with early age-related maculopathy. How
ever, in recent clinical trials of high-dose vitamin E (500 IU)\textsuperscript{33} or vitamin E (50 IU) and/or beta- carotene (20 mg),\textsuperscript{34} no benefit was observed among the study sub-
jects, most of whom had no or mild signs of AMD.\textsuperscript{27}

How can we generalize the results of AREDS to patients in indi-
vidual practices? People who par-
ticipated in AREDS were healthier
than the general population, hav-
ing half the rate of mortality of a
comparable general population.\textsuperscript{35} The
benefit could be greater or less in a
population that is less healthy. We
will be more certain about the mag-
nitude of impact and ability to
project this potential benefit across
the broader population of people
with AMD when there are results
from long-term prospective cohort
studies, which generally represent a
wider cross section of the popula-
tion. Physicians sometimes are asked
whether people with a family his-
tory of AMD might benefit from the
high-dose supplements tested in
AREDS. To date, there is no evi-
dence to support a benefit of these
supplements and some evidence of
risk (discussed in the next section).

Antioxidants have been hy-
pothesized to improve insulin sen-
sitivity or to reduce the complica-
tions of diabetes in the eye and
elsewhere. Despite substantial ex-
perimental and clinical evidence of
high levels of oxidative stress in
people with diabetes and of the in-
volvement of oxidative stress in the
development of complications, evi-
dence of a protective effect of anti-
obxidants has not been demonstrated
in either large-scale prospective cor-
hort studies or in clinical trials (re-
viewed by Rosen et al\textsuperscript{9}).

Moreover, results from 3 ob-
servational studies do not suggest
lower risk of prevalent retinopathy
among people with diabetes who
have higher intakes of vitamins C or
E from foods and supplements.\textsuperscript{25-27}

However, the changing patterns of
eating and supplementation in
people with diabetes make poten-
tial protective effect hard to ob-
serve in studies, such as these, that
use a cross-sectional design. In one
of these studies, in which diet and
supplement information was col-
lected 6 years before retinal photo-
grahs were obtained to assess reti-
nopathy in the Atherosclerosis Risk
in Communities Study, the use of
supplements containing ascorbic
acid or vitamin E for 3 or more
years was associated with lower
risk of retinopathy.\textsuperscript{37} However,
because of the overall unsupportive
epidemiologic data at this time, the
value of antioxidant supplements in
slowing or preventing diabetic reti-
nopathy is unknown and prospec-
tive studies and clinical trials are
needed to better understand poten-
tial benefits.

Benefits and Risks
to Overall Health

The larger body of current data does
not support other health benefits of
high-dose antioxidants taken indi-
vidually or in combination on over-
all health.\textsuperscript{9} While some early stud-
ies suggested lower rates of heart
attacks among people who take vi-
tamin E at levels higher than 100 IU,
a level only attainable from supple-
ments,\textsuperscript{38,39} numerous other clinical
trials have shown no or limited ben-
efit of vitamin E in supplements (re-
viewed by Willett and Stampfer\textsuperscript{9}), es-
pecially those with high risk of heart
disease. Recently, high-dose anti-
obxidants in people who were also tak-
ing high doses of niacin and statin
drugs resulted in an unexpected re-
duction in high-density lipoprotein
levels, and the risk of heart attacks
and strokes was increased.\textsuperscript{40} The
pos-
sibility that vitamin E will help, rather
than hurt, people at earlier stages of
atherosclerosis has not been demon-
strated but is still being studied.

Oxidative stress has been hy-
pothesized to contribute to the de-
development of Alzheimer disease,
as well as cancer. Studies of the ben-
enefits of antioxidant supplement use
in lowering the risk of Alzheimer dis-
ease have conflicting results.\textsuperscript{41-43}

Similarly, clinical trials of specific an-
tioxidants (ascorbic acid, vitamin E,
and beta carotene) usually have not
supported the benefit in prevent-
ing cancer, with the exception of vi-
tamin E in prostate cancer in male
smokers and selenium in prostate,
lung, and colon cancer (reviewed by
Willett and Stampfer\textsuperscript{9}).

There are other added health
risks associated with the consump-
tion of nutrients at these high lev-
els. After consideration that vitamin E consumption results in slightly
higher risk of hemorrhagic stroke,
the Food and Nutrition Board set an
intake of up to 1000 IU of vitamin E
to be safe.\textsuperscript{35} Short-term (4 months)
vitamin E supplementation of less
than 800 IU showed no adverse ef-
effects on plasma lipid or lipoprotein
profile, white blood cells, platelet
numbers, or bleeding time.\textsuperscript{44} How-
ever, high-dose supplementation
may warrant caution when anti-
thrombotic compounds such as as-
pirin are taken, because of a de-
crease in platelet adhesion and
possible bleeding (previously re-
viewed by Horwitt\textsuperscript{45}).

