**An ideal ocular nutritional supplement?**

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**Keywords**

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**Abstract**

The role of nutritional supplementation in prevention of onset or progression of ocular disease is of interest to healthcare professional and patients.   The aim of this review is to identify those antioxidants most appropriate for inclusion in an ideal ocular nutritional supplement, suitable for those with a family history of glaucoma, cataract, or age-related macular disease, or lifestyle factors predisposing onset of these conditions, such as smoking, poor nutritional status, or high levels of sunlight exposure.  It would also be suitable for those with early stages of age-related ocular disease.

Literature searches were carried out on Web of Science and PubMed for articles relating to the use of nutrients in ocular disease.  Those highlighted for possible inclusion were vitamins A, B, C and E, carotenoids beta-carotene, lutein, and zeaxanthin, minerals selenium and zinc, and the herb, Ginkgo biloba.

Conflicting evidence is presented for vitamins A and E in prevention of ocular disease; these vitamins have roles in the production of rhodopsin and prevention of lipid peroxidation respectively. B vitamins have been linked with a reduced risk of cataract and studies have provided evidence supporting a protective role of vitamin C in cataract prevention. Beta-carotene is active in the prevention of free radical formation, but has been linked with an increased risk of lung cancer in smokers.  Improvements in visual function in patients with age-related macular disease have been noted with lutein and zeaxanthin supplementation. Selenium has been linked with a reduced risk of cataract and activates the antioxidant enzyme glutathione peroxidase, protecting cell membranes from oxidative damage while zinc, though an essential component of antioxidant enzymes, has been highlighted for risk of adverse effects.  As well as reducing platelet aggregation and increasing vasodilation, Gingko biloba has been linked with improvements in pre-existing field damage in some patients with normal tension glaucoma.

We advocate that vitamins C and E, and lutein/zeaxanthin should be included in our theoretically ideal ocular nutritional supplement.

**Introduction**

The hypothesised role of oxidation in development of disease (Beatty et al., 2000) has promoted interest in the role of antioxidants in treatment and prevention.  One hypothesis for the aetiology of age-related disease involves the breakdown of antioxidant systems within the body.  An antioxidant can be defined as 'any substance that when present at low concentrations compared to those of an oxidisable substrate, significantly delays or prevents oxidation' (Halliwell, 1999). In the retina, normal metabolic processes, as well as exposure to high-energy visible light generate potentially damaging forms of oxygen (Eye Disease Case Control Study (EDCCS) Group, 1993)

called reactive oxygen species (ROS).  Normal aerobic metabolism produces ROS such as superoxide, hydroxyl radicals, singlet oxygen radicals and hydrogen peroxide. ROS can initiate lipid peroxidation, which is thought to lead to oxidative damage to DNA, protein and carbohydrate within cells (Curcio and Millican, 1999).

The body has several defence mechanisms against the production of ROS. The first involves antioxidant enzymes such as catalase and peroxidase (Sies, 1991). Other micronutrients such as selenium, zinc, manganese, and copper facilitate these antioxidant enzymes (Sies, 1991; Bressler and Bressler, 1995). The second involves antioxidant nutrients such as vitamin E (alpha-tocopherol) (Machlin, 1980; Fukuzawa and Gebicki, 1983; Ozawa *et al.*, 1983; Burton *et al.*, 1985; McCay, 1985), beta-carotene (Burton and Ingold, 1984a) and vitamin C (ascorbate) (Nishikimi, 1975; Bodannes and Chan, 1979; Bielski, 1982; Hemila *et al.*, 1985; Sies, 1991). Other antioxidants believed to play a part in maintenance of ocular health include the carotenoids lutein and zeaxanthin (Snodderly *et al.*, 1984). Further defence mechanisms include antioxidant compounds such as metallathionein, melanin, and glutathione, and DNA repair.  Compartmentalisation is another defence mechanism and this involves the separation of reactive oxygen species (ROS) from cellular components that are susceptible to oxidative damage (Sies, 1991).  Insufficient intake of dietary antioxidant vitamins and minerals can decrease the efficiency of the body's natural antioxidant systems and may allow cellular damage by ROS (Machlin and Bendich, 1987; Pippenger *et al.*, 1991).

