Antioxidant micronutrients and cataract: a review of epidemiological evidence

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Recibido: 16 de octubre de 2001.
Aceptado: 3 de mayo de 2002.

Abstract

Cataract is one of the leading causes of blindness among the elderly and an important public health problem worldwide. Life expectancy has increased considerably during this century in both developing and developed countries. Population ageing will lead to increased resources required to treat cataract. Epidemiological studies have suggested that intake of foods containing micronutrients with antioxidant potential may be protective against cataract, but the role of the individual antioxidant micronutrients on the cataract process has not been yet elucidated.

Although surgical treatment to remove cataract is very effective, the incidence in developing countries is so high that it will overwhelm the capacity of surgical programs.

An increased understanding of the aetiology of cataract may lead to the development of non-surgical strategies to delay o prevent cataract. A preventive approach appears to be essential to the global problems of cataract.

Key words: Cataract. Antioxidants. Ageing. Prevention.

Resumen

La catarata es una de las principales causas de ceguera en la tercera edad y supone un importante problema de salud pública en todo el mundo. La esperanza de vida ha aumentado considerablemente durante este último siglo tanto en países desarrollados como en aquellos en vías de desarrollo. El envejecimiento progresivo de la población probablemente dará lugar a un incremento de las necesidades de recursos para el tratamiento de la catarata.

Los estudios epidemiológicos señalan que los alimentos que contienen micronutrientes con capacidad antioxidante podrían proteger frente al proceso de la catarata. Sin embargo, el papel que cada antioxidante desempeñaría en la etiología de la catarata es aún desconocido.

Aunque el tratamiento quirúrgico de la catarata es muy eficiente, la altísima incidencia de la catarata en países en vías de desarrollo sobrepasaría la capacidad de cualquier programa de tratamiento. Así pues, una mejor comprensión de la etiología de la catarata podría llevar al desarrollo de estrategias de prevención no quirúrgicas para retrasar o prevenirla. Las estrategias de prevención constituyen el abordaje esencial al problema global de la catarata.

Palabras clave: Catarata. Antioxidantes. Envejecimiento. Prevención.

Cataract as a global health issue

Cataract is one of the most common causes of preventable blindness in the older worldwide. The term *age-related cataract* is used to distinguish lens opacification associated with old age from opacification associated with other causes, such as congenital and metabolic disorders or trauma. By far, the most common of these disorders are referred to as senile or age-related cataracts. The prevalence of the disease increases dramatically after age 60. In Spain, cataract extraction is the most frequently performed ophthalmic operation. In the decade up to 1980 the number of cataract surgeries performed in people 65 years old and over doubled[1] and in England and Wales[2] there was an increased of two-thirds in the decade before 1985.

Over the last 30 years, the elderly population of developed countries has shown an unprecedented increase, with developing countries showing similar trends[3,4]. In Spain, the percentage of elderly people above 65 years of age has doubled in just 45 years, from 6% in 1950 to 16% in 1998. The predictions indicate that people of 65 years of age and over will experience the highest demographic growth comparing to other groups[3]. As the average lifespan in the population increases, the incidence of cataract will increase as well.

Although surgical treatment to remove cataract is very effective, cataract surgery carries risks. Moreover, in developing countries cataracts are more common and develop earlier, more than 90% of the cases of blindness and visual impairment are due to cataract[5]. The incidence of cataract is so high, that new cases will always outstrip the capacity of surgical programs. A preventive approach appears to be essential to the global problem of cataract[2].

The etiology and natural history of cataract is unknown. It is considered that cataract is a multi-etiological process. Laboratory investigations suggest that age-related cataract might result from oxidative stress after sunlight exposure[6,7]. Animal and observational studies suggest that a diet low in antioxidant micronutrients may increase the risk of lens opacification. The possible role of antioxidants as a potentially modifiable risk factor has drawn considerable interest with major public health relevance. Epidemiological studies have also suggested that associated risk factors may include age, sex, race, low socioeconomic status, smoking and alcohol consumption, diabetes mellitus, hypertension, and use of some drugs.

A basis for preventive strategies depends upon adequate understanding of the causes of lens opacification. Strategies to prevent or delayed cataract have not been identified.

This article reviews the epidemiological information about the relation between cataract and antioxidant vitamins and minerals for several important reasons: *a)* antioxidants might be a plausible risk factor from a biological point of view; *b)* results from epidemiological studies about the role of different antioxidants are inconsistent, and *c)* if antioxidants are important factors on cataract prevention, the level of these could be increased through the diet, according to the presumed needs of the organism for antioxidant protection.

In this context, this narrative review examines the evidence from epidemiological studies about the extent to which existing knowledge on the relationship between antioxidant micronutrients and lens opacification can account for the disease in the elderly.

