Possible contraindications and adverse reactions associated with the use of ocular nutritional supplements

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Abstract

The role of oxidation in the development of age-related eye disease has prompted interest in the use of nutritional supplementation for prevention of onset and progression. Our aim is to highlight possible contraindications and adverse reactions of isolated or high dose ocular nutritional supplements. Web of Science and PubMed database searches were carried out, followed by a manual search of the bibliographies of retrieved articles. Vitamin A should be avoided in women who may become pregnant, in those with liver disease, and in people who drink heavily. Relationships have been found between vitamin A and reduced bone mineral density, and beta-carotene and increased risk of lung cancer in smoking males. Vitamin E and Ginkgo biloba have anticoagulant and anti-platelet effects respectively, and high doses are contraindicated in those being treated for vascular disorders. Those patients with contraindications or who are considered at risk of adverse reactions should be advised to seek specialist dietary advice via their medical practitioner.

Keywords

Nutritional supplementation, adverse reactions, contraindications, vitamin A, vitamin E, zinc, Ginkgo biloba.

Introduction

People are increasingly taking an active interest in their well-being, and seeking alternative medical therapies (Eisenberg *et al.*, 1998; Gilbert, 1999). Traditional health-care providers have been perceived to have a negative attitude towards these therapies (Goodwin and Tangum, 1998). This may explain why many people do not consider their medical practitioner a major source of nutritional information (Schutz *et al.*, 1982; Barr, 1986; Levy and Schucker, 1987) and do not always report unconventional therapy use to their physicians (Eisenberg *et al.*, 1993).

Use of ocular nutritional supplementation has been investigated with regard to prevention of onset or progression of glaucoma, cataract, and age-related macular disease. There is particular interest in the use of nutrition as a prevention and treatment strategy for age-related

macular degeneration (AMD) as it is the leading cause of visual disability in the developed World (Klein *et al.*, 1997), and because treatment options are currently lacking (Zarbin, 2004).

Eye-care practitioners require information about the benefits, and potential hazards, of ocular nutritional supplements in order to be able to discuss their use with patients. It should be emphasised that the risk of side effects from nutrients is much lower than from over the counter or prescription drugs. As an example, the National Health and Nutrition Examination Survey II estimated that 35 % of the US population use vitamin A supplements (Koplan *et al.*, 1986), and the rate of toxic reactions has been reported as 1 case per 1.1 million per year exposed.

The aim of this review is to highlight possible contraindications and the potential for adverse reactions for those nutrients reported to be beneficial to ocular health.

Methods

We identified pertinent articles on nutrition, nutritional toxicity, and ocular disease published in peer-reviewed journals, through a multi-staged, 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 between 1980 and July 2004. The terms 'ocular disease AND nutrition', 'nutritional supplement AND adverse reactions', and 'nutritional supplement AND contraindications' were 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 toxicity of those nutritional supplements reported to be beneficial for ocular health was incorporated in to the manuscript.

Terminology

In accordance with the International Classification and Grading System for Age-Related Maculopathy (ARM), and Age-Related Macular Degeneration (AMD) (Bird *et al.*, 1995), these abbreviations will be used throughout. The term age-related macular disease will be used to encompass ARM and AMD. Dietary Reference Values (DRV) were established in 1991 to replace Recommended Daily Allowances (RDA). The term DRV is used to cover Lower Reference Nutrient Intake (LNRI), Estimated Average Requirement (EAR), Reference Nutrient Intake (RNI), and safe intake (Mason, 2001). RNI refers to the amount of protein, vitamin or mineral that is sufficient for almost every individual to maintain good health.

Nutrition in prevention of disease

The human body has complex defence systems to combat the damage caused by activated oxygen. Nutrients involved in this defence process include the minerals selenium, copper, magnesium, and zinc, the vitamins E, C and A, and the carotenoids.

Damaging forms of oxygen can be referred to as reactive oxygen species (ROS). ROS is an umbrella term used to describe free radicals, singlet oxygen, and hydrogen peroxide. Free radicals have an unpaired electron in their outer orbits, which makes them damaging to the body. In order to achieve stability they pluck electrons from other molecules, producing further ROS and fuelling a disease-generating cytotoxic chain reaction. Examples of free radicals include the superoxide anion radical, formed from the reduction of molecular oxygen to water, and the hydroxyl radical. The hydroxyl radical is particularly damaging as it can take electrons from almost any organic molecule.

The reduction of oxygen to water also produces hydrogen peroxide, which interacts with the superoxide anion radical to form the hydroxyl radical. Although singlet oxygen does not have an unpaired electron in its outer orbit, it does have a peripheral electron that is excited to an orbital above that which it normally occupies, making it highly reactive (Diplock, 1991).

The hydroxyl radical is the biggest potential threat to living systems because of its high reactivity, which does however, suggest that it is likely to have a short in vivo half-life (Diplock, 1991). Singlet oxygen is scavenged by vitamin A and other retinoids, as well as beta-carotene (Levin *et al.*, 1997) and other carotenoids (Di Mascio *et al.*, 1989). The superoxide anion radical is efficiently removed by the enzyme superoxide dismutase (SOD), which in the mitochondria contains manganese, and in the cytosolic compartment contains copper and zinc. Hydrogen peroxide is metabolised by the selenium-containing enzyme, glutathione peroxidase.

