Age-related macular degeneration and nutritional supplementation: a review of randomised controlled trials

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Abstract

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in the developed world. The lack of effective treatment modalities, coupled with evidence supporting an oxidative pathogenesis, has increased interest in the potential preventative role of nutritional supplementation.

This article reviews seven randomised controlled trials (RCTs) that have investigated the role of nutritional supplementation in AMD. Three of these trials reported a positive effect of nutritional supplementation on AMD; the Age-Related Eye Study (AREDS), the Lutein Antioxidant Supplementation Trial (LAST), and the oral zinc trial by Newsome et al. (1988). However, the oral zinc trial by Newsome et al. (1988) was unlikely to detect any difference between treatments smaller than 72%, and the AREDS results were based on a subgroup of their study population. Lutein was considered for the AREDS formulation, but was not commercially available at that time. The findings of the LAST support a possible therapeutic role of lutein in AMD.

Keywords

Age-related macular degeneration, randomised controlled trials, antioxidants, carotenoids, lutein

Introduction

Randomised controlled trials (RCTs) are considered to be the gold standard in clinical research (Gray, 1997; Huwiler-Muntener, 2002). The aim of this review is to evaluate RCTs that relate to the effect of nutritional supplements on age-related macular degeneration (AMD). RCTs involve random assignment of participants into treatment and placebo groups. The advantage of trials of this type is the ability to reduce, by masking, the influence of confounding variables by random assignment of the treatment (intervention), and the ability to reduce bias or the possibility that any observed effect is due to other factors. The term 'double-masked' or 'double-blinded' refers to the fact that neither investigator nor participants know who is in the treatment or placebo group. In RCTs designed to investigate the effect of nutritional supplements, this is usually achieved by coding of the tablet containers. At the end of the trial period the code is broken and the gathered data analysed.

In summary, any RCT will involve the following steps (Hulley *et al.*, 2001):

1. Sample selection from the population
2. Baseline variables measured
3. Participants randomised
4. Interventions applied (one will be a placebo)

5. Follow up of the cohort
6. Outcome variables measured
7. Results analysed

The role of nutritional supplementation in ocular health is of interest to eye care practitioners. Many have expressed a need for clearer guidance regarding the recommendation of supplements to their patients (Evans, 2002; Stainer, 2002). The increase in advertising and marketing of nutritional formulations has, in turn, increased awareness of the potential benefits of these supplements within the general population.

Terminology of age-related macular degeneration

The International Classification and Grading System for Age-Related Maculopathy (ARM) and Age-Related Macular Degeneration (AMD) has been developed in an attempt to standardise terminology (Bird *et al.*, 1995):

ARM is characterised by soft, confluent drusen, areas of hyperpigmentation associated with drusen, areas of hypopigmentation of the RPE without any visibility of choroidal vessels associated with drusen (also known as 'early AMD').

AMD is a late stage of ARM and includes both non-exudative and exudative macular degeneration.

In this article the terms ARM and AMD will be used according to this classification.

Aetiogenesis of AMD

AMD is the leading cause of blindness in the developed world (Klein *et al.*, 1992; Klein *et al.*, 1995; Evans and Wormald, 1996). Diet has been related to AMD as well as other chronic conditions such as hypertension and cardiovascular disease (Williams *et al.*, 1971; Manson *et al.*, 1991; Osilesi *et al.*, 1991; Jacques, 1992a; Jacques, 1992b; Gey *et al.*, 1993; Vitale *et al.*, 1993; West *et al.*, 1994).

Oxidation hypothesis

One hypothesis for the aetiology of AMD involves the breakdown of antioxidant systems within the retina. 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, activated forms of oxygen (Eye Disease Case Control Study (EDCCS) Group, 1993) called free radicals. Free radicals are molecules that have one or more unpaired electrons and are produced via the process of oxidation. Normal aerobic metabolism produces free radicals such as superoxide, hydroxyl radicals, singlet oxygen radicals and hydrogen peroxide. Free radicals can initiate lipid peroxidation, which is thought to lead to oxidative damage to DNA, protein and carbohydrate within cells (Curcio and

Millican, 1999). The retina is particularly susceptible to damage via this process for several reasons:

1. Polyunsaturated fatty acids are abundant in the retina, particularly the macular region. They are found in photoreceptor outer membranes and are readily oxidised (Machlin and Bendich, 1987; Beardsley, 1991; Van der Hagen *et al.*, 1993).

2. The retina is subjected to high levels of light exposure. Light (particularly blue light) is a strong oxidising agent. The simultaneous presence of light and oxygen promotes production of free radicals (Schalch, 1992).

3. Phagocytosis, which itself produces free radicals, occurs within the retinal pigment epithelium (RPE).

4. The retina is highly active metabolically and has a much higher blood flow than other tissues (Schalch, 1992).

The body has several defence mechanisms against the production of free radicals. 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 free radicals (Machlin and Bendich, 1987; Pippenger *et al.*, 1991).

Other factors in AMD pathogenesis have been proposed, such as the declining function of Bruch's membrane with age (Feeney-Burns and Ellersieck, 1985; Bird and Marshall, 1986; Chuang and Bird, 1988), vascular insufficiency (Klein 1999), and genetic predisposition (Hyman *et al.*, 1983; Smith and Mitchell, 1998).

Bruch's membrane deterioration

As the conductivity of Bruch's membrane declines with age (Feeney-Burns and Ellersieck, 1985; Bird and Marshall, 1986; Chuang and Bird, 1988); the consequential impedance of fluid flow from the RPE towards the choroid results in RPE detachment. Geographic atrophy may result if there is a reduction in

metabolic exchange between the choroid and the RPE. The material in Bruch's membrane may be derived from the RPE (Ishibashi *et al.*, 1986; Sheraidah *et al.*, 1993; Moore *et al.*, 1995). Blockage of nutrition or proliferation of choroidal blood vessels under the retina caused by this thickening of Bruch's membrane, may initiate choroidal neovascularisation. These new blood vessels destroy structures around them as they grow (Silvestri, 1997).

Vascular insufficiency

Changes in choroidal circulation may effect the normal diffusion of substances and gasses across the RPE-Bruch's membrane complex and have been linked with development of AMD (Verhoeff and Grossman, 1937; Potts, 1966; Kornzweig, 1977; Bischoff and Flower, 1983; Pauleikhoff *et al.*, 1990). Removal of waste materials and disruption the supply of metabolites and gasses to the neural retina is disturbed. Deterioration of the RPE may result from this build up of waste products. (Friedman *et al.*, 1995).

Genetics

Several studies have shown that there is an increased risk of AMD with a positive family history (Hyman *et al.*, 1983; Smith and Mitchell, 1998). A genetic basis for AMD is supported by the occurrence of the condition in families. Genes for other macular dystrophies such as Stargardt's macular dystrophy and Best's vitelliform macular dystrophy have been mapped to specific chromosomes (Stone *et al.*, 1992; Kaplan *et al.*, 1993; Stone *et al.*, 1994; Zhang *et al.*, 1994). AMD is a multifactorial condition and it is likely that

those with an inherited predisposition for the condition will develop it only with exposure to appropriate environmental factors (Bird, 1996; Silvestri, 1997).

