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Nutritional Supplement Use and Age-Related Macular Degeneration

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1. Introduction

Age-related macular degeneration (AMD) is a leading cause of irreversible visual impairment and blindness in the aging population [1]. Yet, individuals with AMD have limited treatment options. Given the high prevalence and considerable public health burden, it is essential to understand the etiology and pathogenesis of AMD.

AMD is a multifactorial disease, with complex genetics and confounding environmental risk factors. The etiology of AMD still remains unknown, but oxidative stress to the retina and the retinal pigment epithelium (RPE) is one of the leading hypotheses in AMD pathogenesis.

2. Oxidative stress and AMD

Oxidative stress and the cellular damages caused by reactive oxygen species (ROS) has been implicated in aging and age-related eye diseases [2]. Most intracellular ROS are derived from the mitochondria in the electron transport chain. During fuel metabolism, oxygen consumption and ATP synthesis in the mitochondria, electrons are shuffled in sequential reduction and oxidation reactions in the electron transport chain. Yet, these reactions are not 100% efficient; electrons may "leak" out and result in the formation of ROS. ROS are highly reactive and unstable oxygen-containing atoms, ions, or molecules such as hydroxyl radical ($OH\cdot$), superoxide anion ($O_2^{-\cdot}$) and hydrogen peroxide (H_2O_2). Due to the presence of the "unpaired" electron in the outer shell, ROS are very unstable. In trying to achieve stability, ROS will then participate in further reduction and oxidation reactions, oxidizing target molecules and resulting in generation of other free radicals by chain reaction.

Oxidative damages by ROS affect DNA and lipids inside the cell. Earlier senescence, which may be related to shortening of telomeric DNA, occurs after oxidative damage [3-6]. Oxidative damage also results in point mutations and deletions in mitochondrial DNA [7]. In fact, mitochondrial DNA is more susceptible to ROS-induced damage than nuclear DNA [8]. As for lipids, ROS causes oxidation of lipid in a process called lipid peroxidation. The polyunsaturated fatty acids, a common and significant component of cell membrane, are particularly vulnerable to oxidation by ROS as a result of their many conjugated double bonds. Oxidation of polyunsaturated fatty acids results in the formation of reactive aldehyde intermediates which are toxic to the cell [9].

The retina is a structure that is particularly susceptible to oxidative damage by ROS. Firstly, the retina has the highest oxygen consumption in the body [10]. In addition, constant exposure to incoming light in the retina can lead to photo-oxidation. The high oxygen consumption and high light exposure in the retina may in turn generate ROS. Moreover, the retina has a high lipid content, with abundant polyunsaturated fatty acids in the photoreceptor outer segments which are most prone to lipid peroxidation. In the neighborhood of photoreceptors are the RPE cells. Besides providing metabolic support to the photoreceptors, they also phagocytose the constantly shed parts of the photoreceptor outer segments. All these factors contribute to the susceptibility of the retina and RPE to oxidative stress.

With age, the susceptibility to oxidative damage in the retina increases. Aged rat retina showed decreased GSH-Px and catalase activities, which are related to increased lipid peroxidation with age [11]. In particular, RPE cells accumulate lipofuscin granules during life. Lipofuscin granules are lysosomal residual bodies containing undigested end products from phagocytosis of photoreceptor outer segments [12]. It was estimated that lipofuscin can occupy up to 19% of RPE cytoplasmic volume by the age of 80 when compared with only 1 % during the first decade of life [13]. Lipofuscin has been shown to contain toxic substances, such as retinoids (products of the visual cycle) and oxidized proteins [14]. Lipofuscin was also able to reduce RPE lysosomal and antioxidant activity [15]. *In vitro* studies using porcine RPE cells showed that visible light irradiation can degrade RPE melanosomes, reduce melanin amount and increase ROS production, changes that also occur in human RPE melanosomes with aging [16].

3. Nutritional supplements and AMD

Oxidative stress has a recognized role in aging and AMD; treatments for AMD are therefore aimed at reducing oxidative stress-induced damage within the retina and RPE cells. This can be approached in two ways, either by decreasing the source of oxidative stress or by increasing the defense against oxidative stress. Among them, a tempting measure in lowering oxidative damage would be by dietary antioxidant supplementation. Data from observational studies have supported a link between nutritional factors with antioxidant properties and risks of AMD [17,18]. Carotenoids, vitamin C and vitamin E with their antioxidant properties have been identified as having a potentially protective role. Other nutrients such as zinc and omega-3 fatty acids have been shown to be associated with reduced risk of AMD. Recently, B vitamins (folic acid, B_6 and B_{12}) have also been proposed to provide protection by a non-oxidative mechanism. Another nutritional supplement that has gained interest recently is the extracts from a group of fruit, berries.

Common nutrition supplements include:

1. AREDS and AREDS-type formulation
2. Carotenoids (β-carotene, lutein and zeaxanthin)
3. Vitamin C (L-ascorbic acid)
4. Vitamin E (α-tocopherol))
5. Zinc
6. Omega-3 Long chain polyunsaturated fatty acids
7. B vitamins
8. Berry extracts

A summary of studies investigating the effect of nutritional supplements on the prevention and progression of AMD is shown in Tables 1 and 2.

	Study	**Nutrients investigated**	**participants (number; age)**	**Follow-up**
Randomized trials				
Teikari 1998 [43]	Alpha-tocopherol and beta-carotene study (ATBC)	beta-carotene; vitamin E	Finland (941; ≥65 years old)	6-year prevalence
Taylor 2002 [74]	Vitamin E, cataract, and age related maculopathy trial (VECAT)	vitamin E	Australia (1,193; 55-80 years old)	4-year incidence
Christen 2009 [132]	Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS)	folic acid/B_6/B_{12}	Female health care professionals in USA (5,442; ≥40 years)	Av 7.3 years
Christen 2010 [75]	Women's Health Study (WHS)	vitamin E	Female health professionals in USA (39,876; ≥45 years)	Av 10 years follow up
Weigert 2011 [61]	Lutein Intervention Study Austria (LISA)	lutein	126 AMD patients	6-month follow up
Population-based studies				
VandenLangenberg et al [23]	Beaver Dam study	alpha-carotene; beta-carotene; beta cryptoxanthin; lutein + zeaxanthin; lycopene; vitamin E; zinc; fruit and vegetables; supplements	USA (1,709; 43-84 years old)	5-year incidence
Smith 2000 [107]	The Blue Mountains Eye Study (BMES)	dietary fat, fish	Australia (3654; ≥49 years old)	
Cho 2001 [88]	Nurses' Health Study (NHS) and Health Professional Follow-up Study (HPFS)	zinc	Health professionals in USA (104,208: 66,572 women, 37,636 men; ≥50 years old)	8-10 year incidence
Cho 2001 [108]	Nurses' Health Study (NHS) and Health Professional Follow-up Study (HPFS)	Dietary fat	Health professionals in USA (72,489: 42,743 women, 29,746 men; ≥50 years old)	
Heuberger 2001 [145]	Third National Health and Nutrition Examination Study (NHANES III)	Dietary fat	USA (11,448; 40-79 years old)	