A little about the lens

The primary function of the eye lens is to collect and focus light on the retina. To do so, it must remain clear throughout life. The lens is an encapsulated organ, located posterior to the cornea and receives nutriture from the aqueous humor[5]. This capsule completely isolates a compact mass of epithelial cells, which form a single layer on the anterior surface of the lens. At the equatorial region the epithelial cells elongate migrate posteriorly, and transform into fiber cells, a process that continues throughout the life of the organism. These fibers elaborate the proteins of the lens called *crystallins*. Therefore, new cells are formed throughout life, but older cells usually are not lost. Instead, they are compress into the nucleus of the lens[5]. The nucleus is the region of the lens, which lacks protein turnover opposite to the single layer of epithelial cells, which is incessantly rejuvenated by molecular renewal[8]. The cellular maintenance and repair of the nucleus depends upon the synthesis and transport of antioxidant enzymes and micronutrients from the cortical area into the nucleus to maintain lens integrity[9].

Possible mechanism of lens opacification

As the lens ages, or on stress due to oxidative insults such as exposure to ultraviolet light[10,11], environmental pollutants, cigarette smoke, car exhaust fumes, alcohol and certain drugs[12] the proteins of the lens are damaged, aggregate and form opacities. It is generally agreed that oxidation of the lens is an important and probable mechanism of cataract genesis in humans[13]. Oxidation is a biochemical process of loss of electrons associated with another of reception call reduction. Oxidative stress appears when oxidation is excessive[14]. This mechanism would generate the production of oxygen species, the free radicals, which carry an unpaired electron. These species, which are highly reactive and very unstable, are capable of damaging biologically relevant molecules such as the lens crystallins to depart from their unstable state. In the lens, the free radicals would impair the function of proteolytic enzymes, which normally eliminate the damaged proteins. These proteins, the lens crystallins, would aggregate and precipitate forming lens opacities[12]. Depending where the opacification is located the cataracts will be cortical, posterior subcapsular, nuclear, or mixed cataracts (multiple locations).

The antioxidant defense system in the eye

To counteract these potentially damaging stresses, the lens has an elaborate antioxidant defence system including vitamin C (ascorbic acid), vitamin E (tocopherol), and carotenoids[13]. They could interrupt the chain reaction of free radicals if free radical generation is not so great as to overwhelm the defence network. The important presence of some of these antioxidant micronutrients in the lens is well documented. Vitamin A and the major lens carotenoids, lutein and zeaxanthin, are also present in the cataract lens. The findings that oxidation reactions might be important factors in cataractogenesis, and that antioxidants would help to ameliorate that risk implies that antioxidant micronutrients might be expected to prevent or retard the cataract process.

Material and methods

The computerized bibliographic database MEDLINE was used as a source to search for published epidemiological studies on cataract and antioxidants. The search strategy included: *a)* the key words: «cataract AND antioxidant micronutrients» and covered the year period from 1970 up to the end of 2001. The screening of the articles was done firstly from the titles, secondly from the abstracts and finally from the complete article, and *b)* citation of other published studies in the different articles found through the MEDLINE database was also used as a source of reference for more articles to be included.

With this strategy I have tried to cover all articles published during the last thirty years. However, although efforts were made to search for all articles published during that period, I cannot guarantee that may be some relevant old or new publications could have been missed.

The present review first focus on observational studies identifying the controversial issues and then, on interventional trials examining the effects of different antioxidant on cataract prevention or development.

Evidence from observational epidemiological studies in the elderly

Though the explanation of high cataract prevalence in one country need not necessarily be the same as that in another, the worldwide distribution of increased risk in both sexes suggests that there may be a common underlying mechanism. Laboratory studies have shown an important role for a protective effect of some antioxidant micronutrients against cataract. However, epidemiological evidence is less consistent. Although some epidemiological studies suggest that low levels of antioxidant micronutrients are associated with an increased risk of cataract, there is considerably less agreement on the role of individual antioxidants[15,16]. Epidemiological evidence is provided primarily by case-control and cohort studies and more recently by cross-sectional studies and intervention trials. Most epidemiological studies have been conducted in the US and far less is known from other populations such as the European populations with different diet and lifestyles patterns. Across Europe, there is considerable variation in dietary intakes, especially in the consumption of fresh fruits and vegetables, main food sources of antioxidant micronutrients, with Northern European populations having lower intakes compared with «Mediterranean» diets.

Vitamin C

Vitamin C is considered to be the most prominent water-soluble molecule with antioxidant properties. Animal experiments have shown an important role for a protective effect of vitamin C against cataract[17,18]. The high concentrations of ascorbate present in the normal lenses, cornea, and aqueous humor with 20-30 fold the level found in human plasma suggests that ascorbic acid might be of relevant importance to the eye's health[13]. The concentration of vitamin C in the lens has been found to be related to vitamin C supplementation. Two studies clearly demonstrated that supplementation with vitamin C significantly increased plasma, aqueous humour, and lens levels[19,20]. On the other hand, levels of ascorbic acid have been found to be low or absent in cataractous lenses and increased ascorbate free radicals are found in human lens with progression of cataracts[21].

