1040-5488/14/9108-0821/0 VOL. 91, NO. 8, PP. 821–831
OPTOMETRY AND VISION SCIENCE

FEATURE REVIEW ON LINE

Nutrition and Age-Related Macular Degeneration: Research Evidence in Practice

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ABSTRACT

Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment in developed countries. In the absence of effective treatments to slow AMD progression, it is predicted that the prevalence of AMD will double over the next 20 years. One area of significant interest is the potential role that nutrition may play in preventing and/or delaying the progression of AMD. Specifically, is there any benefit in oral antioxidant and/or mineral supplementation? This review critically evaluates the currently available evidence relating to nutrition and AMD, with particular reference to the key findings of two large National Eye Institute–sponsored clinical studies, namely, the Age-Related Eye Disease Study (AREDS) and AREDS2. Topical controversies relating to nutrition and AMD are considered and analyzed in the context of the published literature to guide practitioners through assessing the merit, or otherwise, of common claims. This article provides a foundation for clinicians to provide informed advice to AMD patients based on available research evidence.
(Optom Vis Sci 2014;91:821–831)

Key Words: age-related macular degeneration, nutrition, diet, nutritional supplements, vitamin, mineral, antioxidant, zinc, AREDS, drusen

Age-related macular degeneration (AMD) is the leading cause of irreversible vision impairment in developed countries, accounting for more than 50% of blindness in the United States.[1] In the context of continued worldwide demographic shifts toward enhanced longevity, and in the absence of effective treatments to slow AMD progression, it is predicted that the prevalence of AMD will double over the next 20 years.[2] Clinically, AMD manifests as a spectrum of retinal changes that occur within a two-disc diameter radius of the fovea. In the early stages of AMD, a key ocular fundus sign is the development of drusen, consisting of focal accumulations of lipoproteineous material located between the retinal pigment epithelium (RPE) and Bruch's membrane. Drusen may be accompanied by disruptions of the RPE, as evidenced by areas of hyperpigmentation or hypopigmentation. The disease can then progress to geographic atrophy (GA) of the RPE and/or the development of choroidal neovascularization (CNV), which may both be associated with significant visual loss. Although effective treatments of neovascular AMD exist, at present, there is no approved treatment for early or intermediate AMD or GA. There is therefore a strong clinical need for effective strategies to mitigate the development and/or progression of the earlier stages of AMD.

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DIET AS A MODIFIABLE RISK FACTOR FOR THE DEVELOPMENT OR PROGRESSION OF AMD

Other than the main modifiable risk factor of smoking,[3] one area of great interest is the potential role that nutrition may play in preventing and/or delaying the progression of AMD; in particular, is there any benefit in oral antioxidant and/or mineral supplementation?

Antioxidants have been proposed to limit photoreceptor damage at the macula, by protecting against the cumulative effects of oxidative stress, a mechanism of cellular injury that is caused by reactive oxygen intermediates. The retina is regarded as susceptible to oxidative stress because of its high oxygen consumption, significant proportion of polyunsaturated essential fatty acids (EFAs), and chronic natural exposure to high levels of cumulative irradiation.[4] Animal studies demonstrate that exposure to ultraviolet light can lead to free radical formation[5] and lipid peroxidation of photoreceptor outer segments.[6] Furthermore, studies have shown that this form of light-induced retinal damage, termed the *blue-light hazard*, is similar to the pattern of degenerative changes that are evident in human AMD.[7]

Enhancing the antioxidant capacity of the retina has therefore been targeted as a potential avenue for preventing and/or delaying

AMD progression. The purported role for antioxidants in attenuating human disease is not exclusive to the eye, with interest in the potential merit of such interventions for cancer and cardiovascular disease.[8,9] As a consequence, there has been considerable marketing of high-dose antioxidant, typically vitamin and mineral, supplements. Such formulations are freely available, usually without a medical prescription, which has contributed to their widespread use. There is a common misconception that all dietary supplements are naturally derived products and therefore inherently safe, and, moreover, that higher doses of antioxidants may deliver enhanced therapeutic benefits—the concept that "antioxidants are good, so more antioxidants must be better." Indeed, this has not proven to be the case, with evidence that such practices can even potentially be harmful.[10,11]

Over the past 12 years, two large National Eye Institute–sponsored, multicenter, randomized, controlled clinical studies have sought to evaluate the safety and efficacy of high-dose antioxidant vitamins and other nutrients for altering the natural history of AMD. These studies, namely, the Age-Related Eye Disease Study (AREDS)[12] and AREDS2,[13] have improved scientific understanding of the potential role of nutritional supplementation in reducing the clinical progression of AMD. The findings from AREDS2, in particular, were eagerly anticipated due to their potentially important implications for AMD management. Although AREDS2 provides some further insight into the association between high-dose antioxidant supplementation and a reduction in AMD progression in "at risk" eyes, a number of important questions remain.

It is still not clear what minimum effective dose is required for a given antioxidant to impart a protective effect. It is also not certain whether a single component, or a combination of components, represents the optimal formulation. When considered in the context of the different regulations covering foods as distinct from therapeutic goods, there is therefore a particular need for practitioners to critically appraise the reported findings to ensure that they are accurately interpreted and not inappropriately extrapolated. The study designs and reports of AREDS and AREDS2 are complex. The task for a clinician to first unravel the relative significance of the findings of different studies and subsequently assess how this information should be applied to their patients with AMD is not trivial.