	Study	**Nutrients investigated**	**participants (number; age)**	**Follow-up**
Flood 2002 [44]	The Blue Mountains Eye Study (BMES)	alpha-carotene; beta-carotene; beta cryptoxanthin; lutein + zeaxanthin; lycopene; vitamin A; vitamin C; zinc; supplements	Australia (1,989; ≥49 years old)	5-year incidence
Cho, 2004 [52]	Nurses' Health Study and men in the Health Professionals Follow-up Study	alpha-carotene; beta-carotene; beta cryptoxanthin; lutein + zeaxanthin; lycopene; vitamin A; vitamin C; vitamin E; fruits and vegetables; supplements	Health professionals in USA (118,428; ≥50 years old)	12-18 year incidence
van Leeuwen 2005 [42]	Rotterdam Eye Study	alpha-carotene; beta-carotene; beta cryptoxanthin; lutein + zeaxanthin; lycopene; vitamin A; vitamin C; vitamin E; zinc	Netherlands (4,170; ≥55 years old)	Mean 8-year follow-up
Chua 2006 [110]	The Blue Mountains Eye Study (BMES)	omega-3 fatty acid; fish	Australia (3654; ≥49 years old)	5-year incidence
Moeller 2006 [53]	Carotenoids in Age-related Eye Disease Study (CAREDS)	lutein + zeaxanthin; fruit and vegetable	Women's Health Initiative (1,787; 50 to 79 years old), women only	6 year prevalence
Delcourt 2007 [112]	Pathologies Oculaires Liees a IAge (POLANUT)	total fish; white fish; fatty fish	France (832; ≥70 years old)	
Augood 2008 [114]	EUREYE	DHA; EPA; oily fish	Europe (4,753)	
Cho 2008 [54]	Nurses' health Study and Health Professionals Follow-up Study	lutein + zeaxanthin	(113,058: 71,494 women and 41,564 men; ≥50 years old)	Up to 16 years in men, Up to 18 years in women
Wang 2008 [117]	The Blue Mountains Eye Study (BMES)	fish	Australia (1,881; ≥49 years old; *CFH* genotype)	10 year
Tan 2008 [45]	The Blue Mountains Eye Study (BMES)	alpha-carotene; beta-carotene; beta cryptoxanthin; lutein + zeaxanthin; lycopene; vitamins A; vitamin C ; vitamin E; iron; zinc	Australia (2,454; ≥49 years old)	Mean 5.1 years and 10.5 years
Tan 2009 [116]	The Blue Mountains Eye Study (BMES)	omega-3 fatty acid; fish	Australia (3654; ≥49 years old)	10-year incidence
Ho 2011 [91]	The Rotterdam Study	beta-carotene; lutein/zeaxanthin; DHA; EPA; zinc;	Netherlands (2,167; ≥55 years old; *CFH* and *LOC387715/ARMS2* genotype)	Mean 8.6 years

	Study	Nutrients investigated	participants (number; age)	Follow-up
Retrospective study				
Mares-Perlman 1995	Beaver Dam Study and Nutritional Factors in Eye Disease Study	total fat; saturated fat; oleate; linoleate; cholesterol; seafood	USA (2,152; 45-84 years old)	
Klein 2008 [90]	AREDS	AREDS, zinc	USA (876; *CFH* and *LOC387715/ARMS2* genotype)	
Case controlled study				
Seddon 2006 [111]	US Twin Study of Age-Related Macular Degeneration	omega-3 fatty acids; fish	USA (681 twins; male only)	
SanGiovanni 2007 [113]	AREDS	DHA; omega-3 fatty acids; fish	USA (4,519; 60-80 years old)	
Cross-sectional study				
Chiu 2009 [146]	AREDS	DHA; EPA; lutein/zeaxanthin; vitamin C; vitamin E; zinc	USA (4,003)	

Table 1. Studies investigating nutritional supplements in the prevention of AMD

	Study	Nutrients investigated	participants (number; age)	Treatment duration
Newsome 1988 [24]		zinc	USA (151: 56 men, 95 women; 42-89 years old)	12-24 months
Stur 1996 [87]		Zinc	Austria (112: 48 men, 64 women; ≥50 years old)	24 months
AREDS [19]		beta-carotene;vitamin C; vitamin E; copper; zinc	USA (3640, 56% women; average 69 years old)	6 years
Seddon 2001 [109]		Dietary fat, fish	USA (349; 55-80 years old)	
Richer 2004 [55]	Veterans LAST study (Lutein Antioxidant Supplementation Trial)LAST	lutein /antioxidants/vitamins and minerals broad spectrum supplementation formula	USA (90: 86 men, 4 women)	12 months
SanGiovanni 2008 [115]	AREDS	omega-3 fatty acid; fish	USA (2,132)	
Weigert 2011 [61]	Lutein Intervention Study Austria (LISA)	lutein	Austria (126 AMD patients)	6 months

Table 2. Studies investigating nutritional supplements in the progression of AMD

3.1 AREDS and AREDS-type formulation

The Age-Related Eye Disease Study (AREDS) was a clinical trial sponsored by the National Eye Institute [19]. This was to date the largest prospective randomized controlled trial to investigate the effect of an active supplement formula on the risk of development of AMD. The dosages of the supplements were at a high-than-normal level, because it was considered a form of active treatment, instead of a simple supplement pill. There were a total of 3,640 subjects, being monitored for an average of 6.3 years. Each subject was given either the AREDS formula, or placebo, to be taken on a twice-daily basis. Main components of the AREDS formula are vitamin A, vitamin C, vitamin E, and zinc. These were chosen because of their anti-oxidative abilities [20-25]. When compared with the Dietary Reference Intake (DRI) issued by the Institute of Medicine, US National Academy, the dosage of ingredients in the AREDS formula was at a much higher level [26]. For instance, the dosage of vitamin C in the AREDS formula was 500 mg/day, while that of the DRI was only 90mg per day. As far as vitamin C was concerned, one has to take at least 7 to 8 oranges per day, just to match up with what is provided by the AREDS pill [27]. A comparison of the dosage in AREDS formulation with common fruits is given in Table 3.