Epidemiological studies have investigated the association between dietary or plasma vitamin C, or vitamin C supplements and cataract. Most studies do not give percentile cut-offs to define the dietary vitamin C categories nor blood vitamin C levels but rather categories of high, medium or low. Table 1 shows a selection of the most relevant studies about vitamin C and cataract and discussed in this section.

Several studies have examined the relation between serum vitamin C levels and risk of cataract. One small North-American case-control study found that levels lower than 0.80 µmol/l of ascorbic acid were associated with an increased risk for cataract (OR = 11.3; $p < 0.10$). However, this study had methodological problems, numbers were too small (77 cases and 35 controls) and confidence intervals were not given[22]. Two studies found an inverse association. In the National Health and Nutrition Examination Survey II (NHANES II)[23] a strong inverse association between serum ascorbic acid and self reported cataract was found whereas in the Nutrition and Vision Project[24] a marginal inverse association was found with prevalence of nuclear cataract. In contrast, in the Baltimore cross-sectional study[25] and the population-based POLA study[26] no association was found for blood ascorbic acid levels and any type of cataract. On the other hand, a study, which was conducted in India, found that high levels of ascorbic acid were associated with an increased risk of cataract (OR = 1.87; 95%CI, 1.29, 2.69)[27]. In a case-control study[28] conducted in a Spanish Mediterranean region, blood levels of ascorbic acid above 49 mmol/l were found to be associated with a 64%

Table 1. Studies on vitamin C an cataract

Study design	Country	Measure of vitamin C	Outcome	Risk	Comments
Case-control (Jacques et al, 1991)	USA, 77 cases and 35 controls	Blood levels of ascorbic acid	Prevalence of cataract	OR = 11.3; 95%CI not given	Sample size was too small; confidence intervals were not given
National Probability Survey (NHANES II)	USA, 4001 participants	Blood levels of ascorbic acid	Self-reported cataract	Each 1 mg/dl increase in serum ascorbic acid level was independently associated with a 26% decreased in the prevalence of cataract (OR = 0.74; 95%CI, 0.56-0.97; p = 0.03)	Analyses were adjusted for potential confounders: age, sex, smoking, BMI, sunlight exposure. There was no evidence that sex modified the association between serum ascorbic acid level and prevalence of cataract
Case-control nested into a cohort study (Jacques et al, 2001)	USA, a sub-sample of the Nurses Health Cohort study, 478 women without cataract	Blood levels of ascorbic acid	Prevalence of nuclear cataract	Significant linear trend for quintiles of ascorbic acid and prevalence of nuclear cataract (p = 0.04) but OR in the highest quintile was not significant (OR = 0.54; 95%CI, 0.28-1.02)	Statistical analyses adjusted for potential confounders. Potential limitations due to the retrospective nature of the study
Longitudinal (Vitale et al, 1993)	USA, 600 subjects	Blood levels of ascorbic acid	Prevalence for cortical or nuclear cataract	No association was found for any type of cataract	Statistical analyses were adjusted by some potential confounders but not for all (e.g., sunlight exposure). There's a possibility for confounding residual effect
Population-based cross-sectional study (Delcourt et al, 2000)	Finland	Blood levels of ascorbic acid	Prevalence of different types of cataract	No association was found	Statistical analyses were adjusted for potential confounders. Limitations due to the cross-sectional nature of the study
Case-control (Mohan et al, 1989)	India	Blood levels of ascorbic acid	Prevalence of cataract	(OR = 1.87; 95%CI, 1.29-2.69)	No adjusted for important potential confounders
Case-control (Pastor Valero et al, 2002)	Spain, 343 cases and 334 age-sex frequency matched controls aged 55 to 74	Blood levels of ascorbic acid	Prevalence of different types of cataract	Plasma levels of vitamin C above 49 mmol/l were found to be associated with a 64% reduced odds for cataract (p < 0.0001)	The effect of potential confounders or effect modifiers, such as years of sunlight exposure, episodes of severe diarrhea smoking and alcohol history, education, intake of other antioxidants, and use of supplements was examined. Analyses were adjusted for energy intake, education smoking and alcohol consumption
Case-control LOCS (Leske et al, 1991)	USA, 1380	FFQ	Prevalence of type of cataract	OR = 0.45 (95%CI, 0.23-0.88) for nuclear cataract, and 0.60 (0.37-0.96) for mixed cataract. ORs highest quintil against lowest	Statistical analyses were adjusted by sex and age. Although data on medical, sunlight, smoking alcohol consumption and iris color were collected, statistical analyses were carried out separately for each group of risk factors
Population based Cohort study (Mares-Perlman et al, 1995)	USA, 2152	FFQ	Nuclear cataract	OR = 0.54 for men (95%CI, 0.45-1.12) fifth quintile versus lowest quintile	ORs only significant for men when combined with supplements
Nurses' cohort study (Hankinson et al, 1992)	USA, 50828 women	FFQ	Reported cataract extraction	No association was found with intake of vitamin C; but use of supplements for more than 10 years was associated with an OR = 0.55 (95%CI, 0.32-0.96)	Statistical analyses were adjusted by potential confounders. Using cataract extraction as the end point might decrease the chance for variation in the thresholds for diagnosis of disease. All subjects were nurses and their access to medical care and surgery likely to be higher and more uniform than general population

Table 1. Studies on vitamin C an cataract (Cont.)