The purpose of this review is to critically evaluate the currently available evidence relating to nutrition and AMD, with particular reference to the key findings of AREDS and AREDS2. Topical controversies relating to nutrition and AMD will also be considered and analyzed in the context of the published literature to guide practitioners through assessing the relative merit, or otherwise, of common claims.

PART 1: ESTABLISHING A FRAMEWORK FOR EVIDENCE-BASED PRACTICE RECOMMENDATIONS FOR NUTRITION AND AMD

Classification of AMD

Fundamental to a coherent and consistent interpretation of clinical studies relating to AMD is the adoption of a common definition and clinical classification scheme for the disease. Over the past 20 years, a number of AMD classification schemes have been described in the literature[14–16]; these guidelines have assisted clinicians and researchers in documenting AMD severity and progression. However, until recently, there has been a lack of universally accepted terminology or a disease staging system for either research or clinical purposes. An article published last year by the Beckman Initiative for Macular Research Classification Committee defines a basic clinical classification system that is based on ocular fundus appearance and structured to be of value in predicting the risk of developing late AMD[17]; the concept of using retinal phenotypes to stratify for incident risk is similar to a classification of hypertensive retinopathy for cardiovascular endpoints.[18] The AMD five-stage grading scheme (Table 1) is designed to allow a simple, unified AMD classification to improve communication between clinicians and enhance patient care.[17] For clarity, the AMD nomenclature and clinical staging that is defined in this classification scheme is adopted throughout this review.

There are some important aspects that are worth noting in the new classification system. First, the committee considered the terms *wet* and *dry* as descriptors for AMD to be confusing, particularly as dry AMD has been used historically for a wide range of contexts, extending from simple drusen to GA.[17] To avoid ambiguity, it was proposed that a description of "dry AMD" refers specifically to GA, rather than earlier stages of the disease. Indeed, it can be suggested that it is worthwhile to avoid the use of "dry" as a category of AMD altogether. Furthermore, a standard staging nomenclature being "early," "intermediate," or "late' (rather than advanced, as used in both AREDS and AREDS2) AMD was defined.

This classification system also specifies criteria to differentiate a "normal" macula from a macula with "normal aging changes" from a macula with "early AMD."[17] The use of descriptors such as "soft" and "hard" for drusen are not adopted. Rather, the size of the druse at its smallest diameter is used to grade disease severity. The

TABLE 1.

Beckman Initiative for Macular Research Classification Committee age-related macular degeneration classification scale (from Ferris et al.[17])

AMD classification	Definition (lesions assessed within two disc diameters of the fovea in either eye)
No aging changes	No drusen and no AMD pigmentary abnormalities*
Normal aging changes	Only drupelets (small drusen ≤63 μm) and no AMD pigmentary abnormalities*
Early AMD	Medium drusen (>63 and ≤125 μm) and no AMD pigmentary abnormalities*
Intermediate AMD	Large drusen (>125 μm) and/or any AMD pigmentary abnormalities
Late AMD	Neovascular AMD and/or any geographic atrophy

*AMD pigmentary abnormalities denote any definite hyperpigmentary or hypopigmentary abnormalities associated with medium or large drusen but not associated with known disease entities.

authors propose the term *drupelets* to describe small drusen (less than 63 μm in diameter) that have a low association with risk of disease progression to late AMD. The presence of drupelets, within two disc diameters of the fovea, in the absence of other funduscopic indicators of AMD is regarded as indicative of normal aging, rather than an early stage of AMD. Another important distinction relates to the significance of macula pigmentary abnormalities relative to the risk of disease progression. Data from AREDS showed that eyes with pigmentary changes, either hyperpigmentation or hypopigmentation within two disc diameters of the fovea and not associated with at least medium drusen (≥63 and <125 μm), are at very low risk (1.4%) of progressing to late AMD within 5 years, and although the risk increased 10-fold to 12.5% for bilateral pigmentary abnormalities, it should be noted that this progression rate derived from a single case (1 of 8 patients) with bilateral pigmentary abnormalities and no more than small drusen present.[17] The additional presence of at least medium drusen increased the 5-year risk of late AMD substantially. Based on this evidence, the Beckman Initiative committee redefined "AMD pigmentary abnormalities" as "hyper- or hypo-pigmentation (that is) present within two disc diameters (radius) of the center of the macula, in eyes with drusen of 63 microns or more in diameter and without known retinal disease entities or other reasons for such abnormalities."[17] With this logic, eyes without pigmentary abnormalities but possessing medium-sized drusen are defined as early AMD. The presence of any pigmentary abnormalities and/or large drusen (defined as being at least 125 μm, or approximately as wide as a major branch retinal venule crossing the optic disc margin) constitutes intermediate AMD.

The development of neovascularization and/or GA within the macula represents late AMD. Currently, GA is defined, using ocular fundus appearance, as a sharply delineated round or oval region in which the underlying choroidal vessels are visible.[14] With time, such clinical definitions will no doubt be revised; advancements in ocular imaging techniques, such as optical coherence tomography, demonstrate the capacity for high-resolution imagery of the outer retina to more accurately detail the retinal abnormalities that characterize GA. Neovascular AMD is characterized by the accumulation of subretinal or intraretinal fluid and hemorrhage at the macula; this may be the result of choroidal neovascularization and/or sub-RPE or subretinal fibrovascular proliferation.