Nutrients	Unit	AREDS	DRI*	Apple#	Orange#	Banana#	Blueberry#
Vitamin A@	International Unit (IU)	5000	3000	54	225	64	22
Vitamin C	milligram (mg)	500	90	4.6	53.2	8.7	0.7
Vitamin E	mg	400	15	0.18	0.1	0.1	0.23
Zinc	mg	80	11	0.04	0.07	0.15	0.1
Copper	mg	2	0.9	0.027	0.045	0.078	0.12
Lutein + Zeaxanthin	microgram (μg)	None	No data **	29	129	22	33

@ Vitamin A as beta-carotene
* Dietary Reference Intakes from the Institute of Medicine
** 2.0-2.3 mg/day for men and 1.7-2.0 mg/day for women in United States
(Food and Nutrition Board, 2001)
Nutrient contents of common fruits are expressed per 100 grams

Table 3. Dosages of the Age-Related Eye Disease Study (AREDS) type formulas in comparison to common fruit items

After categorizing the subjects according to their macular status (Table 4), they were then monitored serially with fundus photographs. Results of the AREDS were first released in 2001. It showed a 25% risk reduction in progression to advanced AMD, for category 3 and 4 subjects only. For other subjects, i.e. those under category 1 and 2, results were not statistically significant. In the US, 80% of those over 70 years of age fall under either category 1 or 2 [28]. Hence, the protection offered by the AREDS formula may not be applicable to all. Therefore, it was only recommended to high-risk individuals (those under category 3 or 4).

Risk associated with regular intake of the AREDS formula was of particular concern, mainly because it was meant for long-term use. In particular, the risk of regular intake of such a high level of vitamins and minerals was unknown. Potentially, vitamin A (in the form of

beta-carotene) may be associated with an increased risk of lung cancer in smokers; vitamin C may cause renal stones; vitamin E may be associated with increased risk of hemorrhagic stroke; zinc can cause anemia, stomach upset, and may reduce serum high-density lipoprotein level.

	Brief description	Clinical features	Visual acuity
Category 1	No AMD in both eyes	<5 small drusen in one or both eyes	20/32 or better in both eyes
Category 2	Mild to borderline AMD in one or both eyes	Multiple small or intermediate drusen in one or both eyes Pigment abnormalities in one or both eyes	20/32 or better in both eyes
Category 3	Absence of advanced AMD in both eyes	Intermediate or large drusen Geographic atrophy Features not involving central macula	20/32 or better in better eye
Category 4	Advanced AMD in one eye	Advanced AMD or geographic atrophy in worse eye No such features in better eye	20/32 or better in better eye

Key: small drusen, <63 um in diameter (disc diameter around 1500 um); intermediate drusen, 63-124 um in diameter; large drusen, >125 um in diameter; pigment abnormalities refer to either hyperpigmentation or depigmentation [27]

Table 4. Categorization of AMD according to AREDS guidelines

However, observations from the AREDS cohort failed to show any statistically significant serious side effects as mentioned above. Documented minor side effects included 1) increased genitourinary symptoms; 2) increased self-reported anemia; and 3) yellow discoloration of skin due to high level of vitamin A. Self-reported anemia was not correlated with any genuine reduction in blood hematocrit level. Smokers in the AREDS were discouraged from smoking, therefore whether the risk of lung cancer was increased was not being addressed. However, this has already been confirmed in two other trials [29,30]. Hence, all smokers should be discouraged from smoking before the commencement of the AREDS formula. If he or she is not willing to quit smoking, the risk of having lung cancer may outweigh the potential benefit in AMD protection.

In general, the AREDS formula was deemed safe and effective, in selected high-risk individuals [31]. Inadequacy of the AREDS formula was that it did not include other potential ingredients such as lutein, zeaxanthin, and omega-3 fatty acid, which are also of particular interest due to their antioxidant abilities. In view of this, the National Eye Institute has launched the Age-Related Eye Disease Study 2 (AREDS2) in 2006, in hope to fill up the knowledge in this gap [32,33]. In the AREDS2 formula, lutein, zeaxanthin, and omega-3 fatty acid have been added to the existing AREDS formula, and vitamin A was removed, mainly due to the potential risk associated with lung cancer. Results of the AREDS2 are expected to be available in 2012. Until then, the AREDS formula remains the only evidenced-based formula to reducing the risk of development of advanced AMD.

3.2 Carotenoids (β-carotene, lutein and zeaxanthin)

Carotenoids are organic pigments naturally occurring in plants as well as in some algae, fungus and bacteria. Animals generally cannot synthesize carotenoids; they have to obtain carotenoids in their diet. There are two classes of carotenoids, xanthophylls (which contain oxygen) and carotenes (which are purely hydrocarbons, and contain no oxygen) accounting for over 600 known carotenoids. A well known carotene is beta-carotene, the pigment that makes carrots orange. Interestingly, there are only two carotenoids that are present in the human retina [34,35], namely lutein [(3R,3'R,6'R)-beta,epsilon-Carotene-3,3'-diol] and its stereoisomer, zeaxanthin [(3R,3'R)-beta,beta-Carotene-3,3'-diol]. These carotenoids are enriched in the macula in high concentrations, thus giving the macula its yellowish color.

In human, four carotenoids including beta-carotene, alpha-carotene, gamma-carotene, and beta-cryptoxanthin can be converted into retinal, which is an important molecule in the photo-transduction pathway and therefore vision. Carotenoids can also absorb light and act as antioxidants by scavenging ROS such as $\cdot O_2$ and peroxyl radicals [36]. In particular, two xanthophylls, lutein and zeaxanthin, have been shown to absorb the damaging blue light [36] as well as protect the retina [37] and retinal ganglion cells [38] from oxidative damage *in vitro*. In animal studies, lutein protected the inner retina against acute retinal ischemia/reperfusion injury due to its antioxidant properties [39].

Due to their antioxidant properties and blue light-filtering effects, the association of carotenoids with risk of AMD was explored. There have been conflicting results. Decreased risk of neovascular AMD has been found to be associated with higher levels of carotenoids in the serum samples [40]. In monkeys, feeding a xanphophyll-free diet has been shown to promote drusen formation [41]. In an early study based on National Health and Nutrition Examination Survey I data, an inverse association between the consumption of fruits and vegetables rich in pro-vitamin A carotenoids and the prevalence of AMD was demonstrated [22]. In the Beaver Dam Eye Study, VandenLangenberg *et al* also found a significant but modest inverse association between intake of pro-vitamin A carotenoids and the incidence of large drusen [23]. Later studies using the AREDS formulation suggested a beneficial effect of beta-carotene [19]. The Rotterdam population-based study also reported a high dietary intake of beta-carotene together with vitamins C and E and zinc reduced the risk of AMD in elderly individuals [42]. A 35% reduced risk of AMD was observed when an above-median intake of these 4 nutrients was given.