Clinicopathogenesis of AMD

The first indication that the metabolic state of the normal, healthy retina has been altered can be seen as deposition of metabolic debris between the basement membrane of the RPE and Bruch's membrane. This accumulation of metabolic debris occurs in the senescent RPE and involves remnants of incomplete degradation from the phagocytosis of rod and cone cell membranes. Photoreceptor outer segments that are not digested in the lysosomes of RPE remain in the RPE cells as highly oxidised lipid material (lipofuscin) (Curcio and Millican, 1999). Part of the accumulation of lipid material on the inner collagenous layer of Bruch's membrane (Pauleikhoff *et al.*, 1990) is clinically visualised as large drusen (Curcio and Millican, 1999), eventually leading to a drusenoid pigment epithelial detachment (PED). Inflammatory cells are thought to invade the drusenoid PED, leading the way to choroidal neovascularisation (Algvere and Seregard, 2002).

Inclusion criteria for review studies

Type of study	Randomised controlled trial comparing nutritional supplementation with a control.
Type of intervention	Any antioxidant vitamin or mineral, alone or in combination. The vitamins or minerals have antioxidant properties themselves, or are a

component of an antioxidant enzyme within the retina.

A literature search was carried out on Web of Science and PubMed using the terms, ‘age-related macular degeneration’, ‘macular degeneration’, ‘randomised controlled trial’, ‘controlled trial’, ‘supplementation’, ‘antioxidant’, ‘carotenoids’, ‘lutein’. The reference sections of those papers located in this way were then searched for other relevant studies.

RCTs included in this review are shown in table 1, and the nutrient amounts included in each study formulation are shown in table 2. Recommended daily allowance (RDA) values for nutrients included in the review are shown in table 3 (where RDA values have been determined).

Insert table 1.

Insert table 2.

Insert table 3.

Statistical analysis

One way of comparing the reliability of RCTs is to calculate the ability of the trial to detect a difference between treatment means. An approximate formula for this calculation is,

$R = 2C\sqrt{2}/\sqrt{r}$ (Ridgman, 1975)

where ‘R’ is the percentage difference detectable in an experiment, ‘C’ is the coefficient of variation (the standard deviation as a percentage of the mean), and ‘r’ is the number of participants in each group. For example, if R = 10% then a true difference between the treatments of less than 10% is unlikely to be detected by the trial (Armstrong *et al.*, 2000).

R values have been calculated for the trials shown in table 4 because C and r could be determined. R values could not be calculated for the other trials reviewed because the required data was not available in the publications.

Insert table 4

Review of trials

Zinc in AMD

Subjects

A computer-generated table of random numbers was used to randomise 151 participants. For inclusion visual acuity in one eye had to be 20/80 or better and ARM or AMD had to be evident by varying degrees of pigmentary change and drusen visualised with fundoscopy.

Experimental design

The treatment group took one tablet containing 100mg of zinc sulphate twice daily and the placebo group took identical tablets containing lactose and fructose. All tablets were provided in identical containers.

Outcomes

Visual acuity with current glasses, pinhole visual acuity, colour vision, glare recovery time and serum zinc levels were all recorded, as well as fundus photographs. Masked independent observers graded baseline and final fundus photographs.

It has been found that zinc interacts with copper by stimulating metallothionein levels of the intestinal wall. Metallothionein binds to dietary copper preventing absorption, which leads to copper defiency. 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). Although copper was not included in the intervention formulation, the hematocrit (percentage of the whole blood that is comprised of red blood cells) was determined serially throughout the study period for each subject. No evidence of copper-deficiency anaemia was found.

Results

The investigators determined that 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 (see figure 1). Figure 2 shows the change in the number of drusen assessed by each observer, for example, observer 1 found that 12 participants in the zinc group and 1 participant in the placebo group had fewer drusen at the end of the trial period than at baseline.

Figure 1 (Newsome *et al.*, 1988).

Figure 2 (Newsome *et al.*, 1988)

Limitations

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. The authors 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.

Although five different parameters were measured, it would have been beneficial to measure the refractive error of subjects at each visit rather than relying upon pinhole visual acuities. The number of participants was small compared with the AREDS, ATBC and VECAT trials, but larger than the Visaline® trial. The use of a single nutrient provides more specific information about the role of zinc in AMD.

Visaline® in the treatment of AMD

Subjects

This trial investigated the effect of Visaline® on the progression on AMD in 20 subjects with early stages of the condition. The subjects were over 50 years of age and had consulted an ophthalmologist due to non-exudative AMD. Follow up occurred at 3 and 6 months.

Experimental design

Visaline® is registered in Switzerland for the treatment of AMD. Eleven patients were allocated to Visaline® and nine to the placebo. Participants and investigators were masked as to intervention and placebo allocation. Two tablets were taken twice daily except for weekends, according to clinical recommendations.

Outcomes

Lens opacity was quantified with the Opacity Lens Meter (LOM) 701 (Interzeag, Switzerland), to assess the effect of cataract on results. This instrument assesses cataract by measuring the degree of scatter of a red light beam (700nm) by the lens (Clarke *et al.*, 1990; Costagliola *et al.*, 1990). Retinal visual acuity was measured using the Moire Interferometer (Haag-Streit, Berne, Switzerland). Macular function was evaluated using the Octopus field tester, and distance and near visual acuity, intra-ocular pressure, fundus inspection, contrast sensitivity and the Pandel-15 colour vision test were also measured.

Results

Results showed no significant difference in measured parameters between the intervention and placebo groups.

Limitations

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%. This means that the study was only likely to be capable of detecting a difference between treatments that was greater than 89%. Interestingly, the effect of the Visaline® was subjectively considered to be more effective than placebo, despite the fact that the trial was designed to be double-masked. Investigators hypothesise that this could be a result of increased cerebral perfusion of buphenine (Kaiser *et al.*, 1995), although no mechanism for this effect has been suggested. No information is given about the appearance, taste or smell of the placebo and intervention tablets, or about their packaging. It is possible that masking was not complete. As with AREDS and the ATBC study, the intervention formulation contained more than one substance, limiting the conclusions that may be drawn regarding specific nutrients.

Insert figure 3

An advantage of this trial is the fact that several visual parameters were measured.

Zinc and the second eye in AMD

This study investigated the effect of zinc supplementation on progression to exudative AMD in the second eye of patients with an exudative form of the disease in the first eye (Stur *et al.*, 1996).

Subjects

One hundred and twelve subjects were enrolled, presenting with AMD and exudative lesions in one eye with a visual acuity better than 20/40, and AMD without any exudative lesion in the second eye.

Experimental design

Subjects were randomised into two groups, one receiving 200mg of zinc sulphate and the other receiving placebo, once daily. Tablets were coded and provided in identical containers, so that participants and investigators were masked. Intervention and placebo tablets were lemon flavoured and effervescent to improve gastrointestinal absorption.