Previous studies have shown
that high-dose supplemental beta
carotene (≥20 mg) increased the
risk of lung cancer.\textsuperscript{46,47} There is cur-
rently no upper tolerable intake for
beta carotene, but the Dietary Re-
ference Intake Committee of the
Food and Nutrition Board does not
recommend consumption of beta
carotene supplements for the gen-
eral public.\textsuperscript{12}

Clear benefit of high-dose an-
tioxidant supplements in slowing
progression of AMD is strongly sug-
gested by the results of the AREDS.
Because of potential risks for other
health conditions, we should be cau-
tious in recommending supplemen-
tation at high levels. Nutrients taken
in the high doses that are in such
supplements have pharmacologic
benefits and risks that may not be
present when consumed at the
physiologic levels provided in foods.
With time, it is likely that we will
have a better understanding of which
diseases high-dose antioxidants may
most likely benefit and which may
be exacerbated. An understanding of
a patient’s clinical and family his-
tory may guide a physician in mak-
ing recommendations that are tai-
lored to the diseases a person is likely
to be at risk for. At this time, such
knowledge is limited.

However, some general guide-
lines for maximizing benefit and
minimizing harm can be consid-
ered. If high-dose antioxidant
supplements are taken, the risk may
be less if several are taken concur-
rently. Antioxidant enzymes and mi-
cronutrients interact with each other
in a chain of events to lower oxidative stress within cells. If one element of this complex set is taken in high levels, there is potential for a perturbation of this balance and greater harm. Combination supplements and concurrent intake of a balanced diet may lower the chance for harm. Some antioxidants, like vitamin C, have been shown to be pro-oxidants in high levels or under certain conditions. For these reasons, patients who are advised to take antioxidants can be given guidance about prudent levels to consume (Table 1), the use combination preparations, rather than single nutrients, and the importance of eating a well-balanced diet.

ZINC

Zinc concentrations are high in the retinal pigment epithelium, relative to other tissues in the body, where it may protect the eye from age-related damage as a cofactor for antioxidant enzymes or other enzymes that are important to normal functioning of the retinal pigment epithelium cells (reviewed by Mares-Perlman and Klein). Alternatively, zinc may protect against the effects of inflammation. A possible role of inflammation in the pathogenesis of AMD is suspected.50

High-dose zinc supplements (80 mg/d, which is 5 to 10 times above the RDA in men and women58), together with antioxidants, were shown in the AREDS to reduce the risk of progression to advanced AMD among patients who already had extensive drusen. This level of zinc is above the recommended upper tolerable limit for zinc intake (Table 1). The zinc in this study was provided as the zinc oxide salt. Because of the different bioavailability of different zinc salts that are available in supplements,54 the effective and safe level provided by other zinc supplements (such as zinc gluconate or zinc sulfate) may differ. This benefit of zinc was similar to that provided by antioxidants alone or in combination with zinc. This result is in agreement with one52 but not another smaller and shorter-term clinical trial of zinc supplementation. Observational studies in 2, 54, 55 but not 2 other, populations also support the possibility of lower risk of certain types of age-related maculopathy (ARM) among people with higher intakes of zinc. Thus, the evidence generally suggests that zinc supplementation may reduce the progression of AMD in people who already have intermediate stages, but the influence on early stages is unclear.

Benefits and Risks to Overall Health

The influence of zinc on other aspects of health has been controversial. Studies of benefit of zinc on protection against the common cold are conflicting.57 There are no other reports, to our knowledge, that zinc supplements benefit overall health. There are, however, several cautionary reports on the possible adverse health effects of zinc supplementation. Acute zinc toxicity is fairly rare. However, excess zinc ingestion (100-300 mg/d) has been observed to result in gastric pain, nausea, and dizziness.58 Long-term excess zinc supplementation may reduce copper or iron absorption.58 Zinc supplementation of only 50 mg/d has been shown to decrease high-density lipoprotein cholesterol, but this may be secondary to interference with copper absorption. In the AREDS, zinc supplementation (together with copper) did not significantly influence blood lipid levels, but longer-term effects have not been studied.