On the other hand, opposing results were obtained from other clinical trials and population-based studies. The Alpha-Tocopherol and Beta-Carotene (ATBC) Study in Finland assessed the involvement of beta-carotene in occurrence of AMD among smoking males [43]. Over 29,000 smoking males aged 50 to 69 years were given alpha-tocopherol (50 mg/day), beta-carotene (20 mg/day), both of these, or placebo randomly. After 5 to 8 years of supplementation, Teikari *et al* found no beneficial effect of long-term beta-carotene supplementation on the incidence of AMD. The Blue Mountains Eye Study also reported no associations between beta-carotene intake and 5-year incidence of AMD [44]. This is a population-based study including 1,989 individuals who finished a food frequency questionnaire. This questionnaire assessed the baseline intake of nutrients including alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein and zeaxanthin, lycopene, retinol, vitamin A, vitamin C, and zinc. For beta-carotene, Teikari *et al* suggested no evidence of protection by beta-carotene on the 5-year incidence of AMD. Further studies in the same

population after 10-year of follow-up showed some interesting results. Instead of showing no effect of beta-carotene in AMD, Tan *et al* actually reported an increased risk of neovascular AMD with increasing beta-carotene intake [45]. The authors found that increasing beta-carotene intake, either from diet alone or diet plus supplementation, was associated with higher risk neovascular AMD. This association also existed when the smoking status of the individuals was adjusted.

In fact, one has to bear in mind about the possible harmful effect of beta-carotene supplementation. Apart from the skin coloration, changes in scotopic b-wave during electroretinography and crystal formation have also been shown with long-term beta-carotene use [46]. More importantly, daily supplementation of beta-carotene in smokers was associated with a higher mortality rate due to ischemic heart disease and lung cancer [29,30]. Since smoking also increases the risk of AMD, beta-carotene supplementation should be avoided in smokers. Currently, no biological explanation has been offered to clarify the harmful effect of beta-carotene in human.

Lutein and zeaxanthin are the only two carotenoids that exist in the human retina [34,35]. They are particularly dense in the macula in humans, where they are referred to as macular pigment [34]. Macular pigment is thought to be protective against retinal damage. Three case-controlled studies showed that there was an inverse association between the macular pigment density in the human retina and the risk of AMD [47-49]. In an early study investigating the effects of high dietary carotenoid intake, lutein and zeaxanthin were found to be the specific carotenoids that are most strongly associated with reduced risk of AMD [20]. This result was also supported by two other studies. The population-based Pathologies Oculaires Liees a l'Age (POLA) Study measured the plasma carotenoid levels by high-performance liquid chromatography (HPLC) in 899 subjects and correlated them with the risk of AMD [50]. It was shown that high plasma levels of lutein and zeaxanthin were associated with a significant reduced risk of AMD. Similarly, a study in U.K. involving men and women aged 66 to 75 found that subjects with the lowest plasma level of zeaxanthin has a two-fold increased risk when compared with those with the highest plasma zeaxanthin, supporting the view that zeaxanthin may protect against AMD [51].

Other studies also provide evidence in the association of lutein and zeaxanthin with AMD risk. In the Blue Mountains Eye Study, Flood *et al* reported a possible association between baseline intake of lutein and zeaxanthin and the 5-year incidence of early AMD [44]. A longer, 10-year follow-up study reported that high dietary lutein and zeaxanthin intake (top tertile) was associated reduced risk of incident neovascular AMD [45]. Participants with above median intakes had a reduced risk of indistinct soft or reticular drusen.

Conversely, several studies showed different results on the association of lutein and zeaxanthin. An early study in Beaver Dam (Beaver Dam Eye Study) reported no significant association between lutein and zeaxanthin and the risk of large drusen when 1,709 participants were followed up for 5 years [23]. In a prospective follow-up study of women in the Nurses' Health Study and men in the Health Professionals Follow-up Study, Cho *et al* followed 77,562 women and 40,866 men ≥50 years old for up to 18 years for women and up to 12 years for men. It was reported that lutein and zeaxanthin were not strongly related to either early or neovascular AMD risk [52]. The Carotenoids in Age-related Eye Disease Study (CAREDS), an ancillary study of the Women's Health Initiative, followed 1,787 female

participants aged 50 to 79 for 4 to 7 years [53] and assessed their diet by a food frequency questionnaire. Subjects were divided according to their lutein and zeaxanthin intake, but there was no statistical difference between the amount of lutein and zeaxanthin intake and the prevalence of intermediate AMD. A later large prospective follow-up study also reported similar results [54]. Two cohorts, the Nurses' Health Study and the Health Professionals Follow-up Study which included 51,564 men and 71,494 women aged ≥50 years were followed up for up to 18 years. Cho *et al* reported that there was no association between lutein/zeaxanthin intake and the risk of self-reported early AMD. Yet, a non-significant and nonlinear inverse association between lutein/zeaxanthin intake and neovascular AMD risk was observed.

More recently, lutein itself has gained special interests. Two prospective randomized controlled trials have investigated the association of lutein supplementation and the incidence of AMD. The larger Veterans LAST study (Lutein Antioxidant Supplementation Trial) involved 90 subjects with atrophic AMD who were randomly divided into three groups: lutein (10mg) group, lutein (10mg) plus additional antioxidants and nutrients group, and maltodextrin placebo group [55]. Subjects were followed for 12 months and those who received lutein alone or lutein plus antioxidants and nutrients had improved visual acuity. Richer *et al* concluded that lutein alone or in combination with other nutritional supplements (including zinc, beta-carotene and vitamins C and E) is protective and slow down the progression of AMD. On the other hand, a smaller prospective trial measured the contrast sensitivity in 25 subjects after lutein supplementation (6mg) with vitamins and minerals or placebo over a 6-month period [56]. No statistical difference was observed between the lutein and placebo group, suggesting no significant association between lutein supplementation and AMD. However, one has to be careful about these findings. The sample sizes in both studies were fairly small and the follow-up periods were limited to 12 months or less.

More supportive evidence came from a recent study in which participants in AREDS were genotyped for the hepatic lipase (*LIPC*) gene [57]. Hepatic lipase is a protein in the high-density lipoprotein cholesterol pathway and has been shown in a large genome-wide association study to be a novel locus for advanced AMD risk [58]. It was observed in the AREDS participants that lower dietary lutein intake was significantly associated with increased risk of advance AMD, after controlling for the *LIPC* genotype. This suggests that high dietary lutein intake may reduce the risk of advanced AMD, after adjusting for genetic variants.