Glaucoma, cataract, and age-related macular disease have been investigated regarding the potential of antioxidant therapy, and this paper forms a mini-review of relevant literature. Our aim is to identify those antioxidants most appropriate for inclusion in an ideal ocular nutritional supplement, suitable for those with a family history of glaucoma, cataract, or age-related macular disease, or for those lifestyle factors predisposing onset of these conditions, such as smoking, poor nutritional status, or high levels of sunlight exposure.  It would also be suitable for those with early stages of age-related ocular disease.

**Terminology**

In accordance with the International Classification and Grading System for Age-Related Maculopathy (ARM), and Age-Related Macular Degeneration (AMD), these abbreviations will be used throughout (Bird *et al.*, 1995). The term age-related macular disease will be used to encompass ARM and AMD.  The safe upper limit applies to chronic/lifetime intake by healthy adults in the general population.  It is expressed in terms of mg per person per day. If these limits are exceeded then harmful effects may be experienced. Dietary Reference Values (DRV) were established in 1991 to replace Recommended Daily Allowances (RDA).  The term DRV is used to cover LRNI (Lower Reference Nutrient Intake), EAR (Estimated Average Requirement), RNIV (Reference Nutrient Intake Value), and safe intake (Mason, 2001). RNIV refers to the amount of protein, vitamin or mineral that is sufficient for almost every individual.

**Statistical terms**

The term odds ratio (OR) is to quantify association and it is defined as the ratio of the odds of an attribute, such as cigarette smoking, being present in individuals with a disease such as AMD, to the odds of the attribute being present in individuals without the disease. The statistic used to quantify risk is the relative risk (RR), defined as the ratio of the risk of the disease among those with the attribute (e.g. female gender), or exposure (e.g. sunlight), of interest, to the risk in those without the attribute or exposure (Hawkins *et al.*, 1999). Confidence intervals (CI)

provide an estimation of the range of values we would expect to see in the population based on the sample (Moseley, 2003). Estimates of OR and RR are considered to be statistically significant and supportive of a positive association or increased risk if they include values greater than 1.0 and have confidence limits above 1.0. Studies that include larger numbers of subjects have narrower confidence intervals and are therefore more likely to provide a precise estimate of association or risk (Hawkins et al., 1999). One way of comparing the reliability of randomised controlled trials (RCT) is calculate the ability of the trial to detect a difference between treatment means. $R$ is the percentage difference detectable in an experiment.

**Method**

In this review we identified pertinent articles on nutrition and ocular disease published in peer reviewed journals, through a multistaged, systematic approach. In the first stage, a computerized search of the PubMed database (National Library of Medicine) and the Web of Science database was performed to identify all articles about nutrition and ocular disease published up to September 2003. The terms 'eye disease AND nutrition' was used for a broad search. In the second stage all abstracts were examined to identify articles that described the use of nutrients in ocular disease. Copies of the entire articles were obtained. Bibliographies of the retrieved articles were manually searched with use of the same search guidelines. In the third stage, articles were reviewed and information relating to the relationship between nutrition and ocular disease was incorporated in to the manuscript.

**Review of nutrients**

*Vitamin A*

Function*:* Vitamin A is fat-soluble and exists in three different oxidative states: alcohol (retinol), acid (retinoic acid), and aldehyde (retinal).  It normally exists within the body as retinol. The functions of vitamin A can be classified into four areas; reproduction of cells, reproductive function, growth and development of embryo and foetus, and vision (Lui and Roels, 1980; Weber, 1983; Zile and Cullum, 1983; Olson, 1984; Pitt, 1985). Quantification of vitamin A can be confusing, as three different units are used.  Micrograms (μg), retinol equivalents (RE), and international units (IU). They can be interchanged as follows; 1RE = 1μg retinol, 1 RE = 6μg beta-carotene, 1 RE = 3.333 IU vitamin A.