Polyunsaturated fatty acids are particularly vulnerable to attack by the hydroxyl radical resulting in production of lipid peroxyl radicals and lipid hydroperoxide. The formation of lipid hydroperoxides is dependant on the availability of hydrogen, which can be obtained from vitamin E or from other polyunsaturated fatty acid molecules. The use of vitamin E as the donor is preferable, as it prevents the production of more free radicals and the initiation of chain reactions. The resultant vitamin E radical is though to be reformed to vitamin E via a system involving vitamin C and glutathione (Tappel, 1962).

Ocular tissues are particularly susceptible to oxidative damage. The transparency of the cornea, aqueous humor, lens and retina allow continuous exposure to light, which along with aging, inflammation, air pollutants, and cigarette smoke, has been shown to increase production of ROS (Borish *et al.*, 1987; Machlin and Bendich, 1987). The role of oxygen in cataract formation

has been demonstrated (Schocket *et al.*, 1972) and the retina is particularly vulnerable because of its abundance of polyunsaturated fatty acids, the occurrence of phagocytosis within the RPE, and the fact that it has much higher blood flow than other tissues. Phagocytosis results in the production of ROS and high blood flow increases the availability of oxygen.

The antioxidant network

A system of antioxidant nutrients exists to neutralize ROS. Vitamin C reacts with superoxide in the aqueous phase, and vitamin E reacts with peroxy radicals in the lipophilic phase. In the process, vitamins C and E themselves become free radicals. However, they have aromatic ring structures, which delocalize the unpaired electron and are therefore less reactive. They also form part of the 'antioxidant network', in which vitamin C is able to regenerate vitamin E from the vitamin E radicals (Packer, 2001a).

Alpha lipoic acid is a vitamin-like antioxidant that is soluble in both fat and water (Kagan *et al.*, 1990). It is manufactured within the body and is also found in food such as liver and yeast. Dihydrolipoic acid (DHLA), a powerful metabolic antioxidant, is formed when alpha lipoic acid is reduced by enzymes. DHLA has an important role in antioxidant defence through maintenance of high levels of the reduced (potent) forms of vitamins C and E. Alpha-lipoic acid also boosts cellular levels of glutathione, a major cellular antioxidant. Levels of glutathione decline with age, and low levels are associated with higher incidence of disease in the older people. Glutathione concentrations are recognised as a predictor of the susceptibility to disease as well as a marker of biological age (Packer, 2001b).

Review of nutrients

Nutrients that are considered to be beneficial for ocular health have already been reviewed (Bartlett and Eperjesi, 2004) and include vitamins A, B, C and E, beta-carotene, lutein/zeaxanthin, magnesium, selenium, zinc, essential fatty acids, and Ginkgo biloba (see table 1). Drug interactions of these nutrients are shown in table 2.

Insert tables 1 and 2 about here.

Vitamin A

Humans obtain vitamin A in two forms; provitamin A (carotenoids), found mainly in foods of plant origin such as green leafy vegetables or yellow fruit, and preformed vitamin A from animal products such as milk, meat, and liver (Combs, 1998). Provitamin A compounds can be split oxidatively into forms of vitamin A. Vitamin A is essential for maintaining the integrity of epithelial tissues, and normal growth and differentiation of epithelial cells. It is also involved with reproduction, and the growth of developing bony structures (Burton and Foster, 1988). Pro-vitamin A in the form of beta-carotene was used in combination with other nutrients for the Age-

Related Eye Disease Study (AREDS) (The AREDS Research Group, 2001b) and the Roche European American Cataract Trial (REACT) (The REACT Group, 2001). These randomised controlled trials (RCTs) found positive effects of intervention for age-related macular disease and cataract respectively.

Provitamin A is not considered to be potentially toxic as the efficiency of absorption falls with increased dietary intake (Brubacher and Weiser, 1985). Absorption of preformed vitamin A, however, remains efficient (approximately 90%) even when dietary intake is high; absorption of high dose supplements is closer to 50%. When high doses of preformed vitamin A are consumed, oxidation produces retinoic acid, which has a potent effect on differentiation and gene expression (Allen and Haskell, 2002). Vitamin A capsules are available without prescription in concentrations of 25 000 IU. The estimated daily biological requirement for vitamin A is 2667 IU retinol for women and 3300 IU retinol for men (National Research Council, 1989). Marketing of vitamin A for treatment of acne and certain cancers may result in high dose supplementation and increase the risk of toxicity.

Lutein/zeaxanthin

Lutein, and its stereo-isomer, zeaxanthin, are xanthophylls, and are the only carotenoids found in human serum that are also found in the retina and macula (Bone *et al.*, 1985; Handelman *et al.*, 1988; Handeman *et al.*, 1992) and the crystalline lens (Yeum *et al.*, 1995). It has been suggested that they play a similar role in humans as in plants, as antioxidants and screeners of high-energy blue light (Krinsky, 2002).