Zinc supplementation resulted in more frequent hospitalizations due to genitourinary conditions and self-reported anemia (but not hematocrit) among AREDS participants. However, overall mortality was not higher during the 7-year period. Negative disturbances in glucose homeostasis have been documented with large-dose zinc supplementation in mice and in some patients with type 1 and type 2 diabetes mellitus. There is also evidence to suggest that zinc might play a role in the initiation and promotion of a variety of neoplasias, and a recent report of higher rates of advanced prostate cancer among men who took either high doses of zinc (>100 mg) or zinc supplements for longer than 10 years. The relationship between zinc supplementation and diabetes and cancer has not been well studied.

Until there is more information about the safety of zinc supplements, caution is warranted. It is easy to overdose on zinc, as it is for other minerals, because the body does not have efficient ways to eliminate excesses as it does for water-soluble vitamins. The National Academy of Sciences has currently set an upper limit of safety at 40 mg/d for adults. This is based on the interference with copper status. Some supplements (such as the one used in AREDS) also provide copper, which would reduce concern regarding the influence on copper status. However, the longer-term impact of taking high levels of zinc in supplements and the impact in broader populations of people are currently unknown. Because zinc was not a frequent component of vitamin supplements before 1980, the long-term risks of supplementation with this nutrient, particularly at high levels, have not been well studied.

How Much Zinc Should Be Taken?

The current recommended dietary intake is 8 mg/d in women and 11 mg/d in men. Factors that might increase

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Table 1. Recommended Daily Levels of Nutrients

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended Dietary Allowance for People Aged &gt;50 y</th>
<th>Daily Tolerable Upper Intake Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid (vitamin C), mg</td>
<td>75-90</td>
<td>2000</td>
</tr>
<tr>
<td>Vitamin E, mg</td>
<td>15</td>
<td>1000*</td>
</tr>
<tr>
<td>Zinc, mg</td>
<td>8-11</td>
<td>40†</td>
</tr>
<tr>
<td>Selenium, µg</td>
<td>55</td>
<td>400</td>
</tr>
</tbody>
</table>

*Levels of vitamin E that are healthful may be lower for individuals who currently take aspirin or lipid-lowering medications.
†Supplements that contain zinc in excess of this amount should also provide copper to minimize potential adverse effects, discussed in the “Benefits and Risks to Overall Health” subsection of the “Zinc” section.
the level of zinc needed in a supplement are vegetarian diets, intake of iron supplements, and heavy alcohol intake (previously reviewed). However, for most people, it is currently prudent to get adequate zinc by eating meats and drinking milk. In general, zinc bioavailability from a diet that is high in animal protein, as compared with vegetable protein (such as soy), is high. Standard multivitamins with minerals provide zinc (13 mg/d) at levels that are commonly provided in foods.

**LUTEIN AND ZEAXANTHIN**

**Possible Benefits to Eyes**

Recent attention has focused on dietary components that are not essential nutrients, but may otherwise have beneficial health effects. The potential for the plant pigments lutein and its isomer zeaxanthin to slow the development of age-related eye disease is under investigation. These are plant pigments from the carotenoid family, like beta carotene. Unlike beta carotene, they cannot form vitamin A. Their importance to eye tissues is suggested by the fact that they are the only carotenoids in the eye, unlike all other body tissues, which contain a wide variety of carotenoids such as beta carotene. This may be due to their abilities to absorb blue light, to function as antioxidants, or both. Evidence (reviewed by Mares-Perlman et al) suggests that lutein and zeaxanthin may reduce the risk of developing age-related macular degeneration. Currently, however, the evidence is far from conclusive. There are many pieces of evidence still to be evaluated and inconsistencies across studies. There is also the untested possibility that lutein and/or zeaxanthin may improve vision or slow progression once these conditions are present.

**Overall Benefits and Risks to Health**

The intake of lutein and zeaxanthin has been associated with lower risk of cardiovascular disease or cancers in some previous studies (reviewed by Mares-Perlman et al). However, there are few studies that evaluate the association with overall health. Also, as is the case with eye diseases, there is no experimental proof that lutein and zeaxanthin benefit health.

Long-term risk of taking lutein supplements is unstudied. For this reason, it is prudent to rely on foods to get these pigments or consider taking levels in supplements that are commonly consumed from foods. The average intake in Americans is 1.3 mg/d; 10% of Americans consumed more than 6 mg/d. Because lutein can compete with other carotenoids for absorption and because harmful effects of other similar carotenoids (beta carotene, as discussed earlier) have been observed, taking higher levels is not recommended before more is known.

**HERBALS**

Herbal medicines have long been used in some cultures to improve eyesight. Today, a wide variety of herbal supplements sit aside more traditional nutrient mixtures in the “eye supplement” section of drug stores. Some preparations on the market combine high-dose antioxidant mixtures with herbal ingredients.