Lutein is also a macular pigment. Due to lutein's antioxidant properties and blue-light filtering capacity [36], it was hypothesized that macular pigment may provide protection against the development of AMD [59]. The first prospective follow-up study, Muenster Aging and Retina Study (MARS), recently investigated the determinants of macular pigment optical density and its relation to AMD [60]. Foveal macular pigment optical density was accessed in 369 participants including patients with different stages of AMD and healthy controls. In the 2.6-year follow-up study, it was observed that serum level of lutein, lutein supplementation in particular, was the strongest determinants of macular pigment optical density. However, the hypothetical protective effect of macular pigment in AMD could not be confirmed. On the other hand, a recent double-masked controlled study, Lutein Intervention Study Austria (LISA), investigated the association of 6-month lutein

supplementation with macular pigment optical density and visual acuity in 126 AMD patients randomly assigned to lutein supplementation or placebo [61]. Weigert *et al* observed that lutein could significantly increase macular pigment optical density despite having no effect on mean differential light threshold or visual acuity. Interestingly, a significant correlation was found between the lutein-induced increase in macular pigment optical density and the change in mean differential light threshold and visual acuity. This finding suggests that patients who experience a pronounced increase in macular pigment optical density after lutein supplementation may benefit in terms of visual function.

As lutein and zeaxanthin were not ready for manufacturing as a research formula, neither of them was included in the AREDS formula [28]. The US Food and Drug Administration (FDA) has conducted an evidence-based review to evaluate the role of lutein and zeaxanthin in reducing the risk of AMD [62]. After reviewing a number of intervention and observational studies, the FDA denied a health claim about the intake of lutein or zeaxanthin (or both) and the risk of AMD in 2006. However, in view of the conflicting findings, the National Eye Institute (Bethesda, Maryland, USA) launched the Age-Related Eye Disease Study 2 (AREDS2) in 2006, hoping to resolve the link between carotenoids (lutein and zeaxanthin) intake and AMD protection [32,33]. The AREDS2, a large, multi-centered, randomized trial, is currently underway to address the effects of high dose lutein and zeaxanthin supplementation and/or omega-3 fatty acids on the progression of AMD. Beta-carotene, which increases the risk of lung cancer in smokers [29,30], is removed from the AREDS2 formula. Another on-going, similar randomized controlled trial is the Carotenoids in Age-Related Maculopathy (CARMA) Study [63]. In this study, 433 participants with either early AMD features or any level of AMD in one eye and advanced AMD in the fellow eye were recruited. Either lutein and zeaxanthin, in combination with antioxidants (including vitamin C, vitamin E, zinc, and copper) or placebo was given. Again, beta-carotene was excluded in the preparation due to the increased risk of lung cancer in smokers [29,30].

Although the beneficial effects have not been proven, lutein and zeaxanthin are included in daily supplements and food additives and can be obtained over the counter. Moreover, the addition of crystalline lutein into food and beverage products is considered GRAS (generally recognized as safe) and is approved by the FDA [64]. Lutein toxicity studies in animals using high doses of purified crystalline lutein revealed no unfavorable events [64] and no adverse events are reported for lutein and zeaxanthin at doses up to 40 mg/day in human for 2 months [65]. The risk profile of lutein was also recently reviewed in 2006 by the Council for Responsible Nutrition (CRN) in Washington, D.C. It was concluded that apart from the reversible skin discoloration, no other adverse effects were observed [66]. The CRN suggested an upper level of intake for lutein up to 20 mg/day. Currently, the average daily intake for lutein and zeaxanthin is 2.0-2.3 mg/day for men and 1.7-2.0 mg/day for women in United States (Food and Nutrition Board, 2001).

In view of their potential benefits as well as minimal side effects, lutein and zeaxanthin may be recommended for those who are keen and at risk of AMD [27].

3.3 Vitamin C (L-ascorbic acid)

Vitamin C is a water-soluble nutrient that is synthesized in almost all animals and plants. It is well known for its potent antioxidant activities [67,68]. It also acts as an important co-factor

in mammals as in the synthesis of collagen; therefore vitamin C is used in the treatment and prevention of scurvy. In ophthalmology, there has not been any randomized controlled trial in assessing the efficacy of vitamin C as a single supplement in AMD. Yet, in other studies combining vitamin C with other supplements, data on the protective effects of vitamin C has been mixed. Vitamin C is shown to be beneficial in the AREDS study [19]. In two large prospective studies of 135 men and 329 women with up to 18 years of follow-up [52], it was found that higher fruit intake was related to a reduced risk of neovascular age-related maculopathy but none of the vitamins (including vitamin C) or carotenoids examined was clearly related to the disease. In a population-based cohort study involving 1,586 middle-aged and older adults, the researchers found no significant associations between the risk of large drusen and intake of vitamin C [23]. Another population-based cohort study even suggested that an increasing baseline vitamin C intake from diet and supplements was associated with an increased risk of incident early age-related maculopathy when compared with the lowest quintile [44]

3.4 Vitamin E (α-tocopherol)

Vitamin E is a collective term for a group of natural lipid-soluble compounds containing the tocopherols (α-, β-, γ- and δ-) and tocotrienols (α-, β-, γ- and δ-) with antioxidant properties. Among them, α-tocopherol is the only form to meet human requirements. In the eye, α-tocopherol can be found in the retina, RPE and choroid [69]. Its concentration in the retina increases after oral supplements [70].

As an antioxidant and a nutritional factor, vitamin E has been explored in its association with prevention of AMD. Again, data for vitamin E have been mixed. Some studies reported that higher intake are associated with lower risks of AMD or signs [23,42,71] whereas some concluded no associations [45,52,72,73].