Nutrition and Dietary Supplementation

Nutrition, being the process of obtaining the food necessary for health and growth, encompasses both whole foods and dietary supplements. The *Dietary Guidelines for Americans*, which provide the basis for US federal food and nutrition policy, states that nutritional needs should be achieved primarily through food.[19] Dietary supplements are not intended to act as food substitutes as they cannot replicate the full spectrum of nutrients that exist in whole foods.[20] Importantly, unlike prescription medications, dietary supplements are also not intended to treat or prevent disease. Nevertheless, many supplements are promoted as a potential means of delaying the onset of disease and/or as a reasonable means of improving health and well-being.

Those arguing in favor of the routine use of dietary supplements will often claim that the "required" dose of nutrients cannot be readily consumed from eating whole foods.[21] Furthermore, the consumption of a supplement has been suggested to be a "more convenient and possibly (more) cost-effective" means of dietary modification.[21] However, this seems to be a spurious argument. At present, there is little evidence regarding the "minimum effective dose" or "maximum tolerated dose" that is required for individual nutrients to impart specific health benefits, including antioxidant supplements for slowing the progression of intermediate to late AMD. Dose escalation studies, which aim to determine the dosage range for a therapeutic intervention, are not routinely conducted for dietary supplements as they are for scheduled medications. The optimal dose for possible therapeusis therefore often remains unclear. Although the AREDS2 Study Group did report a dose-ranging study of lutein supplementation in persons aged 60 years or older[22] and another examining the effect of oral supplementation of omega-3 long-chain polyunsaturated fatty acids on changes in serum levels of lutein and zeaxanthin during supplementation in persons 60 years or older,[23] the minimum therapeutically effective dose for the various components and combinations of components for the AREDS2 supplements remains unclear, and that limitation, unresolved. Nevertheless, it is common for manufacturers to make claims relating to specific health benefits. For instance, omega-3 EFAs have often been reported to "help assist in the maintenance of normal eye and brain function,"[24] but with the standard disclaimer, "The statements above have not been evaluated by the Food and Drug Administration. The products are not intended to diagnose, treat, cure, or prevent any disease."

Understanding the context of such claims demands an appreciation of the regulation of dietary supplements by the United States (US) Food and Drug Administration (FDA). Oral products containing vitamins and nutrients are categorized as complementary and alternative medicines by the FDA and are regulated as a general food product in the domain of "dietary supplements." This categorization provides considerable freedom in terms of the claims that can be made in relation to their health benefits. Furthermore, this level of regulation contrasts significantly to scheduled medicines, which require high-quality evidence usually from randomized, controlled clinical trials to validate any assertions regarding the safety and/or efficacy of an intervention. As vitamin supplements are classed as "food products," the responsibility of the manufacturer is to ensure the appropriate safety of the product before marketing. However, the FDA is not required to approve, test, or analyze the vitamin supplement before it is distributed to the public. Only should a product come under scrutiny in relation to its safety would the FDA investigate and assess whether a product recall was required. Furthermore, claims that may be made by the manufacturer in relation to the potential health benefits of a particular vitamin are neither tested nor confirmed by the FDA. There is therefore the potential for claims to be made that are not supported by high-level evidence. Such claims are fundamental to the confusion regarding the actual benefits of antioxidant therapy in AMD.

Evidence from Randomized, Controlled Clinical Trials

A critical interpretation of the findings of clinical trials relating to any treatment or intervention for disease requires some

understanding of clinical trial design. Well-designed, well-executed randomized controlled trials (RCTs) are recognized to provide the most reliable evidence on the efficacy of health care interventions; trials with inadequate methods are associated with bias and the potential for apparently exaggerated treatment effects.[25] Such bias can mislead decision making at all levels of health care, from individual patient care to public health policy. To address the need for transparent and accurate reporting in clinical trials, a common set of recommendations were developed, known as the CONSORT (Consolidated Standards of Reporting Trials) statement.[26] The statement comprises a checklist of essential items that should be included in the reports of RCTs.

A significant item in the CONSORT statement is the prespecification and complete definition of primary and secondary outcome measures. Many RCTs have several outcomes, and the primary outcome measure is defined as the "pre-specified result that is considered to be of greatest importance to relevant stakeholders"[26]; it therefore tests the major hypothesis. Secondary outcomes are also preidentified, to investigate additional items of interest. Prespecification of the outcome measures is essential for determining an appropriate sample size to measure the desired effects, using a formal power calculation. Stated simply, in order for there to be a high level of confidence in a particular conclusion from an RCT, it should be based on an analysis of a predefined outcome measure.

Additional outcomes, typically measured with *post hoc* analyses, differ significantly in their statistical rigor. Exploratory analyses are usually not prespecified but instead seek to determine whether there are any other potential trends in the data. Subgroup analyses have been reported to have a high risk of spurious findings and should be interpreted with caution.[27] Furthermore, *post hoc* subgroup comparisons have often been shown to be unlikely to be confirmed by further investigation.[26] Trends determined through exploratory analyses are therefore regarded to have lower credibility than primary or secondary outcomes. Indeed, this position has been discussed in a recent editorial[28] and response[29] that comment specifically on this issue as it relates to AREDS2.

Two systematic reviews published by The Cochrane Collaboration in 2012 significantly contributed to assessing the evidence for nutritional interventions to slow the development[30] and/or progression[31] of AMD. Although the results from AREDS2 have been reported subsequent to these publications[13] and contribute further to the evidence relating to AMD progression, these major reviews, despite some acknowledged limitations, are still of significant value when examining the evidence base.