Study design	Country	Measure of vitamin C	Outcome	Risk	Comments
Case-control nested into a Cohort study (Jacques et al, 2001)	USA, a sub-sample of the Nurses' Health Cohort study. 478 women without cataract	Average of 5 FFQ	Nuclear cataract	OR = 0.31 (95%CI, 0.16-0.58) $p \leq 0.003$ for the highest quintile relative to the lowest	First study to evaluate the intake of vitamin C, 15 years before the ophthalmic examination from 5 FFQ. Analyses adjusted by potential confounders
Population-based cohort study (Mares-Perlman et al, 2000)	USA, 2152	Use of supplements of vitamin C	Prevalence of type of cataract	OR = 0.4 (95%CI, 0.2-0.8) $p \leq 0.002$ for cortical; OR = 0.6 (95%CI, 0.4-0.9) $p \leq 0.08$ for users of supplements for more than 10 years	Statistical analyses were adjusted by potential confounders

FFQ: food frequency questionnaires; BMI: body mass index; CI: confidence interval: OR: odds ratio.

reduced risk of cataract (OR = 0.34; 95%CI, 0.23, 0.50; $p < 0.0001$).

Several studies have reported results for dietary vitamin C from FFQs. The lens opacities case-control study found a 52% reduction of risk of nuclear cataract for those having the highest intake of vitamin C compared with those having the lowest intake. Intake was grouped as low, medium, and high using the lowest quintile, the three middle quintiles, and the highest quintile. ORs compared high vs. low using the latter as the reference group[29]. Jacques and Chylack (1991)[22] found that low vitamin C intake was associated with an increased risk of cortical cataract (OR = 3.7; $p < 0.10$) and posterior subcapsular cataract (OR = 11.0; $p < 0.05$). However, the sample size was too small and the associations observed did not reach statistical significance.

Four studies showed no association between dietary vitamin C and cataract[30-33], whereas in the Beaver Dam Cohort Study the ORs for men for a protective effect of high levels of vitamin C intake (fifth quintile vs. lowest quintile, median 78 mg/day) were 0.71, although only significant when combined with the vitamin C supplements[34]. The prospective Nurses' Study found no association with dietary vitamin C but supplement use of vitamin C for more than 10 years was associated with a 70% reduction in cataract extraction[31]. Later on, in the Nutrition and Vision Project[24], the relationship between newly diagnosed nuclear cataract and usual nutrient intake was examined. A significant inverse association was seen between nuclear opacities and use of vitamin C supplement for more than 10 years. This result corroborates earlier work from the same study[31,35]. These results are consistent with the results from the Beaver Dam Eye study where 5-year risk for nuclear and cortical cataract was 40 and 60% lower among persons who reported the use of any supplement containing vitamin C for more than 10 years[36]. In contrast, no effect of vitamin C supplement was observed in the large prospective cohort Physicians' Study[37] and the longitudinal study of cataract[38,39].

In summary, the evidence from epidemiological studies using food frequency questionnaires is insufficient. They either have found an association between vitamin C intake and cataract[22,29] or a weak one[28,34] or did not find any association[30,33].

Results on blood ascorbic acid are also inconsistent. Three studies found an association[22,23,28] with no association reported in some studies[25,26] while a study in India[27] found an increased risk with higher intake. However, none of the other large cohort studies[31,36] have analyzed blood vitamin C. There is some evidence that long-term supplement use of vitamin C is associated with lower nuclear cataract risk[24,29,36], although no effect was seen in other studies[37-39].

Vitamin E

Vitamin E, a term that encompasses a small group of related tocopherols is also found in the lens but only in concentrations similar to that of plasma[40]. It is believed that most of the vitamin E in the lens is in the epithelial cell membranes and could help to prevent peroxidative damage to these membranes[41]. It has been suggested that peroxide damage to cellular membranes not only accompanies its development but is the initiatory cause of cataracts[42]. Vitamin E is one of the antioxidant liposoluble vitamins found in human lenses[20,43]. Experimental studies in animals have demonstrated that vitamin E is able to reverse cataract formation to some degree suggesting a protective role for vitamin E[44,45].