Outcomes

Outcome measures were visual acuity, contrast sensitivity, colour discrimination and retinal grating acuity, as well as serum levels of zinc and copper, red blood cell count, and grading of fundus photography. This trial was the only one to include and grade fluoroscein angiography. Again, copper was not included in the intervention formulation but no significant change in red blood cell count

was found during the treatment period, providing no evidence for onset of copper-deficiency anaemia.

Results

Investigators concluded that oral zinc substitution had no short-term effect on the course of AMD in patients with an exudative form of the disease in one eye.

Limitations

The investigators planned to recruit 500 participants, and had calculated the power of the trial to be >80% based on this sample size. Recruitment was stopped in June 1993 after statistical evaluation by their sponsors failed to show any treatment benefit. 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.

Alpha-tocopherol Beta-carotene Study (ATBC)

Subjects

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 was carried out on a random sample of 941 male participants aged 65 years or over, to determine whether intervention with AT and/or BC had been associated with a difference in AMD prevalence (Teikari *et al.*, 1998). The size of the main cancer trial provided a

large base from which to select participants for the AMD branch, and the timescale increased the likelihood of determining change.

Experimental design

Participants were randomised into four groups, 1) AT only, 2) BC only, 3) AT and BC, 4) placebo. No information is provided about the appearance or packaging of the placebo and intervention tablets, but they are assumed to be identical as the original trial was designed to be double-masked and placebo-controlled.

Outcomes

This trial examined the inter-group differences in AMD prevalence. The level of AMD was assessed from fundus photography

Results

Investigators concluded that long-term supplementation of AT or BC does not affect the prevalence of ARM in smoking males (Teikari *et al.*, 1998). Figure 4 shows the distribution of ARM and AMD by treatment group.

Insert figure 4

Limitations

A disadvantage of the study is that fundus photographs were not taken at baseline, which means that intra-group variation could not be assessed. The

study was not likely to be powered to assess treatment effects for AMD as the number of participants graded with disciform degeneration or geographical atrophy was just 8/237 for AT, 3/257 for ATBC, 0/234 for BC, and 1/213 for placebo.

The study could have been improved by including measurement of clinical visual parameters such as central visual field analysis, colour vision, contrast sensitivity, and glare recovery. An equal spread of AMD at baseline is assumed due to randomisation, as well as the fact that mean visual acuity was similar in all four groups. Baseline visual acuity was also similar between those who chose to take part in the AMD section of the trial and those who did not, suggesting that selection bias is unlikely.

Age-Related Eye Disease Study (AREDS)

The AREDS trial had two main branches investigating the role of high dose nutrient supplementation on both AMD and cataract. This review will mainly discuss the results of the AMD branch.

Subjects

Eleven retinal speciality clinics enrolled 3640 subjects from 1992 to 1998. Potential participants were identified from medical records of patients seen at AREDS clinics, referring physicians, patient lists from hospitals and health maintenance organisations, public advertisements, friends and family of study participants, screenings at shopping centres, health fairs, senior citizen centres

and other gathering places. The range of ages was 55-80 years with an average of 69 years. The following inclusion criteria were used; 20/32 in one eye, clear ocular media for fundus photography and one eye free from any disease that could complicate assessment of AMD. Participants were grouped into four main categories according to ARM or AMD stage, as shown in table 5.

Insert table 5.

Participants in categories 2, 3 and 4 took part in both AMD and cataract branches and were randomised into four arms; 1) antioxidants, 2) zinc, 3) antioxidants plus zinc, 4) placebo. Category 1 patients (those showing no signs of ARM or AMD) were only included in the cataract branch and so were randomised into antioxidant and placebo arms only. Zinc supplementation was not investigated in the cataract branch due to the lack of evidence for any beneficial effect of zinc supplementation on the progression of lens opacities, combined with the possible toxic effects of zinc.

Experimental design

The treatment and placebo tablets were allocated in coded bottles and participants and providers were masked. The placebo used in AREDS was identical in external appearance and similar in taste and internal appearance, to the active tablet. See table 2 for the formulation of the active tablets.

Some nutritional supplement ingredients degrade throughout the life of the product and before the expiry date. Nutritional products are formulated with slightly different amounts of ingredients than listed in order to achieve appropriate potency at the expiry date. The AREDS tablets were formulated to give the following minimum amounts of each ingredient throughout the shelf life of the product:

Vitamin C (ascorbic acid)	113mg	
Vitamin E (dl-alpha tocopheryl acetate)	68mg	(100IU)
Vitamin A (beta-carotene)	4871mg	(7160IU)
Zinc (zinc oxide)	17.4mg	
Copper (cupric oxide)	0.4mg	

Cupric oxide was added to the tablet formulation to offset the risk of copper deficiency anaemia. Vitamin C, vitamin E and zinc were included at much higher levels than RDA (see table 3). There is no RDA for beta-carotene. Two years into the AREDS the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer prevention Study group proved a relationship between beta-carotene and increased incidence of lung cancer in smoking males (The ATBC Cancer Prevention Study Group, 1994) . This was followed in 1996 by a report from the Beta-Carotene and Retinol Efficacy Trial (CARET) who noted that 28% more of the subjects taking beta-carotene developed lung cancer (Leo and Lieber, 1997). In 1996, smokers taking part in AREDS were given the option of discontinuing supplementation. Two percent (18% of smokers in AREDS) discontinued supplementation in 1996.

Outcomes

AMD was assessed using fundus photography and visual acuity was measured using logMAR EDTRS charts. Primary outcomes were progression to advanced AMD (AMD event) and a 15 letter or more decrease in visual acuity score (VA event). An AMD event was considered to be the development of neovascular AMD or development of geographical atrophy that involved the central macula.

Results

Table 6 shows the probability estimates of AMD events for each AMD category after five years.

Insert table 6.

In category 2, only 15 AMD events occurred after five years and these were evenly distributed across treatment arms. The investigators considered it impossible to assess treatment effects in this category with such a low event rate. Table 7 shows the probability of progression to advanced AMD by treatment arm for categories 3 and 4.

Insert table 7.

There was a 25% reduced risk of disease progression in those participants taking zinc plus antioxidants with intermediate or large drusen, non-central geographic atrophy, or advanced AMD in the second eye, as well as a ‘suggestive’ reduction in risk for the zinc arm (see figure 5).

Insert figure 5

Table 8 shows the probabilities of a visual acuity event (at least a 15 letter decrease in visual acuity score) between baseline and five years for categories 3 and 4.

Insert table 8.

Analysis of the results from categories 3 and 4 show a statistically significant reduced risk of a visual acuity event occurring in the antioxidant plus zinc arm compared to the placebo arm.

Definite serum responses to the study antioxidants were observed and are shown in tables 9 and 10.

Insert table 9.

Insert table 10.

Participants taking zinc had an 18% increase in median serum level of zinc from baseline to year 1. This was maintained throughout the 5-year period. Participants not assigned to a zinc group had smaller increases of 3% and 1%. The median percent changes in serum levels of copper ranged from a 3% decrease to a 2% decrease across all treatment arms, indicating that copper levels were not affected by intervention of zinc oxide with cupric oxide.