One such herbal supplement is bilberry, a species of berry native to northern Europe, Asia, and North America that is closely related to blueberries. These contain anthocyanin pigments that give the characteristic color of blueberries, flavonoids, and a variety of other phenolic compounds. The popularity of bilberry in Japan and Korea relates to the belief that it improves night vision. This may be due to the carotenoid content of bilberries, which contain vitamin A activity, or due to independent influences of anthocyanin, for which there is some evidence of effectiveness but limited to small studies (reviewed by Camire). The effectiveness and safety of such herbal supplements are highly discussed in marketing literature but remain unsubstantiated in the scientific literature.

**RECOMMENDATIONS**

Considering the evidence discussed in this article, we offer the following recommendations for clinicians.

Current evidence supports the benefit of specific supplements (that contain 500 mg of ascorbic acid, 400 IU of vitamin E, and 80 mg of zinc with 2 mg of copper) and beta carotene (25,000 IU) in patients who already have intermediate stages of AMD in slowing progression to end-stage disease. The short-term safety of this supplement is suggested in healthier-than-normal people who participated in this trial. However, longer-term safety is unknown. For these reasons, the following cautionary notes are made. Patients who may be at high risk for adverse effects should be monitored, including (1) patients with diabetes (for possible glucose intolerance with zinc), (2) patients who take aspirin or have a history of hemorrhage or easy bruising (there is evidence that the high dose of vitamin E may contribute to a tendency to bleed), and (3) patients who are currently using statins to lower blood lipid levels; this formulation might, because of the high vitamin E levels, lower high-density lipoprotein cholesterol levels and the cholesterol-lowering response to statins. Smokers should be advised to take formulations without beta carotene. Patients should be advised to discontinue any other supplements that contain these nutrients except a multivitamin that contains levels that are needed daily from foods (the RDAs).

Because there are likely to be other benefits from food components that are not contained in supplements that we do not yet understand, such as the benefit of the plant pigments lutein and zeaxanthin and possibly vitamin E compounds that are not contained in supplements, patients should also be advised to follow the US dietary guidelines for healthy eating. These guidelines include, among other things, getting 3 to 5 servings of vegetables and 2 to 4 servings of fruits, 2 or 3 servings of dairy products, and 2 or 3 servings of meats, fish, eggs, or beans daily. If getting the adequate number of servings of fruits and vegetables and including among them good sources of lutein (dark-green vegetables) is not likely, a lu-
tein supplement that contains levels that are likely to come from foods (1-6 mg) is advisable while research on the specific benefits and risks of consuming these carotenoids continues.

Prevention Against Early ARM or Diabetic Retinopathy

Currently, there is no evidence that taking supplements prevents the early stages of ARM or the development of diabetic retinopathy. Patients who have a family history of these conditions should weigh the many potential adverse effects of supplement use against the unproven benefit. Getting adequate nutrients and other food components in a healthy diet (as discussed earlier) may be the best and safest insurance against nutrient inadequacy contributing to risk of ARM in the future. If patients decide to take supplements, risk is minimized by (1) taking multivitamin or combination supplements rather than single supplements and at levels that are close to the RDA and do not exceed the upper tolerable limit set by the Food and Nutrition Board (Table 1); and (2) avoiding excessive vitamin A intake in supplements by taking supplements that provide vitamin A as beta carotene, rather than preformed retinol, or avoiding concurrent use of vitamin-fortified cereals, high dietary intake of vitamin A (meats and milk), and liquid meal-replacement supplements (Table 2).

Prevention of Age-Related Cataract

Taking multivitamins may slow the development of age-related cataracts, but because this is unproven, patients should consider taking multivitamins on the basis of overall health benefits (providing nutrients to meet daily needs because of inability to eat a healthful diet) or risks (the possibility of hip fracture risk being increased if vitamin A intake from all sources combined is high, as discussed previously). Diets that meet the dietary guidelines may be the safest way to obtain adequate nutrients and have the added benefit of providing nonnutrient diet components such as lutein and zeaxanthin that may also lower risk of cataract.

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REFERENCES


Table 2. Good Dietary Sources of Nutrients Important to Eye Health

<table>
<thead>
<tr>
<th>Vitamin E</th>
<th>Vitamin C</th>
<th>Zinc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole grains, nuts</td>
<td>Fruits and vegetables</td>
<td>Meat, poultry, fish, and dairy products</td>
</tr>
<tr>
<td>and legumes; polyunsaturated oils (vegetable oils);</td>
<td>(especially citrus fruits, melons, and broccoli)</td>
<td>(particularly dark leafy greens and those that are yellow or green)</td>
</tr>
<tr>
<td>monounsaturated oils (olive oil)</td>
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