Evidence for an inverse association of dietary vita-

Table 2. Studies on vitamin E and cataract

Study design	Country	Measure of vitamin E	Outcome	Risk	Comments
Case-control (Jacques et al, 1991)	USA, 77 cases and 35 controls	FFQ	Prevalence of type of cataract	OR = 2.7 for cortical cataract which was not significant	Sample size too small to detect associations. CI not given
Case-control (Leske et al, 1991)	USA, 1380	FFQ	Prevalence of type of cataract	OR = 0.59 (95%CI, 0.35-0.99) for cortical cataract and OR = 0.58 (95%CI, 0.37-0.93) for mixed cataract	Statistical analyses adjusted by sex and age were carried out separately for each group of risk factors: medical information, sunlight alcohol and tobacco consumption
Case-control (Tavani et al, 1996)	Italia, 207 cases and 706 controls	FFQ	Extraction of cataract	OR = 0.5 (95%CI, 0.3-1.0)	Statistical analyses adjusted by potential confounders except for sunlight exposure
Case-control nested into a cohort study (Jacques et al, 2001)	USA, 50828 nurses from the Nurses Health study	FFQ	Prevalence of nuclear cataract	OR = 0.89 (95%CI, 0.47-1.71)	Statistical analyses were adjusted for potential confounders
Case-control (Robertson et al, 1989)	USA, 152	Supplements with vitamin E	Prevalence of cataract extraction	The risk for cataract extraction decreased by 55% for those who were using supplements for more than 5 years	CI were not given. Statistical analyses were not adjusted by sunlight exposure
Cohort study (Mares-Perlman et al, 2000)	USA, 3684 participants	Supplements with vitamin E	Incidence of nuclear, cortical, and posterior subcapsular cataract	Use of supplements for more than 10 years were associated with OR = 0.6 (95%CI, 0.4-0.9) for nuclear cataract and with OR = 0.4 (95%CI, 0.2-0.8) for cortical cataract	Statistical analyses were adjusted for potential confounders. Associations were limited to longer durations of use, and this might reflect the protective influences of other aspects of lifestyle among long term users. On the other hand, this type of study cannot determine the nutrient(s) responsible
Case-control (Leske et al, 1995)	USA, 1380	Blood levels of alpha-tocoferol	Prevalence of nuclear, cortical, and posterior subcapsular cataract	The risk of nuclear opacities was reduced for those with higher levels of vitamin E OR = 0.49 (95%CI, 0.23-1.03)	Statistical analyses were adjusted for some potential confounders but not adjustment was done for sunlight exposure
Cohort (Vitale et al, 1993)	USA, 660 subjects	Blood levels of alpha-tocoferol	Prevalence of nuclear and cortical cataract	α-tocoferol were associated with a decreased risk of nuclear cataract OR = 0.52 (95%CI, 0.27-0.98)	Statistical analyses were adjusted for potential confounders although data on sunlight exposure was missing
Cohort (Leske et al, 1998)	USA, 764 participans	Blood levels of alpha-tocoferol	Incidence of nuclear cataract	The risk of nuclear cataract was reduced by 1/3 in regular users of multivitamin supplements OR = 0.69 (95%CI, 0.48-0.99)	Analyses were adjusted by potential confounders although data on sunlight exposure was not collected

FFQ: food frequency questionnaire; CI: confidence interval; OR: odds ratio.

min E with cataract from epidemiological studies is inconsistent. Table 2 presents a summary of the main studies which found a positive association between antioxidant nutrients and cataract or type of cataract.

Food frequency questionnaires have been used by those studies investigating a role for dietary vitamin E in the cataract process. Three studies showed an association with cataract. In a small case-control study subjects with intakes up to 35.7 mg/day of vitamin E had an increased risk of 2.7 for cortical cataract, which was not statistically significant[22]. In the LOCS study[29] high levels vs. low levels of vitamin E were protective for cortical and mixed cataract (OR = 0.59, 95%CI, 0.35-0.99; OR = 0.58, 95%CI, 0.37-0.93). In an Italian case-control study a reduction of 50% in the risk of cataract extraction was seen for those in the fifth quintile of vitamin E intake vs. those in the lowest quintile group[32]. Two studies found no associations between dietary vitamin E and cataract[27,31], whereas two other studies could not examine vitamin E intake because the food databases used were either insufficient[25] or did not provide vitamin E content of foods[30]. The relation with nuclear cataract was also investigated. No association was found between vitamin E intake and incident of nuclear opacities in the Beaver Dam cohort[46] whereas in the Nutrition and Vision Project there was a decreased risk of nuclear cataract that was non-significant[24].

Epidemiological studies show some evidence for a benefitial role of supplements of vitamin E on cataract risk. In a small case control study supplements with vitamin E during the preceding 5 years showed a 55% reduction in risk of cataract extraction[47]. In the Beaver Dam Cohort study use of multivitamin supplements containing vitamin E for more than 10 years was inversely associated with nuclear cataract[36] and in the longitudinal study of cataract vitamin E supplements were associated with lower risk of increased nuclear opacification during a 5-year follow-up[38]. However, the Physicians' Health Cohort Study[37] showed no association betwewen users of vitamin E supplements and risk of cataract.