These results suggest that the combination of zinc and antioxidants was 'modestly' effective in preventing progression to advanced AMD (The AREDS Research Group, 2001). This effect was seen only in those subjects with extensive intermediate drusen, large drusen or non-central geographic atrophy without advanced AMD. The effect was not seen with antioxidants alone, or in subjects with earlier or later stages of the condition. There was no statistically significant effect of delaying the progression of baseline category 2 eyes to categories 3 or 4. The trial was likely to be adequately powered to assess this.

Limitations

In an attempt to standardise extra supplementation, the investigators asked participants who were already supplementing with zinc or antioxidants (57%) to agree to take Centrum (Whitehall-Robins Healthcare, Madison, NJ) rather than any other nutritional supplements. Centrum was supplied to 95% of these participants, as well as an additional 13% who were not taking supplements when recruited. It would have been inappropriate to ask participants to stop taking other supplements as a pre-requisite to recruitment into the study.

It has been argued that the reason an effect was found was because participants were also taking Centrum (Abramson and Abramson, 2002). Centrum, however, provides nutrients in concentrations of no more than 100% RDA (for nutrients where RDA values have been determined), and these levels could be obtained from the diet. As the intervention formulation introduced the study nutrients in much higher concentrations than RDA, the effect shown is more likely to be attributable to this and not variations in diet or extra supplementation.

Statistical analysis was restricted to a subgroup of categories 3 and 4, which goes against standard clinical trial practice. AREDS investigators state that subgroup analysis was appropriate in this case as only 15 out of the expected 50 category 2 participants developed AMD (The AREDS Research Group, 2001). The statistical analysis method used by the AREDS Group does not allow the calculation of R, so that a measure of the degree of precision of this experiment cannot be determined. The AREDS investigators calculated that a sample size of 3600 would provide at least 80% power to detect a treatment effect of 25% to 50% on progression to advanced AMD. This sample size, however, included the category 2 participants.

The results of this trial may support the oxidative stress hypothesis for development of AMD. Unfortunately, it is not known whether this effect was initiated by one, or all of the nutrients, and to what degree. There was no

statistically significant evidence to show that the intervention slowed the progression of ARM.

Summary

This trial forms an excellent platform for further research into the effect of nutritional supplementation on AMD. The outcome of this study highlights a need for the investigation of, short-term supplementation, individual nutrient supplementation, and the role of nutritional supplementation in preventing the onset of AMD. The AREDS investigators state that lutein and zeaxanthin were considered for inclusion in the formulation but that neither was readily available for manufacturing to a research formulation at AREDS initiation (The AREDS Research Group, 2001). The role of lutein and zeaxanthin in prevention of development and progression of AMD was highlighted for further research.

Vitamin E, cataract, and age-related maculopathy trial (VECAT)

The purpose of the AMD branch of this trial was to determine whether vitamin E supplementation influences the incidence or rate of progression of AMD (Taylor *et al.*, 2002).

Subjects

In total 1193 participants were randomised into two groups and followed up for four years. The investigators use the term ‘early AMD’ as opposed to ARM and the grading system used is shown in table 11.

Insert table 11.

Experimental design

The intervention group took 500IU (approximately 335mg) of d-α tocopherol daily for four years. The placebo was identical in sight, taste and smell.

Outcomes

The primary outcome was development of 'early AMD 3' and secondary outcomes were the progression of AMD and development of late AMD, changes in visual acuity and changes in visual function. Visual function was measured using the Visual Function Index (VF-14) (Linder *et al.*, 1999). The incidence of early AMD was defined as the appearance of early AMD in at least one eye of participants who did not have early AMD in either eye at baseline. Stereophotographs of the macula were graded independently.

Results

No significant difference was found in incidence or progression of early AMD between intervention and placebo groups. The trial concluded that daily supplementation with vitamin E does not prevent development or progression of early AMD (Taylor *et al.*, 2002).

Limitations

No measurement of the degree of precision of the trial is available as the data provided does not permit calculation of R. The trial is unlikely to be adequately powered for assessment of treatment effect in the 'early AMD 4' and 'late AMD' categories as photographs graded for these groups constituted only 2% (vitamin E) and 3% (placebo) of the participants at 4 years. Having said this, photographs appear to have been graded for a total of 56% of the vitamin E group and 61% of the placebo group at baseline, and 55% and 54% respectively at four years. This could indicate that the remaining photographs were not of high enough quality for grading purposes, and the 7% reduction in the number of photographs graded between baseline and four weeks in the placebo group may suggest a high drop-out rate.

The trial was designed with the measurement of various outcome parameters and the masking of treatment and placebo groups. Measurement of parameters such as glare recovery, contrast sensitivity and colour vision would have enhanced the trial. The intervention however, contained a single nutrient, which provides a more conclusive answer to the role of vitamin E in AMD.

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.

Subjects

Ninety, mostly male veterans (74.7 +/- 7.1 years) with atrophic AMD were recruited.

Experimental design

Participants were randomised into three treatment groups; 1) 10mg lutein, 2) 10mg lutein/antioxidants, 3) placebo, and were matched for age, years diagnosed with AMD, smoking/cardiovascular history, iris colour, lens opacification and nutritional status/activity level.

Outcomes

Outcome measures were macular pigment optical density (MPOD) measurement, lens opacification rating, glare recovery, low-luminance low-contrast visual acuity, contrast sensitivity, and activities of daily living associated with AMD (night driving/glare adaptation disturbance).

Results

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).

See table 12 for a summary of the outcomes of the RCTs discussed in this review.

Insert table 12.

Discussion

Vitamin C in AMD

Vitamin C is a water-soluble antioxidant and acorbic acid has been shown to react directly with hydroxyl radicals (Bielski, 1982), superoxide (Nishikimi, 1975; Hemila *et al.*, 1985), and singlet oxygen (Bodannes and Chan, 1979). The EDCCS reported that low plasma levels of vitamin C were associated with increased risk of AMD, but high levels were not found to be protective (EDCCS Group, 1993). Its role in protecting against free radical-mediated oxidative tissue damage may have wide implications in retarding disease progression (Department of Health, 1992).

Vitamin E in AMD

Vitamin E exists in four common forms; α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol (Drevon, 1991). The most predominant form in the human retina and plasma is α-tocopherol (Handelman *et al.*, 1985; Alvarez *et al.*, 1987), which is also the most effective scavenger of free radicals (Burton. and Ingold, 1984). Evidence that it may protect against AMD comes from

observational evidence of dietary and blood levels of vitamins and nutrients in AMD patients (Teikari *et al.*, 1998). It is found in high concentrations within the retina (Dilley, 1970; Hunt, 1984), and as the major lipid-soluble antioxidant present in all cellular membranes, protects against lipid peroxidation (Machlin, 1980). Vitamin E may also have a role as a quencher of singlet oxygen and plasma concentration reduces with age. Higher dietary intake of vitamin E can increase its concentration in the retina (Seddon, 1999), and a relationship has been found between greater plasma vitamin E levels and a reduced risk of AMD (Delcourt *et al.*, 1999).