Safety*:* Excessive intake is potentially toxic to the liver and other tissues (Miller and Hayes, 1982; Bendich and Langseth, 1989; Hathcock *et al.*, 1990; Meyers *et al.*, 1996).  Acute toxicity has been associated with doses of 100,000 RE/day in adults and 10,000 RE/day in children. In humans, teratogenic effects have been associated with doses of 3000-9000 RE/day; women in the first trimester of pregnancy are most at risk. Relationships have been determined between retinol intake and reduced bone mineral density (Freudenheim *et al.*, 1986; Houtkooper *et al.*, 1995), and increased risk of hip fracture. However, for one study smoking was a confounding factor in one study (Melhus et al., 1998), and in another the cohort comprised of mainly white women (Feskanich et al., 2002). The Expert Group on Vitamins and Minerals (EVM) were not able to set a safe upper limit for vitamin A (Expert Group on Vitamins and Minerals, 2003), and RNIVs are 700ug for men and 600ug for women.

*B Vitamins [Riboflavin (B2) and Cobalamin (B12)]*

Function: Riboflavin is a member of the B vitamin group.  It acts as an antioxidant, has a role in synthesis of steroids and red blood cells, and in maintaining the integrity of mucous membranes. (Expert Group on Vitamins

and Minerals, 2003). Cobalamin is a water-soluble vitamin needed for normal DNA replication, nerve cell activity, and production of the mood-affecting substance SAMe (S-adenosyl-L-methionine).

Safety: No safe upper limit was set by the EVM for riboflavin, but a maximum supplemental intake of 40mg/day was advised for guidance purposes (Expert Group on Vitamins and Minerals, 2003). The RNIV is 1.3mg for men and 1.1mg for women. The low toxicity of cobalamin is generally accepted and the EVM found insufficient data to set a safe upper limit. For guidance purposes, supplemental intakes of 2.0mg cobalamin should not produce adverse effects (Expert Group on Vitamins and Minerals, 2003).

*Vitamin C (ascorbic acid)*

Function: Vitamin C (ascorbic acid) is water-soluble and is involved with several biological processes. As a reducing agent it is thought to be active in protection against heart disease. It protects LDL (low density lipoprotein) cholesterol from oxidative damage and reduces platelet aggregation (Wilkinson *et al.*, 1999). By enhancing nitric oxide activity, vitamin C is potentially important in lowering blood pressure (Taddei *et al.*, 1998).

Safety: The EVM found insufficient data to set a safe upper limit for vitamin C, but adverse reactions may occur above 1000mg/day (Expert Group on Vitamins and Minerals, 2003). The reference nutrient intake value (RNIV), (the amount of protein, vitamin or mineral that is sufficient for almost every individual) is 40mg per day for men and women.

*Vitamin E (alpha-tocopherol)*

Function: Alpha-tocopherol is the most effective antioxidant of the vitamin E group, and protects against lipid peroxidation (Machlin, 1980). It protects cell membranes and low density lipoprotein (LDL) cholesterol, (Balz, 1999) and has indirect effects on blood cell regulation, connective tissue growth, inflammation, and genetic control of cell division (Azzi *et al.*, 2000). Units used to quantify vitamin E are IU and α-tocopherol equivalents, where 1mg α-tocopherol equivalents = 1.5 IU.

Safety: Vitamin E is well tolerated up to two orders of magnitude above the nutritional requirement. The Alpha-Tocopherol Beta-Carotene (ATBC) study found an increased risk of mortality from haemorrhagic stroke with 37mg d-α-tocopherol equivalents/day. (The ATBC Cancer Prevention Study Group, 1994). This may be attributed to its anti-platelet and anti-coagulant effect, resulting in inhibition of coagulation. In contrast, several studies have shown no increased risk of haemorrhagic stroke (Stephens *et al.*, 1996; Ascherio *et al.*, 1999; Yusuf *et al.*, 2000; Primary Prevention Project, 2001). The EVM set a safe upper limit for vitamin E of 540mg d-α-equivalents per day (Expert Group on Vitamins and Minerals, 2003). UK safe intake (minimum amount required) values are >4mg for men and >3mg for women.

*Beta-carotene*

Function: Beta-carotene is a fat soluble quencher of singlet oxygen, one type of ROS associated with oxidative stress (Levin *et al.*, 1997).