In particular, three large randomized controlled trials have assessed vitamin E in the incidence of AMD. The Alpha-Tocopherol and Beta-Carotene (ATBC) Study involved over 29,000 smoking males aged 50 to 69 years who were randomly assigned to alpha-tocopherol (50 mg/day), beta-carotene (20 mg/day), both of these, or placebo [43]. Of these, an end-of-trial ophthalmological examination was performed in a random sample of 941 participants aged 65 years or more. No beneficial effect of long-term supplementation with alpha-tocopherol on the occurrence of AMD was detected among smoking males. In the Vitamin E Cataract and Age-related Maculopathy Trial (VECAT), 1,193 healthy volunteers aged between 55 and 80 years were randomly given either vitamin E (500IU = 335 mg) or placebo daily for 4 years [74]. In the study, the incidence of early AMD in those receiving vitamin E (8.6%) was similar to those on placebo (8.1%) whereas for late disease the incidence was 0.8% versus 0.6%. Again, daily vitamin E supplement does not prevent the development or progression of early or later stages of AMD. In the Women's Health Study (WHS) [75], a large scale randomized trial of women, 39,876 healthy female health professionals were randomly assigned to receive with natural source vitamin E (600IU) or placebo on alternate days. There were 117 AMD cases in the vitamin E group versus 128 cases in the placebo group after 10 years of treatment and follow-up. Similar to other studies, no large beneficial or harmful effect on risk of AMD was observed in long term vitamin E supplementation.

More importantly, a negative association between vitamin E and AMD was recently reported. In the Blue Mountains Eye Study involving an Australian population–based cohort, Tan *et al* reported that high vitamin E intake was associated with increased risk of late AMD, suggesting a harmful effect of dietary vitamin E on risk of AMD [45]. However, one has to be cautious about these results. There was a moderate loss of participants in this particular study, while the levels of vitamin E intake between participants followed up and not followed up were significantly different. The authors mentioned that this might affect the interpretation of the observed results.

3.5 Zinc

Zinc is an essential trace element for almost all organisms including plants, animals and microorganisms. It has a multitude of biological roles, playing a fundamental role in cellular metabolism. For example, it plays a structural role in a large number of transcription factors containing zinc fingers and similar structural motifs. Most importantly, it was first shown to be required for the catalytic activity of carbonic anhydrase [76]. Later studies showed that zinc has a catalytic or structural role in at least 300 zinc metalloenzymes [77-79], influencing many metabolic reactions. In fact, approximately 10% of the human genome encodes for proteins that can bind zinc [80].

In the human body, there are about 2-3 g of zinc, making it the second most abundant trace element [79,81]. In ocular tissues, the concentration of zinc is unusually high when compared with other tissues [82]. In the eye zinc is most abundant in the retina and choroid, followed by ciliary body, iris, optic nerve, sclera, cornea, and lens [83]. A number of functions of zinc in the retina have been suggested, including modulation of retinal synaptic transmission, modification of photoreceptor plasma membrane, involvement in retinal vitamin A metabolism, regulation of light-rhodopsin reaction within the photoreceptor, and antioxidant activity [84,85].

There are subtle ocular manifestations associated with zinc deficiency. In a prospective, randomized, double-masked, placebo-controlled investigation of the effects of oral zinc administration on the visual acuity outcome in 151 subjects with drusen or macular degeneration, the treatment group had significantly less visual loss than the placebo group [24]. As elderly patients are found to be at higher risk of zinc deficiency [86], this may suggest an increased risk of vision loss from AMD in elderly patients.

For the past three decades, there have been considerable interest and controversy related to zinc supplementation in AMD patients. To date, results on zinc supplementation and AMD have been mixed. As described above, Newsome *et al* reported significant reduction in visual loss in AMD patients when supplemented with oral zinc [24]. Moreover, Mares-Perlman *et al* reported a weak protective effect of dietary zinc on the development of some forms of early AMD [71]. In the large double-masked clinical trial, The Age-Related Eye Disease Study (AREDS), involving 11 centers, participants taking zinc alone demonstrated an odds reduction of 0.75 for the development of advanced AMD. Zinc significantly reduced the odds of developing advanced AMD in the higher-risk group. A population-based cohort study reported that high dietary zinc intake was associated with a lower risk of incident AMD [42]. In the Beaver Dam Eye Study, it was observed that there is a significant inverse association between zinc and the incidence of pigmentary abnormalities, but there was no

relationship between zinc intake and incidence of early AMD [23]. In fact, an early study by the Eye Diseases Case-Control Study Group reported no association between serum zinc levels and risk of neovascular AMD [40]. In a 2-year, double-masked, randomized, placebo-controlled study, Stur *et al* reported that oral zinc substitution has no short-term effect in patients who have an exudative form of AMD in one eye [87]. Unfortunately, this study was prematurely terminated because of no beneficial effects found in first 40 patients at 24 months. In addition, two large prospective studies involving 66,572 women and 37,636 men do not support a lowered AMD risk associated with higher zinc intake [88]. The Blue Mountains Eye Study Group reported no significant association between baseline zinc intake from diet or supplements and the 5-year incidence of early Age-related maculopathy[44].

A systematic review and meta-analysis involving four prospective cohort studies [23,42,44,88]reported that a pooled odds ratio of zinc for early AMD was 0.91 (95% CI 0.74 to 1.11). Another meta-analysis reported that zinc supplementation can slow down AMD progression (adjusted odds ratio = 0.77, 95% CI 0.62 to 0.96) [89].

Although the evidence is conflicting, recent studies support a protective role of zinc in AMD progression. The AREDS study indicated that the beneficial effect of zinc supplementation was of a similar order to that of vitamin supplementation. Despite the 5-year findings by The Blue Mountains Eye Study Group [44], later studies by the same group published the 10-year data in which individuals with total zinc intake in the highest decile are less likely to develop early or any AMD [45].

Zinc intake and the genetic risk of AMD has also been assessed. In the AREDS population, the single nucleotide polymorphism in the *CFH* (Y402H, rs1061170) and *LOC387715/ARMS2* (A69S, rs10490924) genes of 876 participants who were considered at high risk was genotyped [90]. The findings suggest that there is an interaction between *CFH* genotype and treatment with antioxidant plus zinc when compared with placebo. Moreover, a recent study involving 2,167 individuals from the population-based Rotterdam Study at genetic risk of AMD assessed their dietary intake at baseline using a semi-quantitative food frequency questionnaire and determined the genetic variants using TaqMan assay [91]. In this nested case-control study, it was observed that there is a significant possibility of biological interaction between CFH Y402H and zinc as well as between LOC387715 A69S and zinc ($p < 0.05$). Moreover, individuals with homozygous CFH Y402H with dietary intake of zinc in the highest tertile reduced their hazard ratio of early AMD from 2.25 to 1.27.

Again, one has to be cautious about the risks of high dose supplementary intake of zinc. In the AREDS study, more people in the zinc group reported difficulty in swallowing the tablets (17.8% vs. 15.3%, $p < 0.04$) [19]. Circulatory adverse experiences were also more frequently reported in individuals receiving zinc. Hospitalizations due to genitourinary problems as well as mild or moderate symptoms are also more frequent in these participants. In fact, it was found that there is a significant increase in hospital admissions for urinary complications in patients with high zinc supplementation (11.1% vs 7.6%, $p = 0.0003$) [92]. The risk was greatest in male patients (RR 1.26, 95% CI 1.07-1.50, $p = 0.008$). Significant increase in urinary tract infections was also found ($p = 0.004$), especially in females. Another problem was gastrointestinal symptoms. Of 286 participants, 5/146 zinc-

treated participants withdrew from the studies due to gastrointestinal symptoms when compared with 2/140 in the placebo group [24,87].