Zinc in AMD

Zinc is highly concentrated in ocular tissues, particularly the retina and pigment epithelium (Siegel *et al.*, 1961; Galin *et al.*, 1962; Swanson and Truesdale, 1971; Eckhert, 1979; Ujiie, 1979). It acts as a cofactor for the antioxidant enzymes retinal dehydrogenase and catalase (Sigel, 1983) and is also involved in retinal metabolism. The elderly are at risk from zinc deficiency (Solomons, 1979; Turnland *et al.*, 1981; Wagner *et al.*, 1983; Wagner, 1985), which can lead to a reduction in T lymphocytes and B lymphocytes through increased apoptosis. Zinc deficiency also compromises the function of another immunological cell, the macrophage (Berger, 2002).

Zinc is the second most abundant trace mineral in the body (Karcioglu, 1982) and plays a part in numerous enzyme systems within the eye, including alkaline phosphatase, carbonic anhydrase (important in aqueous production) and

enzyme systems concerned with metabolism and nucleic acids (Karcioglu, 1982). Zinc is a cofactor for retinal dehydrogenase, which is involved in metabolism of a vitamin A transport protein, and also the interconversion of retinol to retinal, which is essential for rhodopsin synthesis (Solomons and Russell, 1980). Zinc deficiency can alter the function of alcohol dehydrogenase in the retina (Huber and Gershoff, 1975), which can result in increased overall vitamin A uptake. The possible accumulation of retinyl esters in the RPE may interfere with normal biosynthesis and could also produce a toxic effect. In the same way, zinc deficiency promotes lipid peroxidation and damage to lipid membranes (McClain *et al.*, 1985).

Beta-carotene in AMD

Carotenoids are regarded as effective antioxidants and beta-carotene has a well documented role as a quencher of singlet oxygen radicals (Burton and Ingold, 1984a). They are pigments which exist in marigolds, coloured fruit and dark green, leafy vegetables (Khachik and Beecher, 1987; Khachik and Beecher, 1988; Khachik *et al.*, 1989; Ong and Tee, 1992; Mangels *et al.*, 1993; Sommerburg *et al.*, 1998). Beta-carotene is the major carotenoid precursor of vitamin A. Vitamin A cannot quench singlet oxygen and has only a very small capacity to scavenge free radicals (Urbach *et al.*, 1951; Mathews-Roth, 1986).

Protective role of carotenoids in AMD

Over recent years the amount of evidence supporting the protective role of carotenoids in the retina has increased. Lutein, zeaxanthin, and meso-

zeaxanthin, which are oxygenated carotenoids known as xanthophylls, form the macular pigment (MP) (Bone *et al.*, 1985; Khachik *et al.*, 1997). It has been shown that the xanthophylls have superior antioxidant properties to hydrocarbon carotenoids such as beta-carotene and exhibit a smaller tendency towards pro-oxidant behaviour (Martin *et al.*, 1999). These nutrients are obtained by the human body exclusively from dietary sources (Khachik *et al.*, 1991; Khachik *et al.*, 1992) and are, for example, found in marigold flowers, mango, papya, kiwi, peaches, spinach, squash, and honeydew melon. The normal Western diet contains 1.3-3mg per day of lutein and zeaxanthin combined (Landrum and Bone, 2001); the recommended daily intake of lutein is 6mg (Seddon, 1999). This value was determined by the EDCCS group, where investigators found that participants with a daily lutein intake above the highest quintile (6mg) had a decreased risk of neovascular AMD (EDCCS Group, 1992).

Lutein and zeaxanthin reach their greatest concentrations at the centre of the fovea and diminish with eccentricity (Snodderly *et al.*, 1991; Hammond *et al.*, 1997; Beatty *et al.*, 1999; Landrum and Bone, 2001). They are present in the axons of the photoreceptors and are responsible for the 'yellow spot' at the macula (Snodderly *et al.*, 1984). In vivo the 'yellow spot' appears dark when viewed under blue light due to the absorption of the blue wavelengths by the yellow pigment (Schalch, 2001). Wald first demonstrated that this macular pigment exhibited a characteristic xanthophyll absorption spectrum (Wald,

1945), and later, the presence of lutein and zeaxanthin in the macula was established (Handelman *et al.*, 1988).

The MPOD can vary within an individual depending on diet and lifestyle (Beatty *et al.*, 2000). Psychophysical techniques used to measure the quantity of MP in the living eye include colour matching, motion anomaloscope, spectral sensitivity and heterochromic flicker photometry (HCFP) (Mellerio, 2001; Bernstein, 2002). Until recently HCFP has been the most commonly used technique, the basic is theory based on the difference between foveal and parafoveal sensitivities to blue light being used as a measure of optical pigment density (Mellerio, 2001). Most recently, a technique based on resonance Raman spectroscopy has been used. Most compounds scatter monochromatic light at the same wavelength, a phenomenon called Rayleigh scattering. A small proportion of the monochromatic light is scattered at different wavelengths that are determined by the molecular structure of the compound, a phenomenon known as Raman scattering. All carotenoids measured in vivo or in vitro have very similar Raman spectra because they share a similar chemical structure. This technique is valuable as an objective measure of macular pigment levels, as opposed to the subjective flicker photometry. Studies using this technique have determined that macular pigment levels decline with age and that levels are significantly lower in non-supplemented AMD eyes compared with age-matched controls (Bernstein, 2002).

Low MPOD, measured using a flicker photometry-based technique, has been found in obese subjects compared with those of normal weight. The MPOD of subjects with body mass index (BMI) greater than 29 was 21% less than subjects with a lower BMI (Hammond *et al.*, 2002). This could be explained by the fact that up to 80% of the total carotenoids in the body are found in adipose tissue (Olson, 1984). Another study using scanning laser ophthalmoscopy and reflectometry techniques found that a daily dose of 6mg of lutein induced an increase in mean plasma lutein by a factor of 5 and a linear 4-week increase in relative macular pigment (MP) density of 4% to 5% (Berendschot *et al.*, 2000).

An age-related decline in the MPOD was found in a group from a Northern European population using heterochromic flicker photometry. This study also found significantly less MP in eyes judged to be at high risk for AMD compared with age-matched controls (Beatty *et al.*, 2001). A previous study had also found a statistically significant inverse relationship between the MPOD and age among subjects living in Arizona (Hammond and Caruso-Avery, 2000). These results contrast with the results of earlier studies on the effects of aging on MPOD (Werner *et al.*, 1987; Bone *et al.*, 1988), although these trials did not take into account more recently identified risk factors such as gender (EDCCS Group, 1992; Klein *et al.*, 1992; Vinding, 1995), and smoking (Klein *et al.*, 1993; Seddon *et al.*, 1996; Smith and Mitchell, 1996; Vingerling *et al.*, 1996; Tamakoshi *et al.*, 1997; Hawkins *et al.*, 1999). A further case-control study found an inverse association between risk of AMD and MPOD, although the authors state that this does not imply a causal association (Bone *et al.*, 2001).