In the retina they are termed the macular pigment (MP). Zeaxanthin dominates in the macula centre, whereas, lutein is more abundant in the medial and peripheral macula (Bone *et al.*, 1997). This suggests a possible protective role of lutein for rod photoreceptors (Sommerburg *et al.*, 1999) and of zeaxanthin for the central cone photoreceptors (Bone *et al.*, 1988).

The MP may prevent light-initiated oxidative damage to the retina and therefore protect against subsequent age-related deterioration (Hammond *et al.*, 1998). The absorbance spectrum of MP peaks at 460 nm. It is purported to act as a broadband filter, reducing the sensitivity of the macular region to short wavelength light that is most damaging in the 440 to 460 nm range (Reading and Weale, 1974; Pease *et al.*, 1987). Zeaxanthin is reported to be a superior photo-protector during prolonged UV exposure; the shorter time-scale of protective efficacy of lutein has been attributed to oxidative damage of the carotenoid itself (Sujak *et al.*, 1999).

The MP also acts as a scavenger of ROS. The relatively high concentration of MP in the inner retinal layers (Snodderly *et al.*, 1984) is very likely to indicate a photoprotective role, while the presence of MP in the rod outer segments (Sommerburg *et al.*, 1999), is suggestive of a ROS-

quenching function. Lutein and zeaxanthin have been found in higher concentration in the rod outer segments of the perifoveal retina than the peripheral retina, again lending support to their proposed protective role in age-related macular disease (Rapp *et al.*, 2000).

The carotenoid lutein has been investigated with regard to preventing onset and progression of age-related macular disease and has been shown to improve measures of visual function in AMD patients (Richer *et al.*, 2004). In a South Pacific population, daily intake of an average of 26 mg/day of lutein yielded no apparent side-effects (Le Marchand *et al.*, 1995).

B vitamins: B2, B6, and B12

The B vitamins are water soluble. Vitamin B2 (riboflavin) 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). Vitamin B6 (pyroxidine) refers to a group of nitrogen-containing compounds with three primary forms: pyridoxine, pyridoxal, and pyridoxamine. B6 participates in over 100 enzymatic reactions and has a reported role in gluconeogenesis (Leklem, 1988), lipid metabolism (Birch, 1938), erythrocyte metabolism (Bottomley, 1983), and immune function (Robson and Schwarz, 1975; Talbott *et al.*, 1987; Meydani *et al.*, 1991; Rall and Meydani, 1993). Cobalamin (B12) is an essential cofactor for two enzymes: methylmalonyl-CoA mutase is needed for fatty acid metabolism, and methionine synthase (Stubbe, 1994), which controls nucleic acid synthesis and methylation reactions within the body. Deficiency leads to megaloblastic anaemia via reduced production of red blood cells and cobalamin-associated neuropathy.

Vitamins B6 and B12 and folate (folic acid) regulate homocysteine concentrations in the blood - a risk factor for cardiovascular disease. There is a reported increased risk of coronary heart disease (CHD) or ischaemic stroke associated with low folate intake or low blood folate levels (Eikelboom *et al.*, 1999). In meta-analysis (Homocysteine Lowering Trialists' Collaboration, 1998), folate lowered plasma homocysteine levels by 25 %, and addition of B12 lowered levels by a further 7 %.

Vitamins B2 (Leske *et al.*, 1991; Kuzniarz *et al.*, 2001) and B12 (Kuzniarz *et al.*, 2001) have been linked with a reduced risk of cataract.

Vitamin C

Almost 35 % of the US population use vitamin C (ascorbic acid) supplements. Side effects are rare and there appear to be no contraindications for doses of up to 2 mg/day (Bloch, 2000). It is water soluble, reduces platelet aggregation (Wilkinson *et al.*, 1999), and may be important in lowering blood pressure (Taddei *et al.*, 1998). RCTs investigating the effect of vitamin C in combination with other nutrients found a positive effect for progression of AMD (The AREDS

Research Group, 2001b) and a small positive effect for cataract (The REACT Group, 2001), although no effect against cataract has also been reported (The AREDS Research Group, 2001a).

Vitamin E

Alpha-tocopherol is the most effective antioxidant of the vitamin E group, and protects against lipid peroxidation (Machlin, 1980). RCTs investigating the effect of vitamin E supplementation on incidence or progression of age-related macular disease have found no positive effect (Teikari *et al.*, 1998; Taylor *et al.*, 2002), although positive effects of vitamin E supplementation in combination with other nutrients have been reported for progression of AMD (The AREDS Research Group, 2001b) and cataract (The REACT Group, 2001). Several studies have found no adverse reactions with vitamin E supplementation in normals (Tsai *et al.*, 1978; Stampfer *et al.*, 1983; Kitigawa and Mino, 1989) cardiac patients (Inagaki *et al.*, 1978), angina pectoris patients (Anderson and Reid, 1974; Gillian *et al.*, 1977), and diabetic patients (Steinberg, 1993).

Zinc

Zinc is an essential component of over 200 enzymes, including antioxidant enzymes such as superoxide dismutases (Machlin and Bendich, 1987). Evidence for (Newsome *et al.*, 1988) and against (Stur *et al.*, 1996) a role of zinc supplementation in prevention of progression or development of AMD is presented by RCTs, although the positive result may be treated with caution (Bartlett and Eperjesi, 2003). Zinc acts as a cofactor for the antioxidant enzymes retinal dehydrogenase and catalase (Sigel, 1983) and is also involved in retinal metabolism.