Safety: Studies have shown an increased risk of lung cancer in smokers with beta-carotene supplementation (20-30mg/day). (The ATBC Cancer Prevention Study Group, 1994; Leo and Lieber, 1997)  The EVM set a safe upper limit of 7mg per day (Expert Group on Vitamins and Minerals, 2003)

*Lutein/zeaxanthin*

Function*: Lutein, and its isomer zeaxanthin, are oxygenated carotenoids known as xanthophylls that form the macular pigment (MP) (Bone et al., 1985). Xanthophylls have been shown to have superior antioxidant properties than beta-carotene, and have a lower tendency for pro-oxidant behaviour (Martin *et al.*, 1999). They are the only carotenoids found within the human lens, although at much lower concentrations than the macula (Yeum *et al.*, 1995). Lutein and zeaxanthin are selectively absorbed by the retina. (Rapp *et al.*, 2000).

Lutein and zeaxanthin are present in rod outer segments, where they would be most needed, and concentrations have been shown to be higher in the macular region than the peripheral retina (Rapp et al., 2000).  This evidence supports the selective uptake of lutein in the retina and suggests that it plays important role in maintenance of ocular health.

Safety*: No adverse reaction to lutein/zeaxanthin have been reported and these nutrients were not included in EVM report. However, in a South Pacific population, daily intake of approximately 26mg/day lutein was found to be protective against lung cancer, with no apparent side effects (Le Marchand *et al.*, 1995)

*Selenium*

Function: Selenium activates the antioxidant enzyme, glutathione peroxidase, which protects cell membranes from oxidative damage (Singh *et al.*, 1984).

Safety: Doses above 0.9mg/day have been reported to cause adverse effects, (Yang and Zhou, 1994).  The EVM set a safe upper limit of 0.45mg per day (Expert Group on Vitamins and Minerals, 2003), and the RNIV is 70ug for men and 55ug for women.

*Zinc*

Function: Zinc is an essential component of over 200 enzymes, including antioxidant enzymes such as superoxide dismutases (Machlin and Bendich, 1987).

Safety*: Zinc supplementation over 150mg/day has been associated with gastrointestinal side effects such as cramping and nausea. The EVM advised a safe upper limit of 25mg supplemental zinc per day (Expert Group on Vitamins and Minerals, 2003) and the RNIV is 9.5mg for men and 7.0mg for women.

*Ginkgo Biloba*

Function: Ginkgo biloba has the following functions; reduction of platelet aggregation and reduction of the development of free radicals (Chung *et al.*, 1987; Braquet and Hosford, 1991), increasing vasodilation and reducing blood viscosity (Jung *et al.*, 1990), quenching of free radicals (Robak and Gryglewski, 1988; Pincemail *et al.*, 1989), and it has a role in neurotransmitter metabolism (Defeudis, 1991).

Safety: Ginkgo biloba was not included in the EVM report. There have been few reports of toxicity, (Blumenthal *et al.*, 1998) and occasional reports of associated nausea, headaches, vomiting, and diarrhoea (Mason, 2001). Clinical trials have used between 120 and 240mg daily (Blumenthal *et al.*, 1998). Dietary supplements generally provide 40-80mg in a single dose.

**Review of evidence**

For each of the conditions, glaucoma, cataract, and age-related macular disease, the evidence for and against the role of nutritional supplementation has been presented as either epidemiological or clinical data. The clinical data consists of studies that have investigated the effect of an intervention, and includes relevant RCTs.

*Epidemiological data*

Cataract

Food frequency questionnaire testing of a population-based sample indicates that vitamin A supplements are protective against nuclear cataract (OR: 0.4; CI: 0.2,0.8). However, the Baltimore Longitudinal Study on Ageing (Vitale et al., 1993a) showed no association between risk of cataract and dietary vitamin A.

Epidemiological studies provide conflicting evidence for a relationship between dietary vitamin C or serum/plasma ascorbic acid and risk of cataract (Jacques *et al.*, 1988; Leske *et al.*, 1991; Hankinson *et al.*, 1992; Mares-Perlman *et al.*, 1994; Tavani *et al.*, 1996). Mares-Perlman and co-workers found that more than ten years previous use of vitamin C supplements was associated with reduced risk of nuclear cataract, (RR, 0.7; CI 0.5-1.0) but an increased prevalence of cortical cataract (RR, 1.8; CI,1.2-2.9) after controlling for age, gender, smoking and heavy alcohol consumption (Mares-Perlman et al., 1994).