DEVELOPMENT VERSUS PROGRESSION OF AMD

It is worth emphasizing the necessity to differentiate between disease onset (i.e., development) and deterioration (i.e., progression), when examining evidence relating to the role of nutrition in AMD, to ensure that interpretations are not inappropriately interchanged between each entity.

Development of AMD

In relation to the potential benefit of antioxidant supplements to prevent the development of AMD, the Cochrane review meta-analysis included four large, high-quality RCTs involving a total of 65,250 participants.[30] These trials were conducted in Australia, Finland, and the United States and compared antioxidants (lutein, zeaxanthin, and vitamins C and E) and/or minerals (zinc and selenium) supplementation (alone or in combination) with placebo control subjects. The duration of supplementation ranged from 4 to 12 years. Data from AREDS were not included in the review as AMD outcomes for study participants without AMD at baseline were not reported. The meta-analysis showed that there was no significant effect of antioxidant therapy for preventing the onset of AMD *per se*.[30] Despite its scientific plausibility, the clinical implications of these findings are that there is currently no evidence from RCTs for patients who do not show signs of AMD to consume antioxidant vitamin and/or mineral supplements to prevent or delay the onset of AMD. Current evidence-based practice (EBP) for patients with normal aging macular changes, which by definition includes the presence of drupelets within a two disc diameter radius of the fovea, should therefore not include recommendations for antioxidant nutritional supplements.

Progression of AMD

The next line of enquiry relates to whether antioxidant vitamins and mineral supplements can slow AMD progression in patients with established disease. The 2012 Cochrane review on this subject[31] considered 13 RCTs; included in the analyses were data from two large trials with long treatment duration and follow-up of 4 to 6 years (i.e., AREDS[12] and the Vitamin E Intervention in Cataract and Age-Related Maculopathy study[32]). The other 11 RCTs included in this systematic review were significantly smaller (n = 20 to 400 participants) and/or had a shorter duration of follow-up (6 to 24 months); these studies included, but are not limited to, the Veterans Lutein Antioxidant Supplementation Trial,[33,34] the Carotenoids in Age-Related Maculopathy Italian Study,[35] the Age-Related Macular Degeneration Study,[36] and work undertaken by Bartlett and Eperjesi.[37] In this Cochrane review, AREDS was described as the primary source of evidence for the benefit of antioxidant vitamin and mineral supplementation in attenuating the risk of AMD progression.[31]

The Age-Related Eye Disease Study was a prospective, multicenter, placebo-controlled RCT (conducted between 1992 and 2006) that was designed to evaluate the clinical aspects, natural history, and risk factors associated with AMD and cataract and the potential benefit of systemic antioxidant supplementation for reducing disease progression. Without focusing on the limitations of the study, AREDS demonstrated that daily, long-term, high-dose supplementation with vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc (80 mg, as zinc oxide), and copper (2 mg, as cupric oxide) in subjects with at least intermediate AMD reduced the relative risk of progression to late AMD from 28 to 20% at 5 years.[12] Importantly, this benefit was only evident for patients with intermediate AMD at baseline. The overall risk of moderate vision loss (defined as 15 or more letters on the Early Treatment Diabetic Retinopathy Study chart) was also reduced in this patient population by 19% at 5 years; there was no statistically significant effect on cataract.[12] Interestingly, the pooled data from RCTs other than AREDS demonstrate little

evidence for the effectiveness of oral antioxidant therapy for preventing either visual loss or AMD progression.[31] This was reported to be potentially due to differences in formulation and/or the duration of the RCTs. Such differences may also be due to the genetic profiles of study participants, which have been recently shown to be influential in determining the relative efficacy of the specific components of nutritional supplements.[38]

The Age-Related Eye Disease Study 2 was based partly on the rationale of animal-based and epidemiological investigations suggesting the possible benefit of other nutrients for reducing AMD progression. Observational studies highlighted the potential beneficial effects of higher dietary intakes of the retinal carotenoids (zeaxanthin and lutein) and omega-3 long-chain polyunsaturated fatty acids (i.e., docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) for lowering the overall risk of developing late AMD.[39–41] Lutein and zeaxanthin are xanthophyll carotenoids that must be ingested and are present in significant proportions in human macular pigment. The roles of lutein and zeaxanthin within the retina are recognized to involve antioxidant protection, filtration of short-wavelength (blue) light, maintenance of structural integrity of cell membranes, and modulation of signal transduction pathways.[42] Lutein and zeaxanthin were considered for inclusion in the AREDS formulation; however, at the time the study commenced, there was no capacity for these carotenoids to be manufactured in a research formulation.[43] Docosahexaenoic acid is the primary structural component of lipid membranes in retinal photoreceptor outer segments.[44] Tissue DHA status has been found to influence mechanisms involved in the phototransduction cascade,[45] with DHA deficiencies linked to retinal functional abnormalities.[46] Docosahexaenoic acid and EPA may also impart a retinoprotective effect through their multiple effects on gene expression,[47] cellular differentiation,[48] and cell survival.[48] These roles provide a basis for both the retinal carotenoids and omega-3 EFAs to influence the biological processes that have been implicated in the pathogenesis of AMD.