Selenium

Selenium is a constituent of the enzyme glutathione peroxidase, which protects cell membranes from oxidative damage (Rotruck *et al.*, 1973; Singh *et al.*, 1984). Glutathione peroxidase metabolises hygrogen peroxide, thereby reducing the risk of free-radical mediated oxidative damage. The efficiency of gluthione peroxidase depends on the nutritional availability of selenium (Diplock, 1991).

Animal studies have shown evidence for a protective role of selenium against development of cataract (Langle *et al.*, 1997), and a marginal relationship between elevated selenium intake and reduced risk of cataract has been proposed (Valero *et al.*, 2001).

Magnesium

Magnesium is related to the stability of cell walls and membranes, and many magnesium-containing enzymes are involved in metabolic processes (Gibson and Reif, 1985; Pasquare and Giusto, 1993; Salvadore and Giusto, 1998). The retina contains many magnesium-containing enzymes that may be related to retinal physiological function (Gong *et al.*, 2001). Magnesium

deficiency has been shown to induce multifocal necrosis in RPE cells of the rat (Gong *et al.*, 2001) and this trace element is essential for maintenance of the structure and function of the cornea (Gong *et al.*, 2003).

Ginkgo biloba

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 a role in neurotransmitter metabolism (Defeudis, 1991). Ginkgo biloba is marketed as a supplement to increase mental alertness and treat peripheral vascular disorders. One of its components is an inhibitor of the platelet aggregating factor (Rosenblatt and Mindel, 1997), and it has also been found to contain a natural nerve toxin (Arenz *et al.*, 1996).

One RCT found an improvement in visual acuity (VA) in AMD patients who supplemented with ginkgo biloba extract (GBE) (Lebuisson *et al.*, 1986), although it has been suggested that these results should be treated with caution (Evans, 2000). GBE has also been reported to improve pre-existing visual field damage in normal tension glaucoma (Quaranta *et al.*, 2003).

Essential fatty acids

Saturated fats consist of a chain of four to 22 carbon atoms. The carbon atoms within the chain are linked to two hydrogen atoms. At one end of the chain the carbon atom is linked to three hydrogen atoms, and at the other end of the chain the carbon atom is linked to an oxygen atom and an oxygen and a hydrogen atom. This is called the carboxyl end and forms the acid group of the molecule. Within the carboxyl group, the lone oxygen atom is linked to the final carbon atom with a double bond.

Essential fatty acids (EFA) are polyunsaturated. This means that they contain double bonds within their carbon chains. Linoleic acid is an 18 carbon chain fatty acid with two double bonds in the middle of the chain. As a result, it is missing four hydrogen atoms, all on one side. The first double bond occurs at the sixth carbon atom. For this reason, linoleic acid is often referred to as omage-6 EFA. Because of its four missing hydrogen atoms, omega-6 EFA is fairly unstable, and reacts with light and oxygen.

Alpha linoleic acid is an 18 carbon fatty acid with three double bonds. This means that it is missing six hydrogen atoms, all on one side. The first double bond occurs at the third carbon atom and so alpha linoleic acid is known as omega-3 EFA, and is sometimes referred to as a super unsaturated fatty acid (SUFA). This molecule is very unstable and readily reacts with light and oxygen.

Sources of omega-6 EFA include oils made from safflower, sunflower, corn, soya, evening primrose, pumpkin, and wheatgerm, as well as, dairy products, beef, poultry and eggs. Sources of omega-3 EFA include oils made from flaxseeds, mustard seeds, pumpkin seeds, soya bean, walnut oil, green leafy vegetables, and grains. Omega-3 and omega-6 EFA are converted within the body to other polyunsaturated fatty acids (PUFA) including EPA (eiocosapentaenoic acid), DHA (docosahexaenoic acid) and arachidonic acid. EPA and DHA are found in mackerel, salmon, sardines, sablefish, anchovies, and cod liver oil (Mann and Skeaff, 2002). Fish oil supplements usually contain 18 % EPA and 12 % DHA.

Within the body, PUFAs are needed for maintaining cell membranes, and making prostaglandins, which regulate many body processes such as inflammation and blood clotting. Omega-3 EFA have been linked with reduced incidence of dry eye (Trivedi *et al.*, 2003). However, a high ratio of omega-3 to omega-6 EFA appears to increase the risk of primary open angle glaucoma (POAG), particularly high-tension POAG (Kang *et al.*, 2004).

Contraindications of supplements

Contraindications: pro-vitamin A

On a previous review of the literature, beta-carotene was promoted as a preferred source of vitamin A due to the fact that it has virtually no adverse effects (Meyers *et al.*, 1996). However, doses of 20 mg/day beta-carotene, alone or in combination with alpha-tocopherol (vitamin E) (The ATBC Cancer Prevention Study Group, 1994), and 30 mg/day in combination with retinyl palmitate (vitamin A) (Leo and Lieber, 1997) have been associated with an increased risk of lung cancer in smokers and those previously exposed to high levels of asbestos. The Physician's Health Study found no effect of 50 mg beta-carotene every other day in a trial population comprising 11 % smokers (Christen *et al.*, 2000). Hypotheses for the proposed increased risk of lung cancer in smokers include pro-oxidant behaviour by beta-carotene initiated by the high oxygen tension within the lungs, and the production of damaging oxidation products by the components of cigarette smoke.