Protective mechanisms of lutein and zeaxanthin

Lutein and zeaxanthin are believed to protect the retina in two ways. Firstly, they filter short wavelengths of light and so reduce the oxidative effect of blue light (Ham, 1983; Ham *et al.*, 1984). These carotenoids act effectively as a blue-light filter for a number of reasons. Action spectrum for light-induced damage shows a maximum at 400nm and 450nm which is consistent with the absorption spectrum of macular pigment (Ham *et al.*, 1984) This is known as the 'blue light hazard function' (Ham and Mueller, 1989). As previously mentioned, the macular pigment reaches its highest concentration in the foveal region, and it has been shown that the orientation of the pigment molecules enhances light absorption (Farber *et al.*, 1985; Beatty *et al.*, 1999). The distribution of macular pigment through photoreceptor cells means that each cell screens other cells as well as itself due to the lateral course of the axons (Farber *et al.*, 1985).

Secondly, carotenoids limit oxidant stress of tissue resulting from metabolism and light (Ham, 1983; Schalch, 1992; Khachik *et al.*, 1997). There are two known mechanisms by which carotenoids quench free radicals. Energy transfer to the carotenoid quenches singlet oxygen. The carotenoid is then able to relax without destructive bond-breaking. The ability to quench free radicals depends on the conjugate double bonds within their molecular structure. Carotenoids are also believed to react with peroxy radicals which are involved with lipid peroxidation (Landrum and Bone, 2001).

Conclusion

It is difficult to compare the results of the studies described here as there are many variables. The results of zinc supplementation determined by Newsome *et al.* (1988), were not confirmed by Stur *et al*. (1996). This is important in that the participants of this second trial were at higher risk of AMD because they already had an exudative form of the condition in one eye. It is interesting to note that a positive effect of zinc supplementation was determined from the Newsome et al. (1988) trial, despite the lower calculated degree of precision. Widespread use of zinc supplementation was not recommended due to the risk of copper deficiency anaemia (Dunlap *et al.*, 1974; Fischer *et al.*, 1983; Flanagan *et al.*, 1983) as well as a potential side effect of worsening of cardiovascular disease. People with ischaemic heart disease have been shown to have reduced levels of cardiac and leucocyte copper, as well as decreased activity of some copper-dependant enzymes (Klevay, 2000).

The AREDS formed a much larger zinc intervention trial, and found a 'suggestive' reduction in the risk of progression to advanced AMD in category 3 and 4 participants (see table 6). These results may suggest a beneficial role of zinc in this subsection of AMD patients, particularly those who smoke and are therefore contraindicated from beta-carotene.

The Newsome and Stur studies used 200mg zinc sulphate; the AREDS used 80mg zinc oxide. Although zinc oxide has the relatively poorer bioavailibility of the two, the most bioavailable forms of zinc are zinc citrate, gluconate, monomethionine, and picolinate (Lazarides, 1997). Using a more bioavailable

form of zinc may have produced a greater treatment effect, but is likely to have also induced more toxicity issues.

Although the amounts of vitamin E used in the VECAT and AREDS differ, (335mg and 273mg respectively), these amounts are both much higher than RDA (15mg). The different conclusions made by these trials could suggest that supplementation with vitamin E is only effective in combination with other nutrients. The negative result from the ATBC trial accommodates this theory, although a lower dose of 50mg was used and it was combined with 20mg of beta-carotene. This trial differs from the others in that only male smokers were enrolled. There was no evidence for a role of nutritional supplementation in slowing the progression of ARM in any of these three studies. The data from the AREDS category 2 participants is positive for patients with extensive small drusen, pigment abnormalities, or at least one intermediate sized druse, as it indicates a 1.3% probability of progression to advanced AMD after 5 years. The antioxidant arm of the AREDS trial contains the same nutrients as the Visaline® trial with the exception of buphenine. However, the doses are vastly different making comparison impossible.

There is evidence to support the hypotheses that antioxidants such as vitamin C, E, carotenoids and zinc may play a role in reducing the risk of progression of AMD (The AREDS Research Group, 2001; Richer *et al.*, 2002). Lutein and zeaxanthin were considered for inclusion in the AREDS formulation, and it is known that they are oxygenated carotenoids, which make up the MP. Their role

in the treatment of AMD has been investigated in the LAST, where results indicated reversal of AMD symptoms. These findings may represent a breakthrough in the therapeutic approach to AMD management, and warrant further investigation.

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Tables

Table 1: RCTs included in the review				
Name of study	Reference	Location	Follow-up period	Completion date
Zinc in macular degeneration	Newsone et al. 1988	USA	1-2 years	-
Visaline® in the treatment of AMD	Kaiser et al. (1995)	Switzerland	6 months	-
Zinc and the second eye in AMD	Stur et al. (1996)	Austria	2 years	1994
Alpha-Tocopherol, Beta-Carotene Trial (ATBC)	Teikari et al. (1998)	Finland	5-8 years	1993
Age-Related Eye Disease Study (AREDS)	The AREDS Research Group, (2001)	USA	6.3 years (average)	2001
Vitamin E, Cataract and AMD Trial (VECAT)	Taylor et al. (2002)	Australia	4 years	2000
The Lutein Antioxidant Supplementation Trial (LAST)	Richer et al. (2002)	USA	1 year	-

Table 2: Nutrients included in RCT formulations		
TRIAL	NUTRIENTS INCLUDED	AMOUNT (mg)
Zinc in macular degeneration	Zinc	200
Visaline®	Vitamin C	200
	Vitamin E	40
	Beta-carotene	40
	Buphenine	1.5*
Zinc and the second eye in ARMD	Zinc	200
ATBC	Vitamin E	50
	Beta-carotene	20
AREDS	Vitamin C	500
	Vitamin E	273
	Beta-carotene	15
	Zinc	80
	Copper	2
VECAT	Vitamin E	335
Lutein Antioxidant Supplementation Trial	Lutein	10
	Lutein/antioxidants (not specified)	10
* Buphenine is not a nutrient but a beta-adrenergic stimulant, which increases peripheral blood flow, mainly by acting directly on arteries and arterioles of skeletal muscle.		

Table 3: Recommended Daily Allowances (RDA) (mg)				
	Male	Female	Male Smoker	Female Smoker
Vitamin C	90	75	125	110
Vitamin E	15	15	15	15
Zinc	15	15	15	15
Lutein	6	6	6	6

Table 4: Trials for which R values could be calculated	
Trial	R value
Visaline®	88.5
Zinc in the second eye (Stur et al. 1996)	16.1
Zinc in macular degeneration (Newsome et al. 1988)	71.9

Table 5: Definitions of AREDS ARM/AMD categories	
Category	Definition
1	No drusen or drusen <63µm with an area <125µm diameter circle and no pigment abnormalities
2	Small drusen (<63µm) with an area ≤125µm diameter circle with possible pigment abnormalities but no geographical atrophy OR no drusen if pigment abnormalities are present
3a	Intermediate drusen (≥63<125µm) with ≥360µm diameter circle if soft indistinct drusen are present, ≥656µm diameter circle if soft indistinct drusen are absent. Pigment abnormalities could be absent or present but geographical atrophy was absent OR large ≥125µm drusen OR no drusen required if non-central geographic atrophy is present
3b	First eye same as category 3a. VA < 20/32 in the second eye not due to AMD
4a	First eye same as category 1, 2 or 3a with advanced AMD in the second eye
4b	First eye same as category 1, 2, or 3a with VA < 20/32 in the second eye due to AMD but not presenting advanced AMD.