Results for blood alpha-tocopherol levels show some evidence for a beneficial role of vitamin E. Two studies found a protective effect of plasma levels of alpha-tocopherol and risk of cataract. A US case-control study[48] found that people with high levels of alpha-tocopherol (42 µmol/l) had a 56% reduced risk of nuclear cataract. In that study however, analyses were not adjusted for cholesterol. In the Baltimore cross-sectional study[25], middle (from 18.57 to 29.72 µmol/l) and high levels (> 29.720 µmol/l) of plasma alpha-tocopherol were associated with a decreased risk of nuclear cataract of 45% and a decreased of 48% for cortical cataract. During the 5-year follow-up Leske and co-workers[38] reported a decreased risk of nuclear opacities with higher plasma vitamin E concentrations. Inverse associations were found between plasma concentration of vitamin E and nuclear cataract in the Beaver Dam cohort[46] and the Nutrition and Vision Project study[24]. A Finish case-control study showed a marginal association with risk of cataract[49], whereas two epidemiological studies did not find any association between plasma alpha-tocopherol levels and risk of cataract[27,30].

Vitamin A

Although the presence of retinol has been confirmed in human lenses[43] results from epidemiological studies are controversial. Two epidemiological studies did not find a protective effect for plasma retinal[22,49]. In the Baltimore study[25] serum retinol levels above 1.3 µmol/l (at both middle and high levels) were associated with an increased risk, approximately of two fold, for cortical cataract whereas in the POLA study[26] strong inverse association with cataracts was found. Dietary vitamin A in other studies was collected using food frequency questionnaires either self-administered or through interviews. Four studies investigated dietary vitamin A but did not analyze plasma retinol[30-32,48]. Of these, two were associated with a decreased risk and two were not. In the Lens Opacities Case-Control Study[29] dietary vitamin A was associated with a decreased risk of 55% for nuclear and 40% for mixed cataract. In the Nurses Health Study[31] dietary vitamin A was associated with a decreased risk of 39% for cataract extraction, whereas no association was seen in two different Italian studies[30,32].

Carotenoids

Carotenoids are also lipid-soluble antioxidants that accumulate in cellular membranes and like vitamin E are thought to play a role in maintaining cell membrane integrity, although it has yet to be demonstrated in the lens[50].

While as many as 42 carotenoids appear to be available in the diet, usually only six of the carotenoids present in most populations are assessed in human serum[51]. These are: beta-carotene, alpha-carotene, beta-cryptoxanthin, lycopene, zeaxanthin and lutein.

Experimental studies give support for a beneficial effect of carotenoids as antioxidants, in particular beta-carotene, as being highly effective quenchers of singlet oxygen, especially at low partial pressures of oxygen (15 mmHg)[52,53].

So far, studies showed that lutein and zeaxanthin are the only carotenoids present in the human lens[43]. There are few epidemiological studies which have investigated the role of individual carotenoids intake in the cataract process, mainly due to the lack until recent years of food composition tables, which contained information on individual carotenoid content of foods.

β-carotene

Blood beta-carotene levels accounts for 10-20% of total serum carotenoids and its concentration reflect recent intake[54]. Evidence for a protective role of beta-carotene in the development of cataract has been shown in experimental studies both *in vitro* and *in vivo*[55,56]. However, no detectable beta-carotene concentrations have been found in human lens extracts[20].

So far, epidemiological evidence for a role of beta-carotene is scarce and insufficient. To date, very few epidemiological studies have studied the relation between dietary and/or blood beta-carotene and cataract. No associations have been found between dietary beta-carotene and cataract extraction in the Nurses' Health Study and in a cross-sectional study conducted in northern Italy[31,32].

Few epidemiological studies have examined the relation between levels of blood beta-carotene and cataract. In the Baltimore Longitudinal Study of Ageing[25], blood levels of beta-carotene were not associated with risk of nuclear or cortical cataract, whereas in a case-control study in Finland, levels lower than 0.095 µmol/l in men and 0.114 µmol/l in women were found to increase risk of cataract. The OR for the lowest thirds of the distribution relative to the higher thirds was 1.7 (0.8-3.8)[49]. In the Nutrition and Vision Project study[24] a decreased risk for nuclear opacities were found which was not significant.

Lycopene

Lycopene, one of the major carotenoids in human serum and other tissues, has not been detected in human cataractous or normal lenses[20,43]. *In vitro,* studies have shown that lycopene is as a very effective circulating singlet-oxygen quencher[57].

Very few studies have investigated the role of lycopene in the aetiology of cataract. In the Beaver Dam Eye Cohort study[34], lycopene intake was measured by means of a food frequency questionnarie. Intake of energy-adjusted lycopene was related to nuclear sclerosis: women in the highest quintile had an increased risk of 51%. This relation was similar in direction in men and women though significantly only in women. Quintiles cut-off points were not shown. The authors also observed adverse associations with the intake of tomato products. In the Spanish case-control study moderately high levels of blood lycopene (> 0.30 mmol/l) were associated with a 46% increased odds of cataract ($p = 0.04$)[28]. High lycopene levels associated with risk of cataract could also reflect other non-nutritive aspects of diet. Carotenoids other than those with provitamin A activity, food additives, food substitutes, pesticides or products formed in the processing of tomatoes, as well as other lifestyle factors, might have been measured through the blood lycopene levels. High serum levels of this carotenoid were also related to more severe nuclear sclerosis in a cross-sectional analysis in the same population.