Beta-carotene may be contraindicated in AMD patients as plasma lutein concentration is reduced following multiple (Micozzi *et al.*, 1992) and single (Kostic *et al.*, 1995) doses. Other studies have, however, found no effect of beta-carotene on serum levels of lutein (Fotouhi *et al.*, 1996). In the ARED Study, serum levels of lutein and zeaxanthin decreased over five years, although changes in the treatment arm were not significantly different from the placebo arm ($p > 0.07$) (The AREDS Research Group, 2001b).

Contraindications: pre-formed vitamin A

There are reports of lower bone mineral density with vitamin A supplementation (Sowers *et al.*, 1985), as well as increased risk of osteoporotic fracture (Melhus *et al.*, 1998). Studies suggest

that bone re-absorption is stimulated by vitamin A (Jowsey and Riggs, 1968; Frame *et al.*, 1974), and also that vitamin A toxicity decreases bone formation (Frankel *et al.*, 1986; Hough *et al.*, 1988). Vitamin A supplementation was inversely related to the rate of change of ulna bone mineral content in post-menopausal women taking part in a four-year clinical trial (Freudenheim *et al.*, 1986). Intake of 1500 µg retinol equivalents (RE)/day compared with 500 µg RE/day was associated with a total body reduction in bone mineral density of 6% ($p = 0.009$) and twice the chance of hip fracture (OR = 2.1, 95% CI = 1.1 – 4.0), although this study may be limited by information bias (Melhus *et al.*, 1998). White women consuming ≥ 3000 µg RE/day had an increased relative risk for hip fractures (RR, 1.48; 95% CI, 1.05 – 2.07) compared to those taking < 1250 µg RE/day (Feskanich *et al.*, 2002), and retinol intake has been associated with decreased bone mineral density and increased bone loss at total daily intakes above 840 µg (Promislow *et al.*, 2002).

However, daily supplementation with 7576 µg of retinol palmitate for six weeks did not affect the serum markers of skeletal turnover in healthy men (Kawahara *et al.*, 2002), and no significant association between fasting serum retinyl esters and bone mineral density was found in a population of 5790 women aged 20 years or over (Ballew *et al.*, 2001).

Teratogenic effects have been reported with high doses of retinoic acid consumed within the first six weeks of pregnancy (Lammer *et al.*, 1985). It has been suggested that vitamin A doses should not exceed 10 000 IU/d during pregnancy (Bauernfeind, 1972); this dosage has been shown to maintain blood vitamin A levels in the mother without increasing them in the newborn (Pereira and Begum, 1976).

Vitamin A supplements have been shown to increase the tendency towards abnormal bleeding in rats (Walker *et al.*, 1947; Doisey, 1961; Schrogie, 1975), which may indicate that it interacts with vitamin K. Vitamin K is required for production of coagulation proteins, and so deficiency reduces blood coagulation. This effect has yet to be determined in humans.

Valporoic acid (anticonvulsant) may interfere with the body's ability to handle vitamin A (Nau *et al.*, 1995).

Isotretinoin is a modified vitamin A molecule used to treat severe acne vulgaris, which has above average toxicity potential. People taking isotretinoin should avoid additional vitamin A supplements as little is known about how the two interact. Combined administration of isotretinoin and vitamin E may reduce the initial toxicity of high-dose isotretinoin without reducing its efficacy (Dimery *et al.*, 1997). High dose vitamin A and isotretinoin should be avoided by women who might become pregnant, patients with liver disease, and those who drink heavily.

Contraindications: vitamin C

Large doses of vitamin C are generally well-tolerated. Vitamin C was investigated with regard to a possible interaction with oral anticoagulants following reports of an unexpected decrease in pro-thrombin time in people taking warfarin (Rosenthal, 1971; Smith *et al.*, 1972). No change in coagulation status occurred in humans supplemented with 1 g/day for 14 days (Hume *et al.*, 1972). Impaired blood coagulation time (Barness, 1975) and interference with anticoagulant therapy (Sigell and Flessa, 1970) have been reported when doses ≥ 1 g are ingested routinely for months or years. Interestingly, studies suggest that the anti-platelet drug, aspirin, promotes loss of vitamin C via the urine (Molloy and Wilson, 1980; Das and Nebioglu, 1992).

Reduced bactericidal activity of leucocytes (Shilotri and Bhat, 1977), reduced insulin production (Levey and Sutur, 1946) may occur with routine doses ≥ 1 g over months or years. High doses of vitamin C have also been reported to interfere with the breakdown of acetominophen (Houston and Levy, 1976).