The primary objective of AREDS2 was to investigate the effect of daily nutritional supplementation with the xanthophyll carotenoids and/or omega-3 EFAs on AMD progression in subjects with at least intermediate disease.[49] The Age-Related Eye Disease Study 2 examined whether the addition of lutein (10 mg) + zeaxanthin (2 mg), DHA (350 mg) + EPA (650 mg), or lutein + zeaxanthin and DHA + EPA to the AREDS formulation further reduced the risk of progression to late AMD. Through secondary randomization, AREDS2 also assessed whether forms of the AREDS formulation with reduced zinc (25 mg) and/or no beta-carotene were as effective as the original supplement. The primary outcome measure was the development of late AMD, detected on either grading of stereoscopic fundus photographs or a history of treatment of late AMD subsequent to enrolment. Secondary outcomes included progression to moderate vision loss from baseline or treatment of choroidal neovascularization. As per the prespecified primary outcome, AREDS2 demonstrated that the addition of lutein + zeaxanthin, DHA + EPA, or both components to the AREDS formulation did not further reduce the risk of progression from intermediate to late AMD, compared with the original AREDS supplement. Although this conclusion is appropriately stated in the AREDS2 report,[13] there have been instances where the extrapolation of the reported findings, beyond the stated primary and secondary outcome measures, has resulted in claims that can be difficult to justify based on the available evidence.

In addition to the effects of antioxidant supplementation on the natural history of AMD, as typically quantified by changes to funduscopic phenotype, it is worthwhile reviewing evidence relating to the potential effects of such interventions on visual function. Measures of visual function have shown promise in the identification of those "at risk" of progression. Currently, high-contrast visual acuity (VA) is still the primary measure of visual function that is consistently used in both clinical practice and research. AREDS reported VA outcomes in a dichotomous format, specific to the loss of 15 or more letters on the EDTRS acuity chart. In a pooled analysis of RCTs restricted to assessing multivitamin and mineral supplements where VA was measured as a continuous variable,[34,36,37,50] it was concluded that there was little effect of such treatments on VA.[31] Although a couple of small randomized clinical trials, with noted design limitations,[31] have suggested the potential for carotenoid supplements to enhance visual function in AMD,[35,51] high-level evidence to substantiate these findings is lacking. Furthermore, given that VA is overall an insensitive measure of visual function and is often maintained until the later stages of AMD, there has been significant scientific interest in the utility of alternate clinical biomarkers with enhanced capacity to detect early retinal functional deficits in AMD. Currently under investigation are such measures as flicker perimetry,[52] microperimetry,[53] cone-contrast thresholds,[54] and the multifocal electroretinogram.[55] Once validated, such functional tests may prove to be particularly valuable in assessing early AMD and more accurately predicting risk of progression to significant visual dysfunction.

PART 2: EBP FOR NUTRITION AND AMD: EXPLORING THE CONTROVERSIES

What is EBP?

A commonly cited definition of EBP is that of Professor David Sackett, and colleagues, which states that EBP is "the conscientious, explicit and judicious use of current best (research) evidence in making decisions about the care of individual patients."[56] In a clinical scenario, this involves a practitioner being able to integrate knowledge about the natural history of a patient's ocular condition with the most recent and best-quality evidence regarding the safety and efficacy of a particular treatment, as relevant to that particular patient. An EBP approach provides a framework to improve clinical decision making.

Applying an EBP approach to clinical practice can be a challenge. Evidence-based practice demands the consideration of a range of types of research data (e.g., observational studies, case-control series, RCTs, meta-analyses) that are of different hierarchical standings. The qualitative ranking of different types of evidence can be complicated, as can attempting to combine and/or compare different forms of evidence to achieve a clear consensus. It is also not uncommon for findings from different studies to appear to be, and to truly be, contradictory and such differences may be difficult to reconcile. Complex study designs,

which are not uncommon in large RCTs, may also be difficult to interpret. Differences in physical accessibility to the research evidence may also affect the implementation of EBP in clinical practice.

The principle of applying evidence from constrained research findings to individual patient scenarios can be met with criticism; that is, EBP is too rigid and does not relate to "real world" experiences. However, it is an incorrect assumption that EBP relates to "research evidence" alone. As every patient context is unique, a practitioner's own professional and/or clinical judgment is an essential element of EBP. Research evidence can assist practitioners in making informed decisions about their practice and articulates with, but does not replace, clinical expertise or judgment. The latter is essential for determining how the available evidence should be used to inform decision making for a particular patient. The ability to successfully translate research evidence into clinical practice may also be complicated by situational factors, such as the physical availability of a particular treatment. In relation to nutrition and AMD, such an example would be the commercial availability of antioxidant supplements; clinicians must use research evidence in the context of products that are available on the market at any given time. Evidence-based practice recommendations can therefore be confounded by limitations in the availability of the formulation.

We will now consider two AMD case scenarios, to explore how EBP can be applied to real-world scenarios and to assess the evidence for and/or against common claims relating to nutrition and/or antioxidant supplements.

Clinical Scenarios

Clinical Scenario 1

A 75-year-old man, who has never smoked, is noted to have medium-sized (100 μm, shortest diameter) drusen positioned within two disc diameters of the fovea in each eye (Fig. 1). There are no associated AMD pigmentary abnormalities. He inquires with regard to whether he would benefit from nutritional supplementation to reduce his risk of AMD-related vision impairment.