Lutein and zeaxanthin

Lutein and zeaxanthin have been the only carotenoids to be detected in human lenses[20,43].

In the Nurses' Health Study[31], spinach, which is rich in lutein and zeaxanthin, was consistently associated with a decreased risk of cataract extraction.

In the Beaver Dam Eye cohort[46] there was a strong inverse association between past lutein intake and incidence of nuclear cataract and a 30 to 40% reduction in risk of incident nuclear opacities for person with serum levels of lutein in the highest tertile relative to those in the lowest tertile. Results from the Nutrition and Vision Project study[24] were consistent with those from the Beaver Dam study. However, in both studies this association was not clearly independent of the relation between cataract and vitamin C intake. In a prospective study[58] a modest decreased of risk of cataract extraction was seen in men in the highest quintile of lutein and zeaxanthin intakes comparing to the lowest fifth. In the Nutrition and Vision Project study[24], there was a decreased risk of prevalence of nuclear cataract in the highest quintile of lutein/zeaxanthin intake. However, no association was found in other studies[32,34].

Selenium

Although animal experiments have shown evidence for a protective role of selenium on cataract formation[59] and selenium levels seem to be lower in serum as well as in aqueous humour of cataractous patients[60], no association have been found in epidemiological studies so far[28,30,48,49].

Alpha-carotene, Beta-cryptoxanthin and zinc

Alpha-carotene, beta-cryptoxanthin and zinc are considered to be part of the eye antioxidant defence system. Very few epidemiological studies have been performed to examine the role of alpha-carotene, beta-cryptoxanthin and zinc on caratact risk. One study showed a significant inverse association of serum alpha-carotene and beta-cryptoxanthin and risk of nuclear cataract for men who smoked[34]. However, no other studies have found a positive association between these antioxidants and risk of cataract.

From the studies reviewed in this section the strongest evidence for a possible beneficial role should be for blood alpha-tocopherol levels[24,25, 38,46,48,49] and long term users of multivitamin supplements, in particular vitamin C[24,29,36] and vitamin E[36,38,47].

Weaker associations have found between dietary vitamin C and/or E and cataract. High levels of dietary vitamin E were found to be a protective antioxidant in several studies[22,29,32] but no association was found in others[27,31,33]. Dietary vitamin C was not associated with risk of cataract in several studies[30-33], while women in the highest quintile group of lycopene had an increased risk of nuclear opacities[34]. High levels of dietary intake of some carotenoids have been found to be protective against cataract. Spinach, a source of lutein-zeaxanthin, was associated with a decreased risk for cataract extraction in the Nurses' study[31]. In the Beaver Dam[33] and the Nutrition and Vision Project[24] studies, high past intakes of lutein were associated with lower risk of nuclear cataract however, no association was found in other studies[32,34].

Finally, some studies have computed an antioxidant index either in plasma or a dietary antioxidant index or both. Because oxidative mechanisms are thought to play a role in cataract formation, the nutrients and enzymes in the eye natural antioxidant defence system, may act synergistically[27]. The majority of these studies have found an inverse association with an antioxidant index and cataract[22,27,29] but not all[30].

Intervention trials

Problems caused by confounding and bias in epidemiological studies are of less concern in randomized clinical trials. Moreover, in observational epidemiological studies, the high degree of correlation between different nutrients make it difficult to identify which nutrient might be important in any observed association.

So far, only limited and inconsistent data are available from such trials. Several other ongoing large-scale randomized trials are underway and will provide complementary information to the total body of evidence on the benefits and risks of supplementation with vitamins. Clinical trials are expected to give relevant information on the role of single antioxidants micronutrients on the prevention of cataract.

The Alpha-tocopherol Beta-carotene Cancer Prevention (ATBC) study[61], was a randomized placebo-controlled clinical trial originally designed to study the effect of alpha-tocopherol and beta-carotene on the incidence of lung and other cancers. A cross-sectional end-of-trial eye examination of 1,828 participants from age 50 to 69 years was conducted to assess the effect of the supplements on cataract prevalence. No effect was found of either vitamin E or beta-carotene on cataract prevalence after a median supplementation of 6.6 years. The strength of the conclusions in this study is limited due to the lack of information on cataract status for each participant at the start of the supplementation. The other trial was conducted in China in a nutritionally deprived population. A beneficial effect for nuclear cataract was noted after 5 or 6 years of supplementation with multivitamins and minerals. However, generalization of the results from this study is made difficult due to several reasons: the nutritionally deficient nature of the study population; a formal eye examination was performed only at the end of the 6 year-trial, no examinations were performed at the beginning of the trial to ensure that all individuals were cataract free and very large number of statistical comparisons were made, hence compromising the alpha level[62].