Contraindications: vitamin E

A randomised controlled trial (RCT) showed that 400 IU/day vitamin E may have an adverse effect on the progress of common forms of retinitis pigmentosa (RP) (Berson *et al.*, 1993). Participants taking this dosage of 400 IU/day vitamin E had a faster rate of decline in electroretinogram amplitude that those taking 3 IU/day. The decline rates were 11.8 % and 10.0 % for the dosage levels respectively. Investigators hypothesised that the 400 IU/day dosage of vitamin E may inhibit the absorption or transport of vitamin A, as the participants receiving this dosage of vitamin E had significantly decreased serum retinol levels compared with those not receiving vitamin E ($p = 0.03$).

Vitamin E may exacerbate the effects of vitamin K deficiency and has been associated with an increased risk of haemorrhagic stroke, and a reduced risk of ischaemic stroke and ischaemic heart disease (The ATBC Cancer Prevention Study Group, 1994). Other studies have found no relationship between vitamin E and haemorrhagic stroke (Gillian *et al.*, 1977; Ascherio *et al.*, 1999; GISSI-Prevenzione Investigators, 1999; Leppala *et al.*, 2000a; Yusuf *et al.*, 2000; Primary Prevention Project, 2001; Heart Protection Study Collaborative Group, 2002), and smokers with diabetes may represent a subset of the population that may benefit from 50 IU vitamin E per day without experiencing an increased risk of bleeding (Leppala *et al.*, 2000a).

Oral anticoagulants, such as warfarin, antagonise the effects of vitamin K and are indicated in deep-vein thrombosis and pulmonary embolism patients. The action of oral anticoagulants may be increased by concurrent administration of vitamin E. Concurrent vitamin E and warfarin use has been associated with abnormal bleeding (Corrigan and Marcus, 1974), and vitamin E appears to add to aspirin's blood thinning effect (Liede *et al.*, 1998; Leppala *et al.*, 2000b).

However, vitamin E does not cause coagulation abnormalities in those who do not have coagulation abnormalities (Diplock, 1995). It has been suggested that anticoagulant-treated patients should avoid megadoses of vitamin E.

Contraindications: zinc

Patients with type I diabetes should consult their doctor before starting zinc supplementation as it has been reported to increase glycosylation (Cunningham *et al.*, 1994). Glycosylation refers to the addition of glucose to proteins, which is thought to be responsible for some of the clinical manifestations of the disease (Otsuji and Kamada, 1982; Huntley, 1995). Zinc supplementation has, however, been shown to reduce blood sugar levels in those with type 1 diabetes (Rao *et al.*, 1987), although it may not improve blood sugar levels in type 2 diabetes (Niewoehner *et al.*, 1986).

Contraindications: Ginkgo biloba

Gingko biloba may thin the blood, and should be avoided prior to surgery, and also by those taking certain anticoagulant and antiplatelet drugs (Rosenblatt and Mindel, 1997; Matthews, 1998).

Adverse reactions

Adverse reactions: pro-vitamin A

Individuals consuming ≥ 30 mg beta-carotene/day may experience hypercarotenemia (high plasma beta-carotene), which has also been observed in infants fed commercial foods containing large amounts of ground carrots (Lascari, 1981). The only adverse effect of hypercarotenemia is a reversible yellowing of the skin (hypercarotenodermia). Babies born with hypercarotenemia from high maternal intakes were otherwise normal, and so beta-carotene is not considered significantly toxic to the human foetus (Mathews-Roth, 1988).

Adverse reactions: pre-formed vitamin A

Globally, the incidence of vitamin A toxicity, or hypervitaminosis A is a minor problem (200 cases per year) compared with the incidence of vitamin A deficiency (VAD) (1 million cases per year) (Bauernfeind, 1980). In 118 countries where foods lacking in carotene are staple, VAD is a serious public health problem (World Health Organisation, 2003), combated by a successful WHO supplementation programme (Vijayaraghavan *et al.*, 1975). In young children, 100 000 IU of vitamin A at 6 – 11 months and 200 000 IU given every 3 to 6 months for children aged between 12 and 60 months gives few side effects and is effective for reducing mortality (Beaton *et al.*, 1993). Nausea, vomiting, headache, diarrhoea and fever have, however, been reported in some children in the Phillipines with doses of 100 000 and 200 000 IU (Florentino *et al.*, 1990).

Symptoms of adult toxicity have, however been reported with single or short-term doses of about 50 000 IU (Bendich and Langseth, 1989), and include nausea, vomiting, increased cerebrospinal fluid pressure, headaches, blurred vision, and lack of muscular coordination. Chronic toxicity, resulting from long term consumption of high dose vitamin A include vomiting, weight loss, bone abnormalities, headache, fever, an enlarged liver and raised intracranial pressure (Bush and Dahms, 1984). Women may experience menstrual disturbances. Response times for vitamin A toxicity range from 6 – 108 months for a dose of 100 000 IU per day, and days or weeks for doses of 1 000 000 IU per day (Bauernfeind, 1980).