The National Health and Nutrition Examination Survey (NHANES) II study found an inverse association between serum ascorbic acid and self-reported cataract extraction (Simon and Hudes, 1999). Vitamin C (>49umol/L) was associated with a 64% reduced odds of cataract in a Mediterranean population (Valero *et al.*, 2001). One group found that in women who had more than 10 years of vitamin C supplementation there was a 77% lower prevalence of early lens opacities (OR: 0.23; CI: 0.09,0.60) and an 83% lower prevalence of moderate lens opacities (OR: 0.17; CI: 0.03, 0.85) (Jacques *et al.*, 1997) compared with women who did not take vitamin C supplements.

Serum levels were also assessed, however, in the Eye Disease Case Control Study (EDCCS) and no significant difference was found between those with low and high levels of vitamin C, and the occurrence of cataract (EDCCS Group, 1993). There was no relationship between cataract prevalence and vitamin C intake in two studies (Group TI-ACS, 1991; Vitale *et al.*, 1993b), and no relationship between cataract extraction and vitamin C intake in a third after controlling for nine potential confounders, including diabetes, energy intake, smoking, and age (Hankinson *et al.*, 1992).

Conflicting evidence for a relationship between vitamin E intake and reduced risk of cataract has been put forward by epidemiological studies. In one study, prevalence of advanced cataract was found to be 56% lower in subjects who consumed > 400 IU/day vitamin E, compared with age and gender-matched controls (RR, 0.44; CI, 0.24-0.77) (Robertson et al., 1989). A 40% lower prevalence of cortical cataract (RR, 0.59; CI, 0.36-0.97) and mixed

cataract (RR, 0.58; CI, 0.37-0.93) was found in subjects with intakes in the highest 20% compared with those with intakes in the lowest 20% after controlling for age and gender (Leske et al., 1991). A significantly reduced prevalence of nuclear cataract has been noted in subjects with high plasma vitamin E levels (RR, 0.44; CI, 0.21-0.90) (Leske et al., 1995).

Other studies have not produced conclusive results; for example, a non-significant relationship between vitamin E intake and nuclear cataract was found by one group (RR, 0.5; CI, 0.3-1.1) (Lyle et al., 1999b), similar to the results for nuclear cataract of another group (RR, 0.9; CI, 0.6-1.5) (Mares-Perlman et al., 1994). A 67% reduced prevalence of posterior subcapsular cataracts (RR, 0.33; CI 0.03-4.13) amongst subjects with plasma levels above 35 μM compared to subjects with plasma levels below 21 μM was not statistically significant after adjusting for age, gender, race and diabetes (Jacques and Chylack, 1991).

Self-reported cataract was not found to be affected by vitamin E intake (RR, 0.93; CI, 0.52-1.67) (Simon and Hudes, 1999), and long term (> 10 years) supplementation did not affect incidence of cataract extraction (RR,0.99; CI, 0.74-1.32) (Chasan-Taber et al., 1999a); these results are consistent with those of a previous study (Hankinson et al., 1992)

A reduced risk of cortical cataract (OR, 0.59; CI, 0.36-0.97) and nuclear cataract (OR, 0.72; CI, 0.35-1.45) was found with high dietary intake of riboflavin (Leske et al., 1991). The risk of cortical cataract was also reduced with riboflavin supplementation in the Blue Mountains Eye Study (OR 0.8; CI, 0.6-1.0) (Kuzniarz et al., 2001).

Lutein intake has been linked with a reduced risk of nuclear cataract (RR, 0.4; CI 0.2-0.8)(Lyle et al., 1999a) and a reduced risk of cataract extraction in men (Brown et al., 1999). In a prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in women, those with the highest intake of lutein and zeaxanthin had a 22% decreased risk of cataract extraction compared with those in the lowest quintile. Increasing intake of foods rich in lutein such as spinach and kale was associated with a moderate decrease in the risk of cataract (Chasan-Taber et al., 1999b). Subjects presenting with total plasma carotenoid levels > 3.3 μM had less than one-fifth the prevalence of cataract compared with subjects presenting with plasma levels < 1.7 μM (RR, 0.18; CI 0.03-1.03). However, there was no associated between cataract prevalence and carotene intake (Jacques and Chylack, 1991).