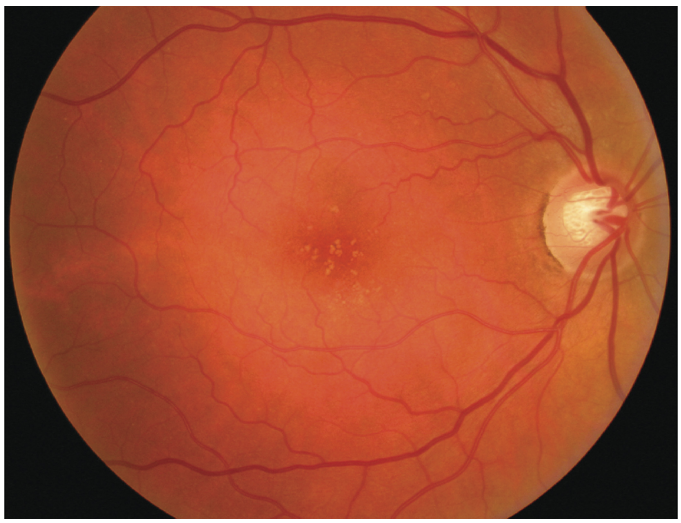

FIGURE 1.
Retinal fundus photograph of the right eye from a 75-year-old man with early AMD, consisting of medium-sized (100 μm, shortest diameter) drusen positioned within two disc diameters of the fovea.

Claim: "Antioxidant vitamin and/or mineral supplementation reduces the risk of progression from early to late AMD."[57]

Assessment

The first relevant consideration is to assess the stage of AMD. Using the Beckman Initiative classification,[17] this phenotype is consistent with bilateral, early AMD. Next, the relevant evidence for the merit of antioxidant supplementation for this stage of AMD should be evaluated. In AREDS, only 1.3% of participants with early AMD progressed to late AMD within 5 years.[12] AREDS demonstrated that there was no statistically significant evidence of a benefit in delaying the progression of eyes with early AMD to more significant drusen-related pathology (i.e., to intermediate AMD) through the use of antioxidant vitamin and/or zinc supplementation.[12] As a consequence of the natural history, with so few patients progressing from early to late AMD over 5 years, a study could never be powered adequately to demonstrate a significant beneficial effect with antioxidant supplementation. Another important aspect relates to the patient's smoking status. Tobacco smoke contains many toxic, carcinogenic, and mutagenic chemicals, as well as stable and unstable free radicals and reactive-oxygen species.[58] Smoking is an important risk factor for the development[59] and progression of AMD.[3] However, one of the challenges in interpreting some of the AMD literature relates to how smoking status has been defined and interpreted. A number of different definitions for categories of smoking status (most commonly: current smoker, former smoker, never smoked) exist.[60] For instance, how often does a person have to smoke to be classed as a "current smoker"? Or, what period must have elapsed for a patient to be considered a "former smoker"? How do we take into account sidestream (passive) smoking? There can also be ambiguity with regard to the specific definition that has been used for a particular study and how to compare studies that use different definitions. One useful categorization system, which is adopted throughout this review, proposes a three-tier system to define a patient's smoking history.[60] A "current smoker" is defined as a person who currently either smokes more than one cigarette per day/one cigar per week or chews 30 g of tobacco per month, for at least the past year. A person who has "never smoked" would need to have smoked less than one cigarette per day/one cigar per week or 30 g of tobacco per month, for no more than 1 year. A "previous smoker" is a person who has not smoked for at least 1 year, but previously either had one or more cigarettes per day/one cigar per week or chewed 30 g of tobacco per month. Using this scheme, this patient is therefore classified as someone who has "never smoked."

EBP Recommendations

There is level 1 evidence[61] to show that there is no benefit in antioxidant vitamin and/or mineral supplements for patients who have less than intermediate AMD.[12] Indeed, this is very different from there being no evidence to demonstrate a benefit, which implies the need for further study to investigate the potential for such an effect.

As has been discussed, nutrition is more than dietary supplementation. As such, a relevant and related question is whether there is evidence to support recommendations in relation to

dietary modification for this patient. A recent survey of eye care practitioners in the United Kingdom found that approximately two-thirds of respondents reported frequently offering dietary advice to patients with established AMD and over half made recommendations to patients that were considered "at risk" of developing the condition.[62] The most common recommendation was to consume "plenty of leafy green vegetables"[62]; the rationale being that these foods are naturally rich in lutein and zeaxanthin.

Evidence for the role of diet in AMD derives predominantly from observational studies[63,64] that have a lower hierarchical evidence level than RCTs owing to confounding and bias. Consistently and uniformly modifying the diets of large numbers of participants for a RCT is, however, unrealistic. Furthermore, it is not currently clear what the "required dose" for specific antioxidants is and/or whether this can be readily attained from consuming whole foods. These, among other factors, have contributed to the use of oral supplements, rather than dietary changes, in the major RCTs to date that have investigated the role of nutrition in slowing the progression of AMD. Despite the absence, and likely continued absence, of RCT evidence about the benefits of dietary changes in modifying risks for progressive AMD, it is worth noting that a number of professional guidelines make recommendations toward the possible benefit(s) of dietary modification.[65,66] As it is unlikely that large RCTs relating to AMD and diet will be conducted, we would argue that it is reasonable for guidelines to recommend changes to encourage a healthy diet that includes the consumption of potentially beneficial whole foods. Food sources are always regarded as preferable to supplementation for improving nutritional status as they are sustainable, less expensive, and have a significantly lower risk of systemic toxicity.[67] Conversely, specific interventions such as antioxidants, particularly at high dose with a risk for adverse effects, require a higher level of evidence before similar recommendations should be made.

Clinical Scenario 2

A 75-year-old male smoker (who currently smokes 10 cigarettes per day) is noted to have large drusen positioned within two disc diameters of the fovea in each eye; areas of hyperpigmentation and hypopigmentation are also evident surrounding each fovea (Fig. 2). He inquires with regard to the best intervention(s) to reduce his long-term risk of AMD-related vision impairment.