Vitamin A has been used therapeutically in retinitis pigmentosa (Berson *et al.*, 1993). A study showed that long-term supplementation with 15 000 IU daily vitamin A in healthy adults aged 18 – 54 years elicited no adverse effects, and no evidence of hepatic toxicity (Sibulesky *et al.*, 1999)

Vitamin A has been shown to reduce vitamin E activity (an important antioxidant) by as much as 30% (Anon., 1985), although plasma levels of vitamin E were not affected in a human study of 25 000 IU/day vitamin A given for 16 weeks (Willett *et al.*, 1983). In animal models, vitamin E has been shown to protect membranes against vitamin A hypervitaminosis-induced damage (Soliman, 1972). Animal studies have shown that vitamins A and D decrease the toxic effects of each other (Metz *et al.*, 1985), and also that zinc may be specifically involved in mobilizing vitamin A from the liver to the circulation within a short period (Ette *et al.*, 1979).

The symptoms of hypervitaminosis-A are usually relieved within a week of discontinuation, but long-term or irreversible effects can include cirrhosis (Hruban *et al.*, 1974) and bone changes (Bauernfeind, 1980).

Adverse reactions: vitamin C

Doses of vitamin C up to 2000 mg per day are well-tolerated, although stomach cramps, nausea, and diarrhoea may occur with higher doses (Olson and Hodges, 1987). An review of the literature concluded that high doses of vitamin C are safe and free of side effects (Diplock, 1995).

Adverse reactions: zinc

Zinc interacts with copper by stimulating metallothionein levels of the intestinal wall. Metallothionein binds to dietary copper preventing absorption, which leads to copper deficiency. This can result in copper deficiency anaemia, since copper is required for production of erythrocytes (Dunlap *et al.*, 1974; Fischer *et al.*, 1983; Flanagan *et al.*, 1983).

Daily supplementation with more than 300 mg zinc per day has been associated with impairment of immune function (Broun *et al.*, 1990). There are reports of a potential role of zinc in Alzheimer-associated neuropathogenesis (Bush *et al.*, 1994), although more recent evidence from four patients showed an improvement in mental function with zinc supplementation (Potocnik *et al.*, 1997).

Acute zinc toxicity has been reported with doses of 200 mg or more (Expert Group on Vitamins and Minerals, 2003). In one study 20 female and 21 male volunteers were given 150 mg/day zinc for six weeks (Samman and Roberts, 1987). Symptoms including headaches, nausea, abdominal cramps, loss of appetite and vomiting were reported in 85 % of the female and 18 % of the male volunteers. These were particularly apparent when small meals or no food was taken with the supplements. The investigators suggested that the high percentage of females experiencing side-effects could be attributed to their lower body weight.

Adverse reactions: *Ginkgo biloba*

One case report associated long term use of GBE with bilateral subdural haematomas and increased bleeding time in a healthy 33-year old female (Rowin and Lewis, 1996).

Conclusions

Practitioners should be particularly aware of potential relationships between vitamin A and reduced bone mineral density, beta-carotene and an increased risk of lung cancer in smokers, and the anticoagulant and anti-platelet effects of vitamin E and Ginkgo biloba respectively (Liede *et al.*, 1998). Vitamin A supplements should be avoided by women who may become pregnant, in those with liver disease and those who drink heavily.

When discussing ocular nutritional supplements with patients, practitioners should be aware of the contraindications and the potential for adverse reactions. Those contraindicated from certain supplements, or identified as at risk of adverse reaction, should be advised to discuss supplementation with their medical practitioner.

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Nutrient	Sources	Main functions	Recommended daily	Safe upper Limit	Tolerable upper

			allowance for adults		intake level (US Food and Nutirion Board)
Vitamin A	As vitamin A: fish liver oils, beef liver, egg yolk, butter and cream As carotenoids (pro-vitamin A): dark green leafy vegetables, yellow fruits and red palm oil	Maintenance of vision, skin, lining of intestine, lungs and urinary tract. Helps protect against infection. Used as the basis of drugs called retinoids that are used to treat severe acne and some cancers.	700-900 µg. 1300 µg for pregnant and breastfeeding women.	500 IU/d to 10 000 IU/d (Meyers *et al.*, 1996).	3000 g (retinol)
Vitamin E	Vegetable oil, wheat germ, leafy vegetables, egg yolk, margarine and legumes.	Acts as an antioxidant.	15 mg	800 IU or 540 mg of d-α-tocopherol equivalents (Expert Group on Vitamins and Minerals, 2003).	1000 mg
Vitamin B2	Milk, cheese, liver, meat, fish, eggs and enriched cereals.	Required for metabolism of carbohydrates and amino acids and for healthy mucous membranes.	1.1 mg women 1.3 mg men	-	-
Vitamin B6	Dried yeast, liver, organ meats, whole-grain cereals, fish and legumes.	Required for metabolism of amino acids and fatty acids, for nerve function, for the formation of red blood cells and for healthy skin.	1.5 mg women 1.7 mg men	10mg/d (Expert Group on Vitamins and Minerals, 2003) although usually safe up to 200 mg/d (Gaby, 1990).	25 mg
Vitamin B12	Liver, meat, eggs, milk and milk products.	Required for the metabolism of carbohydrates and fatty acids.	2.4 µg	2 mg/d cyanocobalamin (Expert Group on Vitamins and Minerals, 2003).	-
Vitamin C	Citrus fruits, tomatoes, potatoes, cabbage, and green peppers.	Required for the formation and growth of bone and connective tissue, for healing of wounds and burns, and for	75 mg women 90 mg men 35 mg extra for smokers	2 mg (Bloch, 2000).	2000 mg