No protective effect of lutein/zeaxanthin against cataract was found in a study using a food frequency questionnaire as a measure of intake (Valero *et al.*, 2001) and a further study showed no significant relationship between specific carotenoid intake and cataract risk (Mares-Perlman et al., 1995).

Age-related macular disease
Subjects who consumed foods rich in vitamin A at least once per day had a 40% reduced risk for AMD than those who ate the foods less than once per week (OR, 0.59; CI, 0.37-0.99) (Goldberg et al., 1988). However, this protective effect has not been demonstrated by other studies (Blumenkranz *et al.*, 1986; VandenLangenberg *et al.*, 1998; Smith *et al.*, 1999).

A nonsignificant protective effect of high oral vitamin C intake against age-related macular disease has been reported (VandenLangenberg et al., 1998); similarly, the Baltimore Longitudinal Study of Aging (BLSA) found a

nonsignificant protective effect of the highest quintile of plasma vitamin C levels compared with the lowest quintile (OR. 0.55) (West et al., 1994). (NHANES), however, found that a diet high in food containing vitamin C was negatively associated with AMD (Goldberg et al., 1988). The Blue Mountains Eye Study (BMES) found no protective effect (Smith et al., 1999).

AMD patients have shown statistically lower serum levels of vitamin E compared with age matched normals (Belda *et al.*, 1999). Similarly, The Baltimore Longitudinal Study of Aging found that higher blood levels of vitamin E were protective, but found no evidence to support the protective effect of vitamin E supplementation (West et al., 1994). The EDCC found no significant effect of vitamin E supplementation on AMD, although the serum used for assessment may not correlate with retinal levels (EDCCS Group, 1993). An inverse relationship between carotenoid, vitamin E and zinc intake and ARM has been determined (VandenLangenberg et al., 1998).

The POLA study investigated the relationship between plasma α-tocopherol and AMD. There was a significant relationship between lipid standardized plasma α-tocopherol and ARM (P = 0.04) and AMD (P = 0.003). The risk reduction for AMD for those in the highest quintile versus the lowest quintile was 82% (Delcourt et al., 1999).

In an investigation into the relationship between plasma concentration of lutein and zeaxanthin and age-related macular disease, those whose plasma concentrations were in the lowest third of the distribution had an odds ratio for risk of the condition of 2.0 (CI: 1.0, 4.1) after adjustment for age and other risk factors, compared with those in the highest third of the distribution (Gale *et al.*, 2003).

A study of retinal levels of lutein and zeaxanthin in donor eyes found an 82% lower risk of AMD in retinae among the 25% with highest lutein and zeaxanthin levels compared to the 25% with the lowest levels (Bone et al., 2001). A 70% reduced risk of AMD has been demonstrated with high (>0.67μmol/L) versus low (0.25μmol/L) lutein/zeaxanthin plasma levels (EDCCS Group, 1993). Measurement of macular pigment optical density (MPOD) in healthy eyes showed an age-related decline, and healthy eyes considered to be at risk for AMD had significantly less MP than healthy eyes not at risk (Beatty et al., 2001). This evidence suggests that there is an increased risk of AMD with lower plasma and retinal levels of lutein and zeaxanthin.

Lutein and zeaxanthin are believed to protect the retina in two ways. Firstly, they act as blue-light filters. Action spectrum for blue-light induced damage shows a maximum at 400nm and 450nm, and this is consistent with the absorption spectrum of macular pigment (Ham et al., 1984). Secondly, they are able to quench free radicals. Energy transfer to them quenches singlet oxygen, and they are also believed to react with peroxy radicals that are involved with lipid peroxidation (Landrum and Bone, 2001).

The Beaver Dam Eye Study reported no protective effect against AMD of dietary intake of lutein and zeaxanthin (VandenLangenberg *et al.*, 1998).

*Clinical data*

Glaucoma

One RCT investigated the effect of 160mg daily of GBE EGb 761 on AMD (Lebuisson *et al.*, 1986). VA improved in both placebo and treatment groups, but more in the treatment group. It has been suggested that these beneficial findings should be viewed with caution as observers assessing outcome were not masked (Evans, 2000).