> *Claim:* "AREDS demonstrated that previous and current smokers who received a supplement formulation containing beta-carotene were at a significantly higher risk of developing lung cancer than non-smokers."

Assessment

The presence of pigmentary abnormalities in association with medium-sized drusen is consistent with this patient having bilateral, intermediate AMD. Smoking increases the risk of developing AMD at least twofold.[68] A direct association exists between the risk of developing late AMD and the number of cigarettes smoked over time.[69] Given the presence of intermediate AMD in an "at risk" patient, it is relevant to consider the evidence for the potential benefit of antioxidant supplementation. It is a misconception that AREDS demonstrated the potential risk of lung cancer in smokers consuming high-dose beta-carotene supplements. At baseline, 8% of AREDS participants were current smokers and 49% were former smokers; explicit definitions for these categories of smoking status could not be determined from the study design publication.[70] AREDS found no statistically significant difference in mortality rates for antioxidant supplementation alone or in combination with high-dose zinc when baseline smoking status was considered.[12] Furthermore, death due to lung cancer showed no statistically significant difference by treatment.[12] It is therefore inaccurate to cite AREDS as the source of evidence for an association between lung cancer and high-dose beta-carotene in current or former smokers. At the time of AREDS being conducted, two important studies reported an increased incidence of mortality among patients who were heavy smokers and were taking beta-carotene supplements with the intention of preventing lung cancer.[10,11] A recent systematic review and meta-analysis of RCTs that assessed the effect of beta-carotene supplementation on cancer incidence also found that the incidence of lung and stomach cancers was significantly increased in individuals supplemented with beta-carotene at 20 to 30 mg/d who were current smokers or asbestos workers.[71] In light of those findings, in AREDS2, current smokers or those who had stopped smoking less than a year before enrolment, were excluded from receiving beta-carotene.[49]

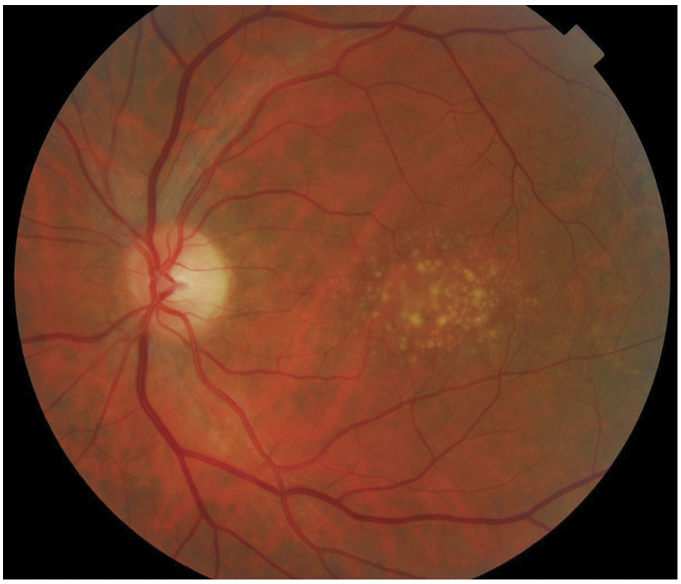

FIGURE 2.

Retinal fundus photograph of the left eye from a 75-year-old man with intermediate AMD, consisting of large-sized drusen and areas of hyperpigmentation and hypopigmentation, positioned within two disc diameters of the fovea.

EBP Recommendations

Any patient who is a current smoker should be advised to cease smoking. The administration of such advice by a health practitioner is associated with improved long-term smoking abstinence rates.[72] Eye care providers therefore have a duty of care to inform patients of not only the systemic health risks associated with smoking but in particular the long-term ocular risk of AMD. Recent evidence suggests that, as a profession, optometrists may

not be adopting a consistently proactive approach to documenting patients' smoking history or advising on smoking cessation.[62]

The decision to recommend that a patient consume antioxidant supplements must balance the possible risks with the benefits of the intervention.[73] As discussed, there is evidence from clinical trials funded by the National Cancer Institute that the risk of lung cancer is significantly increased with high-dose beta-carotene supplementation in current and former smokers.[10,11] Patients with a recent smoking history should therefore be cautioned against consumption of the original AREDS formulation. In this case, what evidence is there to support replacing beta-carotene with alternative components, such as lutein and zeaxanthin, to reduce the risk of late AMD in this patient who is a smoker with intermediate AMD?

> *Claim:* "AREDS2 demonstrated that replacing beta-carotene with lutein and zeaxanthin is a safer and more effective form of antioxidant therapy."[21,74,75]