Table 6: Probability of AMD event for each category	
AMD category	Probability of AMD event at year 5
2 3 4	1.3% 18.3% 42.9%

Table 7: Probability of AMD event by treatment arm	
Treatment arm	Probability of AMD event at year 5
Placebo Antioxidants Zinc Zinc + antioxidants	27.8% 22.6% 21.6% 20.2%

Table 8: Probability of VA event by treatment arm	
Treatment arm	Probability of VA event at year 5
Placebo Antioxidants Zinc Zinc + antioxidants	29.1% 25.9% 25.5% 23.1%

Table 9: Increase in median serum levels from baseline to year 1 in the antioxidants arm	
Antioxidant	% increase
Vitamin C	25
Vitamin E-cholesterol Ratio	82
Beta-carotene	485

Table 10: Changes in median serum levels in the placebo and zinc arms from baseline to year 5		
Antioxidant	% change	
	Placebo	Zinc
Vitamin C	-7	-12
Vitamin E-cholesterol Ratio	+6	+6
Beta-carotene	+4	0

Table 11: VECAT early AMD grading system		
Feature	Grading of photographs	Clinical grading
Early AMD 1	Soft intermediate or soft distinct or soft indistinct or pigment changes (hyperpigmentation or hypopigmentation)	Not applicable
Early AMD 2	Soft intermediate or soft distinct or soft indistinct and pigment changes (hyperpigmentation or hypopigmentation)	Not applicable
Early AMD 3	Soft distinct or soft indistinct or pigment changes (hyperpigmentation or hypopigmentation)	Large/soft drusen or non-geographical RPE atrophy
Early AMD 4	Soft distinct or soft indistinct and pigment changes (hyperpigmentation or hypopigmentation)	Large/soft drusen and non-geographical RPE atrophy

Table 12: Summary of RCT results		
RCT	Nutrients Included	Effect Seen
AREDS	Vit C, Vit E, beta-carotene, zinc	Positive result in combination
ATBC	Vit E, beta-carotene	No effect
VECAT	Vit E	No effect
Visaline® in the treatment of AMD	Vit C, Vit E, beta-carotene, buphenine	No effect
Zinc in macular degeneration	Zinc	Positive effect
Zinc and the second eye in AMD	Zinc	No effect
LAST	Lutein, antioxidants	Positive effect
Table 9: Summary of RCT results		

Abbreviated title

AMD and nutrition – a review of randomised controlled trials

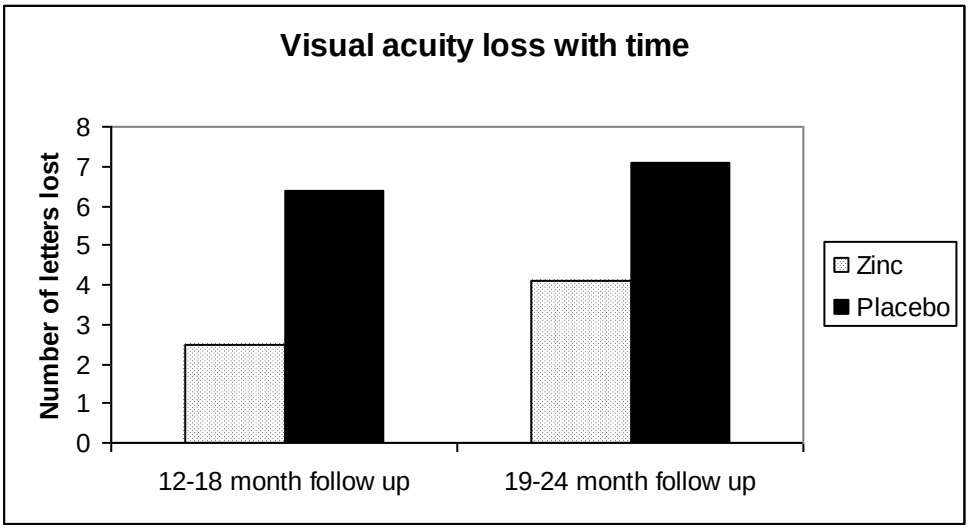
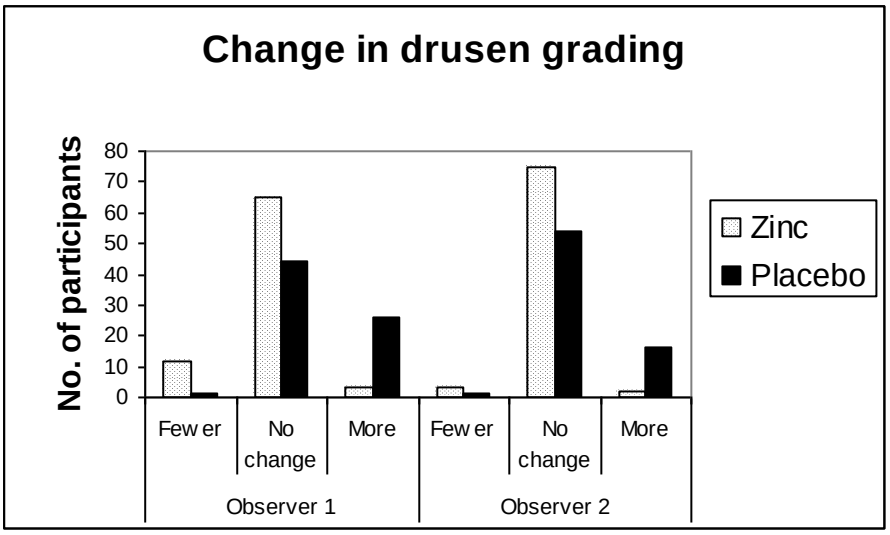