In normal tension glaucoma (NTG), Ginkgo biloba extract (GBE) has been reported to improve preexisting field damage (Quaranta *et al.*, 2003).

Cataract

THE ROCHE EUROPEAN AMERICAN CATARACT TRIAL (REACT)

Investigators determined that three years daily supplementation of a mixture of oral antioxidant micronutrients (mg/day) [beta-carotene (18), vitamin C (750), vitamin E (60)] produced a small deceleration in progression of age-related cataract (The REACT Group, 2001).

AREDS

Investigators concluded that dietary supplementation with high doses of vitamin C (500 mg), vitamin E (273 mg), beta-carotene (15 mg), and zinc (80 mg) for an average of 6.3 years had no statistically significant effect on the development or progression of age-related lens opacities (The AREDS Research Group, 2001a)

Age-related macular disease

AREDS

Investigators concluded that dietary supplementation with high doses of vitamin C (500 mg), vitamin E (273 mg), beta-carotene (15 mg), and zinc (80 mg) for an average of 6.3 years significantly reduced risk of progression of AMD in people with extensive intermediate drusen, large drusen, or non-central geographic atrophy (GA) in one or both eyes, or visual acuity <20/32 attributable to AMD in one eye in those taking a combination of antioxidants plus zinc, and a suggestive reduction in risk for those taking zinc alone (The AREDS Research Group, 2001b).

ALPHA-TOCOPHEROL, BETA-CAROTENE STUDY

This trial was originally designed to investigate the role of BC and vitamin E (AT) in the prevention of lung cancer in over 29,000 smoking males. At the end of the trial an ophthalmological examination carried out on a random sample of 941 male participants aged 65 years or over, determined that long-term supplementation of AT or BC does not affect the prevalence of ARM in smoking males (Teikari *et al.*, 1998).

VITAMIN E, CATARACT, AND AGE-RELATED MACULOPATHY TRIAL (VECAT)

The trial concluded that daily supplementation with vitamin E (d-α-tocopherol, 500 IU) does not prevent development or progression of early AMD (Taylor *et al.*, 2002).

ZINC IN AGE-RELATED MACULAR DISEASE

Investigators concluded that with two years of daily 200 mg zinc sulphate supplementation the decrease in mean visual acuity in the zinc treated group was less than that of the placebo group (Newsome *et al.*, 1988), in other words, zinc reduced progression of AMD. However, Calculation of the R value for this trial shows that it was unlikely to detect any difference between treatments smaller than 72% and that the results should be treated with caution (Bartlett and Eperjesi, 2003). Newsome *et al.*, (1988) suggest potential sources of bias including the use of subjects from a relatively small geographical area, and high soil and water mineral contents in this area.

ZINC AND THE SECOND EYE IN AGE-RELATED MACULAR DISEASE

Investigators concluded that 200 mg daily zinc sulphate supplementation had no short-term effect on the course of AMD in patients with an exudative form of the disease in one eye (Stur *et al.*, 1996). The calculated R value suggests that the trial was likely to be able to detect a treatment effect greater than 16%, which is a much greater degree of precision than the Newsome *et al.* (1988) study.

VISALINE® IN AGE-RELATED MACULAR DISEASE

Results showed no significant effect on measured parameters between the intervention (1.5 mg buphenine HCl, 10 mg beta-carotene, 10 mg tocopherol acetate, and 50 mg ascorbic acid) and placebo groups in patients with non-exudative AMD. The fact that no treatment effect was determined is unsurprising considering the small sample size and the calculated R value for the study of 89% (Bartlett and Eperjesi, 2003).

THE LUTEIN ANTIOXIDANT SUPPLEMENTATION TRIAL (LAST)

The results of this RCT investigating the role of lutein on progression of atrophic AMD have been published in abstract form. Participants were randomised into three treatment groups; 1) 10mg lutein, 2) 10mg lutein/antioxidants, 3) placebo. Investigators have reported a statistically significant concurrent improvement in glare recovery, contrast sensitivity, and distance/near visual acuity in both treatment groups. Combining lutein with other antioxidants appears to provide added improvement to contrast sensitivity (Richer et al., 2002).