Evaluation

There is no evidence to suggest that either lutein or zeaxanthin is associated with increased cancer risks; in this respect, describing lutein and zeaxanthin as "safer" than beta-carotene is not unreasonable. The primary analysis in AREDS2 demonstrated that, overall, the addition of lutein + zeaxanthin and/or omega-3 fatty acids to the AREDS formula was not associated with a statistically significant reduction in the risk of progression to late AMD when compared with the original formulation.[13] It was not a prespecified outcome of AREDS2 to investigate whether it was safer and/or more effective to replace beta-carotene with lutein + zeaxanthin to reduce the risk of progression from intermediate to late AMD. This question was not directly addressed by the study. Rather, exploratory analyses, conducted at the conclusion of AREDS2, suggested that the role of lutein + zeaxanthin in reducing AMD progression requires further investigation. In the original article that reports the outcomes of AREDS2, the authors state that "lutein and zeaxanthin may play a role for reducing the risk of progression to advanced AMD when given without beta carotene. This hypothesis requires further study."[13] Furthermore, subgroup analyses showed that the potential protective effect of adding lutein + zeaxanthin to the original AREDS formulation in reducing progression to late AMD was limited to participants in the lowest quintile of dietary intake of the macular carotenoids. This finding implies that improving dietary intake of lutein + zeaxanthin may be of value in reducing AMD progression. A further confounding factor of AREDS2 was that the dual administration of different carotenoids (beta-carotene and lutein + zeaxanthin) resulted in their competitive absorption within the body. The serum levels of lutein + zeaxanthin in participants who simultaneously received beta-carotene were significantly lower than levels in subjects who were not assigned to a formulation containing beta-carotene.[13] *Post hoc* analyses suggested that lutein + zeaxanthin could be of value in reducing progression to late AMD, when given without beta-carotene; however, again, the authors note that this hypothesis requires further study.

There is currently limited evidence, derived from exploratory analyses in a single RCT, that the substitution of beta-carotene with lutein + zeaxanthin is a possible means of reducing disease progression from intermediate to late AMD. Although this may seem reasonable, especially in patients who are current smokers, it is not actually a recommendation that can be made with any confidence based on the AREDS2 data, as has been claimed. Further research is still required to support the inclusion of lutein + zeaxanthin into antioxidant supplements for AMD.

EBP Recommendations

An EBP approach involves applying the best available evidence, which may include the results of exploratory analyses of RCTs and/or observational studies. Indeed, the exploratory analyses of the original AREDS data set have provided the best available evidence regarding the natural history and risk of progression to late AMD. This information is used to inform the decision-making process, which would be inclusive of an assessment of the individual patient (i.e., their signs and symptoms, ocular and general medical history, etc.).

The first relevant recommendation for this patient, to reduce his risk of progression to late AMD, is to quit smoking. As he has bilateral, intermediate AMD, there should also be a discussion relating to the potential merit of modifying his diet and/or receiving some form of antioxidant supplementation. High-dose beta-carotene supplementation (as present in the original AREDS formulation) is not recommended, because of the potential increased risk of lung cancer in current smokers; thus, what other options may be viable? Based on the findings of AREDS2, it would be reasonable to survey the patient's dietary intake of lutein + zeaxanthin and, if appropriate, potentially recommend a change in diet to enhance the natural consumption of the xanthophyll pigments; such an analysis requires an appropriate understanding of risk factors and categories. However, applying the exploratory analyses of AREDS2 more broadly to justify a formulation that replaces beta-carotene with lutein + zeaxanthin overstates our confidence in these results. There is currently a lack of evidence from primary (as distinct from exploratory) analyses of RCTs to recommend that dietary supplements that replace beta-carotene with lutein + zeaxanthin are more effective for slowing the progression of AMD.

PART 3: THE FUTURE: EBP AND PERSONALIZED MEDICINE FOR AMD PREVENTION

A vital, but long-standing, missing piece to the puzzle in relation to nutrition and AMD is the potential influence of genetics on patient outcomes. Why do some patients seem to benefit from nutritional interventions and others do not? It is reasonable to hypothesize that the effect of nutritional supplementation for individuals, with similar clinical phenotypes of AMD, may differ (either beneficially or deleteriously) depending on the patient's genetics.

An article published recently online, based on a large genetic data set of patients in AREDS, supports the pharmacogenomic selection of nutritional supplements for AMD patients who are at risk of progressing to late disease.[38] In this study, the addition of zinc was found to negate the beneficial effect of antioxidants among a subpopulation of patients possessing one of two complement factor H risk alleles. Conversely, patients with age-related maculopathy sensitivity 2 risk alleles derived maximum benefit from zinc-containing supplements. Based on these findings, the authors estimated that if genotype-directed therapy had been adopted

for the AREDS study population, this would have more than doubled the reduction in AMD progression rate compared with standardized treatment with the AREDS formulation.[38] These exciting findings lay a foundation for further investigations to assess the importance of pharmacogenetics in applying ''personalized medicine'' for the optimal prevention, and/or slowing of progression, of AMD using criteria that extend beyond clinical phenotypes.

FINAL COMMENTS

Evidence-based practice is not what is easier to do, or what one ''believes'' to be true, but is based in scientific skepticism. We need to constantly ask ourselves whether specific claims are scientifically plausible and ''what is the current evidence?'' Evidence itself is not static, but constantly being added to, such that aspects of clinical care that are presently inconclusive may well become clearer in time. At present, however, it is important to understand the limitations of research regarding nutrition and AMD. No matter what our personal beliefs or clinical experiences may be, we are obliged to practice in a manner that is based in a rigorous and critical interpretation of the existing evidence. Nutritional intervention is challenging, in part because of the regulatory environment but also because of the difficulties in designing clinical trials to answer these types of questions. Large, complex studies, such as AREDS and AREDS2, contain within them extraordinary data. We should therefore expect that research groups will conduct exploratory analyses to assess for interesting trends within the data; however, there is a need to be cautious when deriving clinical recommendations from exploratory and *post hoc* analyses. Until such time as higher-level, higher-quality confirmatory data become available, it is expected of us by external stakeholders that we, as a profession, practice within the scope of the available evidence.

Received November 12, 2013; accepted February 17, 2014.

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