3.6 Omega-3 Long chain polyunsaturated fatty acids

The retina contains abundant fatty acids, about 30% of which are polyunsaturated fatty acids [93]. Polyunsaturated fatty acids are classified into 2 groups: ω-3 and ω-6 depending on the position of the first double bond from the methyl end of the molecule. Docosahexaenoic acid (DHA), an omega-3 fatty acid, is highly enriched in the retina, particularly in the disc membrane of photoreceptor outer segments [94]. DHA is the major polyunsaturated fatty acid in cerebral gray matter as well. Yet, the specific role of DHA in the eye is not clear. DHA has been shown to be important for photoreceptor survival [95-98]. DHA may have a role in modulating G protein-coupled signaling pathways that are involved in visual transduction [99]. DHA may also affect rhodopsin function during photoreception by influencing the membrane's biophysical properties [100,101]. In rhesus monkeys, dietary depletion of alpha-linolenic acid, a dietary precursor of DHA, resulted in undetectable plasma DHA level and more importantly, abnormal retinogram and visual impairment [102,103]. Nonetheless, DHA supplementation is effective in improving retinal function in a patient with autosomal dominant Stargardt-like retinal dystrophy [104]. The importance of DHA in retinal function may suggest a possible beneficial role of DHA in retinal disease such as AMD.

Another omega-3 fatty acid, eicosapentaenoic acid (EPA), is the precursor of eicosanoids in the body. It can act as a competitive inhibitor of arachidonic acid conversion to pro-inflammatory eicosanoids prostaglandin E(2) and leukotriene B(4) [105]. As inflammation plays a role in the pathogenesis of AMD, EPA may be one of the protective factors in AMD.

Supplementation of omega-3 fatty acids, DHA and EPA in particular, has received much interest in association with lowering the risk of AMD. Although DHA can be synthesized from alpha-linolenic acid in the body, the process is ineffective. DHA and EPA can readily be obtained from marine fish oils in the diet. Based on their roles in retinal function and inflammation, dietary modification and supplementation of omega-3 fatty acids have become attractive alternatives in lowering the risk of AMD.

Many studies have provided evidence for a protective role of omega-3 fatty acids supplementation in AMD risk [91,106-117]. The first study evaluating the relationship between dietary fat and AMD was published by Mares-Perlman et al [106]. They reported that high intake of saturated fat and cholesterol was associated with increased risk for early AMD. Later, a prospective follow-up study of participants in the Nurses' Health Study and the Health Professionals Follow-up Study showed that total fat intake was positively associated with increased risk of AMD [108]. Yet, a cross-sectional study involving participants in the Third National Health and Nutrition Examination Survey found no association between dietary fat and AMD risk. However, this study assessed only one eye per patient, thereby may have decreased the observed AMD prevalence.

There are further investigations into the association of omega-3 fatty acids with AMD risk. As dietary omega-3 fatty acids are obtained from marine fish oils, fish intake was also investigated. Earlier study on fish intake was performed in the Blue Mountain Eye Study population. In this cross-sectional, population based study, Smith et al showed that a higher

fish consumption was associated with decreased odds of late AMD [107]. After 5 years of follow-up Chua *et al* reported that fish consumption at least once a week was protective against early AMD, whereas fish consumption at least 3 times per week could reduce the incidence of late AMD [110]. After 10 years of follow up in the same cohort, Tan *et al* suggested that a regular weekly serving of fish was associated with a reduced risk of early AMD [116]. Interestingly, it was also noted that fish consumption of more than one serving per week did not have a significant protective effect in reducing AMD risk in this cohort, suggesting a threshold effect. These findings are supported by other studies as well. Seddon *et al* in a multicenter eye disease case-control study reported that higher intake of omega-3 fatty acids and fish was associated with a lower risk for AMD among individuals with low linoleic acid intake [109]. More evidence on the protective role of omega-3 fatty acid came from a recent US Twin Study of Age-Related Macular Degeneration. This study investigated the association between dietary fat intake and fish consumption and risks of AMD in 681 twins [111] and found that both omega-3 and fish intake reduced the risk of AMD.

Oily fish rich in omega-3 fatty acids are also found to be beneficial in two European studies. The population-based POLANUT study from Southern France found that fatty fish intake was protective against AMD when comparing more than once a month and less than once a month and after multvariate adjustment [112]. Interestingly, total and white fish intake has no significant association with AMD risk. Another population-based study, EUREYE, showed that oily fish intake (at least once per week versus less than once per week) was associated with significant reduction of risk for neovascular AMD [114]. Similar findings were also observed for either DHA or EPA intake.

Among the AREDS participants, a prospective cohort of individuals with neovascular AMD and central geographic atrophy was also analyzed for the relationship of omega-3 fatty acids and AMD. It was observed that dietary total omega-3 fatty acids or DHA intake was inversely associated with neovascular AMD [113]. Similar findings were also observed with fish consumption. Further studies showed that dietary omega-3 fatty acids intake is associated with a decreased risk of progression from bilateral drusen to central geographic atrophy [115].

In addition, the association between omega-3 fatty acids and genetic risk of AMD is investigated. In the Blue Mountains Study group, 1881 participants were genotyped for complement factor H (CFH) genetic variants [117]. Wang *et al* reported that AMD risk increased with each additional C allele. Also, weekly compared with less than weekly consumption of fish was associated with reduced late AMD risk in participants with the CC genotype but not the CT or TT genotypes. This study provided evidence that weekly consumption of fish is protective on the development of late AMD, but not early AMD, among individuals with genetic susceptibility to AMD due to the Y402H variant. On the other hand, the dietary intake of 2167 individuals was assessed at baseline in a recent population-based Rotterdam study [91]. Ho *et al* reported a possible interaction between EPA/DHA and either *CFH* Y402H or *LOC387715* A69S. The authors also suggested that high dietary intake of omega-3 fatty acids may reduce the risk of early AMD in those who are at high genetic risk.