A large randomized trial of 15,000 US physicians aged 55 years and older[63] noted no effect on cataract incidence or cataract extraction after 13 years of beta-carotene use. This trial has been designed to test alternate day beta-carotene, alternate day vitamin E, daily vitamin C, and a daily multivitamin, in the prevention of total and prostate cancer, cardiovascular disease, and cataract and macular degeneration.

Recent results of the Age Related Eye Disease (ARED) study[64] found no effect after an average treatment of 6.3 years with high doses of vitamins C and E, beta-carotene, and/or zinc on the development or progression of age-related cataracts or cataract surgery. The ARED study is a US multicentre factorial double-blind, placebo-controlled trial enrolling 5,000 patients from age 55 to 84 years old. Interpreting the ARED study results also requires a consideration of some limitations. A considerable number of ARED study participants had a grade of opacity at baseline (52% had some cortical opacities, 15% nuclear and 10% PSC). It may be that the ARED study intervention was started too late in the process for it to be effective and that cataracts had probably started to develop. The ARED study participants will be followed up for at least another 5 years.

So far, clinical trials have provided little support for a beneficial effect on cataract development. Ongoing clinical trials will provide additional data about whether these antioxidants or other nutrients are important in the cataract process.

Discussion

So far, the available epidemiological evidence does not provide a basis for recommending dietary change for the general population. Errors in the assessment methods could account for the lack of consistency seen among the reviewed epidemiological studies. Moreover, because of the long-term and multifactorial nature of cataract, it is difficult to predict the influence of nutrients on the cataract process when diet is measured at only one time point. Epidemiological studies have assessed the antioxidant status of individuals by measuring intake using food frequency questionnaires and/or by measuring blood antioxidant's levels. In general, the results from the food frequency questionnaires data showed a smaller effect of antioxidants on cataract risk compared with the blood data analyses. The smaller magnitude of associations based on the food frequency questionnaires antioxidant levels may have resulted from the error in the measurement of «usual» dietary intake with the questionnaire, while data obtained from blood analyses are likely to have been less susceptible to error. The resulting error in measuring antioxidant intakes from the food frequency questionnaire be expected to lead to a dilution of the magnitude of association. Food frequency questionnarie's responses are based on memory and the participants may have had difficulty in accurate classification of intakes across a wide range of food products. Of more concern is «recall bias» where errors in reporting food intakes occur because of biased reporting due to knowledge of having cataract. This is of increasing concern given the current widespread publicity about diet in relation to certain diseases. However, this situation seems unlikely. So far doctors do not give dietary advice for patients with cataract. There is no obvious population awareness of possible dietary influences on cataract risk. Other errors might result from inaccurate food composition data and/or incomplete listing of foods in the food frequency questionnaire leading to errors in estimates of the average individual caloric and nutrient intake. For instance, it has only been recently that a few food composition tables have started to incorporate individual carotenoids content of foods. Most of the food composition tables provide data on total vitamin A activity or total carotenoid content of foods and tend to overestimate total carotenoid content and subsequently, vitamin A activity of plant foods.

Observational studies are subject to confounding and design biases. The majority of epidemiological studies reviewed here took account of main potential confounders such as smoking and alcohol consumption, sun exposure, body mass index, iris colour, education energy intake, and other antioxidant micronutrients. However, confounding bias may remain if these variables were measured with error or were classified into broad categories or there may be other unknown factors that protect for lens opacification. On the other hand, some of the studies reviewed here were lacked of statistical power and some real associations could be missed.

Differences in the definition of case patients could also account for the different results found in this review. In some studies, cases were subjects with any grade of lens opacities; in others, they had more severe cataract that required extraction.

Finally, more data on the potential oxidative activity of these antioxidants is needed to better understand the relationship between antioxidants and cataract. It is known from experimental studies, that some of these antioxidants might be acting as oxidants under specific circumstances. Some data have suggested potential adverse effects of vitamin C in the lens[65].

Conclusions

Given the scarcity of available clinical trial data, and the inconclusive results from observational studies about the individual role of the antioxidant micronutrients on cataract risk, no recommendations on supplements should be made. However, epidemiological studies suggest that a diet low in antioxidants might be associated with an increased risk of cataract. It seems therefore prudent to recommend diets rich in fruits and vegetables with high consumption of vitamins C, E and carotenoids. Clinical trials of sufficient size and duration are needed before such recommendations are made. Moreover, more data on the potential oxidative effect of these antioxidants in the lens must be gathered until we confidently could recommend dietary changes or the use of supplements for the prevention of cataract. Other population studies and clinical trials are under way which may elucidate the possible role of these antioxidants on risk of cataract.

Acknowledgments

I am most grateful to Professor Astrid Fletcher, from the London School of Hygiene and Tropical Medicine, for scientific advice.

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