Figure 1



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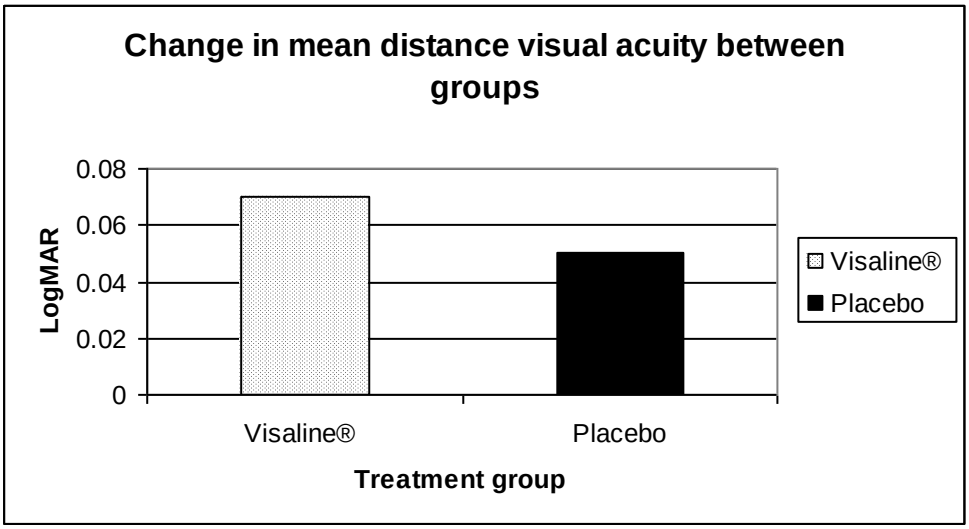


Figure 3

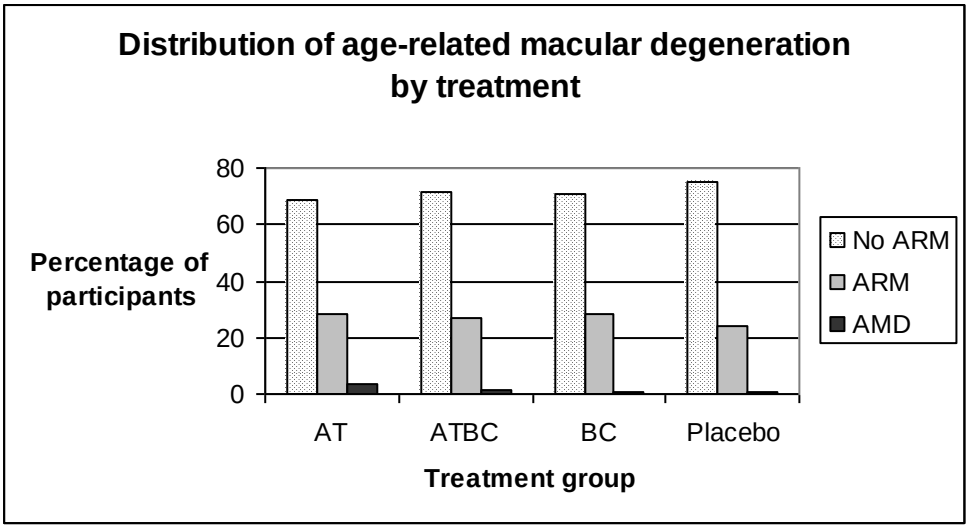
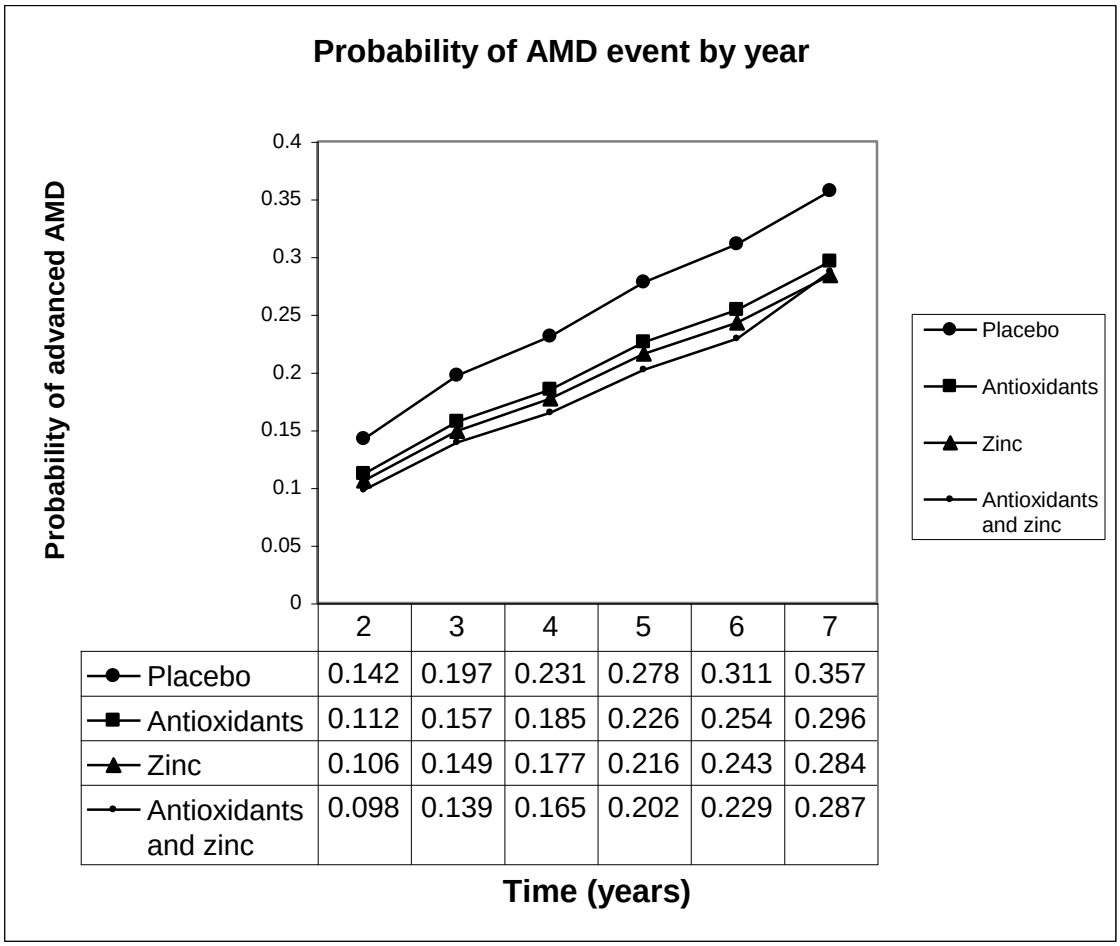


Figure 4



	2	3	4	5	6	7
Placebo	0.142	0.197	0.231	0.278	0.311	0.357
Antioxidants	0.112	0.157	0.185	0.226	0.254	0.296
Zinc	0.106	0.149	0.177	0.216	0.243	0.284
Antioxidants and zinc	0.098	0.139	0.165	0.202	0.229	0.287

Figure 5

Captions to figures

Figure 1: Visual acuity loss with time in the Newsome et al. (1988) study

Figure 2: Change in drusen grading by observer in the Newsome et al. (1988) study

Figure 3: Change in mean distance visual acuity between treatment groups in the Visaline® study (Kaiser et al. 1995)

Figure 4: Distribution of ARM/AMD by treatment group in the ATBC Study (Teikari et al. 1998)

Figure 5: Probability of AMD event at year 5 by treatment arm (Archives of Ophthalmology (2001) 119, 1417-1436)