INTERVENTION STUDIES

Investigators found no protective effect of zinc supplementation against development of AMD over an 8-10 year period (Cho et al., 2001). Lutein supplementation at achievable dietary levels increased and maintained serum levels, and this was associated with and improvement in glare recovery and visual acuity (VA) (Olmedilla *et al.*, 2001). A pilot study found that short term intervention including 15mg lutein, was associated with statistically significant changes in macular focal electroretinogram parameters, suggestive of an improvement in retinal function in ARM (Falsini *et al.*, 2003).

A 35% increase in lutein serum levels and a 20% increase in MPOD was demonstrated in a study supplementing 11 subjects daily with 11mg of lutein from 60g of spinach and 150g or corn/maize (Hammond et al., 1997). Supplementation with 10mg/day of lutein esters for 12 weeks was shown to increase serum lutein levels by five times and MPOD by approximately 20% (Berendschot et al., 2000). Serum levels of lutein doubled over 24 months of taking 15 mg lutein three times weekly (Olmedilla et al., 2001).

**An ideal supplement?**

We have reviewed pertinent literature with a view to developing a formulation for an ideal ocular nutritional supplement. Vitamin A has been excluded in favour of the similarly fat-soluble vitamin E, whose properties appear particularly relevant. The evidence supporting the role of B vitamins is insufficient to warrant inclusion at present. The weight of available evidence supports the role of vitamin C in prevention of lens opacities, and the adverse reactions reported have occurred above the dosage of 1000mg/day. Vitamin C has been included at 40mg, equal to its RNIV. Vitamin E was chosen for inclusion in the formulation as it is the major antioxidant present in cell membranes (Packer and Landvik, 1990; Chow, 1991; Packer, 1992) and is present in high quantities within the rod photoreceptor outer segments and the retinal pigment epithelium (Hunt *et al.*, 1984; Friedrichson *et al.*, 1995). It is also thought to protect vitamin A in the retina from oxidative degeneration (Robinson *et al.*, 1982). Adverse effects have been reported for vitamin E, but have occurred at doses significantly higher than the RNIV values. We advocate 40mg d-alpha-tocopherol equivalents since this dosage is one order of magnitude less than the EVM safe upper limit, but one order above the safe intake value (or minimum amount required).

Beta-carotene has been investigated regarding its carotenoid properties, similar to those of lutein and zeaxanthin. It is, however, not present in the human retina (Bone *et al.*, 1985; Khachik *et al.*, 1997) and has been linked with an increased risk of lung cancer in smokers. Its inclusion is precluded by lutein and zeaxanthin, which have been consistently linked with a reduced risk of cataract and age-related macular disease and appear to be intrinsically protective of the retina. No adverse effects have been reported and no safe upper limit has been set. Intervention studies suggest a dosage of 10-15mg, and we suggest a formulation value of 12mg.

Although one study suggested a link between selenium and reduced risk of cataract, there is insufficient evidence to support its inclusion. Zinc is included in most multivitamin formulations and has a safe upper limit of just 25mg. Two randomised controlled trials investigating the role of zinc in age-related macular disease reported conflicting results. Newsome, *et al.* (1988) reported a positive effect of zinc on VA but it is unlikely that their study had enough statistical power to detect a significant difference between the study and placebo groups (Bartlett and Eperjesi, 2003). The AREDS found a suggestive reduction in the progression of age-related macular disease with 80mg daily zinc supplementation (The AREDS Research Group, 2001b). This high dosage may be appropriate for formulations specifically aimed at those with intermediate to advanced AMD, but not for our more general formulation.

There is little reported regarding the use of GBE in ocular disease, but it was shown improve preexisting field damage in NTG. Its role in quenching ROS and reduction of platelet aggregation suggest potential benefit, particularly for age-related macular disease and NTG. Further research into the role of GBE in ocular disease is warranted. The randomised controlled trial results (Lebuisson *et al.*, 1986) should be viewed cautiously, and as such there is insufficient evidence to warrant inclusion of Ginkgo biloba in our formulation.

The supplement described here would not contain nutrients in quantities likely to increase the patient's intake over the safe limits, should they be supplementing with a typical multivitamin/mineral product. In summary, our theoretically ideal formulation would include; 40mg vitamin C, 40mg vitamin E (d-α-equivalents), and 12mg lutein/zeaxanthin.

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