Taken together, much data suggests that dietary omega-3 fatty acids intake and fish consumption are protective against AMD. Results from a recent meta-analysis also

supported the protective role of omega-3 fatty acids supplementation [118]. It was reported that dietary intake of omega-3 fatty acids was associated with reduced risk of late AMD while fish consumption (at least twice a week) was associated with reduced risk of both early and late AMD. However, the authors also cautioned that due to insufficient evidence, few prospective studies and no randomized clinical trials, recommendation for a routine omega-3 fatty acids supplementation and fish consumption for AMD prevention is not supported. A similar conclusion was also reached in another systematic review [119]. Hopefully, more definite answers on the protective role of omega-3 fatty acids will be provided by the ongoing AREDS2 randomized, multi-center trial.

3.7 B vitamins

B vitamins are a group of water-soluble compounds that are important in cell metabolism. The members of interest in AMD studies are folic acid, vitamin B_6 (pyridoxine) and vitamin B_{12} (cyanocobalamin) because of their ability to reduce homocysteine levels in intervention studies [120]. Homocysteine is an amino acid formed during the metabolism of methionine. It can either be recycled back into methionine or converted into cysteine with the help of B-vitamins.

Serum level of homocysteine has been implicated in increasing the risk of AMD. Recent cross-sectional [121-123]and case-control studies [124-128] showed that there may be a direct association between homocysteine level in the blood and AMD. Hyperhomocysteinemia (plasma homocysteine > 15μmol/L) can also induce vascular endothelial dysfunction [129-131]. It was therefore proposed that lowering blood homocysteine levels with folic acid, vitamin B_6 and vitamin B_{12} supplementation may help to reduce the risk of AMD.

In the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), 5,442 female health professionals participated in this randomized, double-masked, placebo controlled trial [132]. Christen *et al* reported that daily supplementation with folic acid/B_6/B_{12} reduce the risk of AMD in this large cohort of females after an average of 7.3 years of treatment and follow-up. Yet, disease report in this study was done by self-report questionnaires or medical records while no ophthalmic examinations were performed. More evidence and further research in other groups are needed despite the interesting association between folic acid/B_6/B_{12} supplementation and AMD prevention.

3.8 Berry extracts

Diets rich in fruits, nuts, and vegetables have long been considered to be an excellent source of antioxidants. There has been growing interest on berry extracts due to their high antioxidant properties. Among the berries, blueberries have been of specific interest because of their high antioxidant capacity (in some cases as high as 40−50 μmol Trolox equivalents/g) [133]. Indeed, of all the fresh fruits and vegetables tested to date, data indicate that blueberries have the highest antioxidant capacity, as estimated using the average oxygen radical absorbance capacity (ORAC) values [133-135]. Polyphenols in blueberries, specifically the anthocyanins that give the fruit its blue color, are the major contributors to antioxidant activity [133].

Anthocyanin is a water-soluble pigment present in all plants and is richly concentrated in berries. It is a powerful antioxidant *in vitro* [136]. It can absorb blue-green light and protects the cells from light stress in plant studies [137]. In laboratory studies, anthocyanin may protect the eyes from degenerative diseases such as AMD [138-140]. Yet, the evidence for the potential health effects of anthocyanin is mostly laboratory-based [141].

Another berry that recently received lots of interest is the fruit of *Lycium barbaurm*, also called wolfberry or Gouqizi, a commonly used herb in Chinese Traditional Medicine. It is also taken as food in Asian countries. It is well known for improving eye sight. Increasing lines of evidence showed that the polysaccharides in *Lycium barbaurm* can exhibit anti-aging [142] and anti-oxidative effects [143]. Other properties such as anti-tumor effects, cytoprotection, neuromodulation, and immune modulations have also been suggested [142,144]. Unfortunately, most evidence for its beneficial effects is limited to the laboratory level.

At this moment, there are no legal requirements for quality control in the preparation of these extracts. It is not obligatory to disclose the content and the production method. Moreover, the dosage and frequency are unclear while potential toxicity and long-term side effects remain to be investigated. A lot of investigation is needed before the potential of berry extracts in prevention of AMD can be hinted. Currently, berry extracts should not be recommended [27].

4. Future directions

Observational studies have shown beneficial effects from dietary supplementation of lutein and zeaxanthin as well as omega-3 fatty acids in the development of AMD. They are currently tested in AREDS2, the multi-centered randomized clinical trial launched by the National Eye Institute in 2006. The association of oral formulations containing lutein and zeaxanthin, and/or DHA and EPA, with the progression of AMD is being assessed. In AREDS2 participants will be followed for 5 years. Hopefully, data will be available by the end of 2012. Similarly, the ongoing CARMA study will also provide invaluable data on the protective effects of lutein and zeaxanthin in combination with antioxidants (vitamin C, vitamin E and zinc) with the exclusion of DHA and EPA.

5. Conclusions

To date a large body of evidence has supported a protective role of nutritional supplements in the development and progression of AMD. In particular, strongest evidence is present for the protective effect of lutein, zeaxanthin, DHA, and EPA. On the other hand, beta-carotene and vitamin E may have detrimental effects. While awaiting a further proof of the effects of lutein, zeaxanthin, DHA, and EPA, the AREDS formulation remains the best recommendation so far, although not without risk and maybe only for high-risk individuals. One concern for the AREDS formulation is the higher risk of lung cancer in smokers with daily beta-carotene supplementation. Therefore, in offering nutritional supplements to patients, physicians should consider on a case-by-case basis and fully explain the potential side effects from a long-term regular intake. It is also important to remind the patients that even with the AREDS formulation, AMD can still occur. It is equally important to teach the patients self-monitoring methods such as usage of the Amsler grid. Regular fundal examinations by ophthalmologists should also be strongly encouraged.

6. Reference

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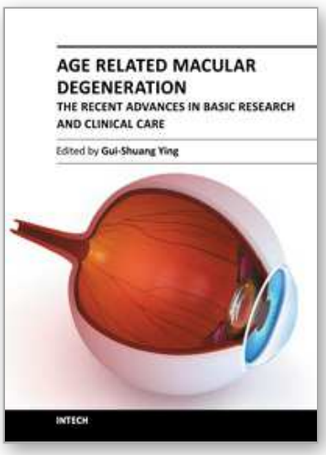

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Age-related Macular Degeneration (AMD) is the leading cause of vision loss and blindness in the developed countries. In the past decade, great progress has been made in understanding the pathobiology and genetics of this blinding disease, as well as in finding new therapies for its treatment. These include the discovery of several genes that are associated with the risk of AMD, new anti-VEGF treatments for wet AMD and new imaging techniques to diagnose and monitor the AMD. All chapters in this book were contributed by outstanding research scientists and clinicians in the area of AMD. I hope this timely book will provide the basic scientists and clinicians with an opportunity to learn about the recent advances in the field of AMD.

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