		normal function of blood vessels. Acts as an antioxidant and helps the body to absorb iron.			
Magnesium	Leafy green vegetables, nuts, cereal, grains and seafood	Required for the formation of bone and teeth, for normal nerve and muscle function, and for the activation of enzymes.	300 mg/d men. 270 mg/d women	Guidance level of 400 mg/d (Expert Group on Vitamins and Minerals, 2003).	250 mg
Selenium	Meats, seafood, and cereals (dependant on the selenium content of the soil where the grain was grown).	Acts as an antioxidant with vitamin E, protecting cells from oxidative damage. Also required for thyroid gland function.	55 µg	500 µg (Gaby, 1990).	300 µg
Zinc	Organ meats such as liver, eggs and seafood.	Used to form many enzymes and insulin. Required for healthy skin, healing of wounds, and growth.	15 mg	25 mg supplemental zinc (Expert Group on Vitamins and Minerals, 2003).	40 mg
Ginkgo biloba	*Ginkgo biloba* tree	Reduction in platelet aggregation and the production of free radicals. Role in neurotransmitter metabolism.	Trials have used between 120 and 240 mg/d	-	-
Omega 3 essential Fatty acids	Fish oils including cod liver oil. Flaxseeds, linseeds, pumkin seeds, soya bean, walnut oil, green leafy vegetables, grains, and oils made from linseed,	Maintenance of cell membranes and production of prostaglandins.	0.2 x to 0.5 x amount of omega 6 EFA.	-	-

	rapeseed, and soya beans.				
Omega 6 essential Fatty acids	Vegetables, fruits, nuts, grains, seeds and oils made from safflower, sunflower, corn, soya, Evening primrose, pumkin, and wheatgerm. Also dairy products and beef.	Maintenance of cell membranes and production of prostaglandins.	3 – 6 % of total calories, or 6 -12 g.	-	-

Table 1: Summary of source, function, recommended daily allowance, and safe upper limits for nutrients and herbs associated with ocular health.

Supplement	Drug	Explanantion

Vitamin A	Anticonvulsant agents	Valproic acid may interfere with the body's ability to handle vitamin A (Nau *et al.*, 1995).
Vitamin B6	Folic acid	B6 may reduce the absorption or activity of folic acid.
Vitamin C	Acetaminophen (pain relief)	High doses of vitamin C may interfere with normal breakdown of this drug. May result in liver-damaging accumulation of acetaminophen (Houston and Levy, 1976).
Vitamin C	Anticoagulants	Impaired blood coagulation time (Barness, 1975) and interference with anticoagulant therapy (Sigell and Flessa, 1970) have been reported when large doses (≥ 1 g) are ingested routinely for months or years.
Vitamin E	Warfarin	800 IU daily vitamin E caused abnormal bleeding when added to the effects of warfarin (Cirrigan and Marcus, 1974)
Vitamin E	NSAIDs	Vitamin E appears to add to aspirin's blood thinning effects (Liede *et al.*, 1998; Leppala *et al.*, 2000b).
Ginkgo biloba	Anticonvulsants	A natural nerve toxin has been found in the seeds of Ginkgo biloba (Arenz *et al.*, 1996).This toxin could prevent anticonvulsants from working as expected.
Ginkgo biloba	Warfarin	Ginkgo biloba appears to reduce the ability of platelets to stick together (Chung *et al.*, 1987). Ginkgo biloba may add to the blood-thinning effects of warfarin (Matthews, 1998).
Ginkgo biloba	NSAIDs	The combination of Ginkgo biloba and aspirin may increase the chance of abnormal bleeding (Rosenblatt and Mindel, 1997).
Magnesium	Amiloride (diuretic)	Amiloride may reduce urinary excretion of magnesium in animals (Devane and Ryan, 1981). People taking more than 300 mg magnesium and amiloride should consult their doctor.
Magnesium	Flouroquinoline antibiotics Tetracyclines Nitrofurantoin (antibiotic)	Magnesium can bind to these antibiotics, greatly decreasing the absorption of the drug (Holt, 1998). It is recommended to take the

		drugs two hours after consuming mineral-containing supplements (Threlkeld, 1994).
Magnesium	Misoprostol (prostaglandin E1 analogue that protects the mucosal lining of the stomach and intestines.	A common side effect of misoprostol is diarrhoea, which is aggravated by magnesium (Sifton, 2000).
Magnesium	Oral corticosteroids	Loss of magnesium from the body may be increased by magnesium (Holt, 1998). Magnesium may interfere with absorption of dexamethasone (Naggar *et al.*, 1978).
Zinc	Fluoroquinolone antibiotics Tetracyclines	Zinc can bind to these antibiotics, greatly decreasing the absorption of the drug (Holt, 1998). It is recommended to take the drugs two hours after consuming mineral-containing supplements (Threlkeld, 1994).

Table 2: Drug interactions of nutritional supplements considered beneficial for ocular health.

Abbreviated title

Adverse reactions of ocular nutritional supplements.