

# Dry Age Related Macular Degeneration – Oral Supplements, Which Combination and When ?

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## Abstract

Age related macular degeneration (AMD), a leading cause of visual loss in the elderly, is emerging as an important public health problem due to the increase in the ageing population. Dry AMD which is the more prevalent form has no effective treatment and so efforts are directed to slow down or prevent progression of retinal changes by optimizing the risk, factors for AMD. Oxidative stress in the retina has been identified as an important predisposing factor which can be most efficiently modified by nutritional supplementation. Two large randomized controlled trials namely AREDS (Age related eye disease study) 1 and 2 provided high quality evidence to support the use of vitamins and micronutrients in preventing the progression of disease, especially in those with intermediate or advanced AMD. Supplementation with oral antioxidants soon became the standard of care for dry AMD, both due to its perceived universal benefit and its cost effectiveness. Though a wide range of antioxidants are available in the market, hardly any of them contain ingredients recommended by AREDS in the correct dosage. It is therefore important that ophthalmologists should be equipped with proper information regarding these products and advise the patients appropriately after considering their individual needs. A comprehensive list of antioxidants available in our country is included in this article which can be used as a reference to guide the patients. Physicians should be familiar with AREDS recommendations and should select patients appropriately. Patient education to improve compliance and counseling regarding life style modifications are also important in controlling this public health problem.

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## Introduction

Age related macular degeneration (AMD) is an emerging public health problem in India with the reported prevalence ranging from 40.8% for early AMD to 1.3% for late AMD in south India and 39.5% for early AMD to 1.2% for late AMD in north India.<sup>1</sup> AMD is divided into early AMD associated with mild to moderate visual loss and late AMD associated with severe visual loss. The characteristic feature of early AMD is drusen which appear as white or yellow dots and is often associated with hyper or hypo pigmentation of retinal pigment epithelium (RPE). Late AMD can be dry or atrophic type with central geographic atrophy or wet AMD (also known as exudative or neovascular AMD) with choroidal neovascularization (CNV).<sup>2</sup> Though the advent of anti VEGF (vascular endothelial growth factor) drugs have drastically improved the management of wet AMD, it still does not offer a permanent cure for this blinding disease. Moreover, it requires regular hospital visits and multiple treatments with its associated economic burden. Therefore it may be prudent to shift our attention to dry AMD which is more prevalent, but yet has no effective treatment.<sup>3</sup> So, the approach should be to focus on prevention by optimizing the modifiable risk factors such as diet and nutritional status. AMD is a disease proven to be related to food intake and therefore nutritional supplementation can be beneficial.<sup>2-4</sup> This simple and cost effective intervention assumes greater relevance as the prevalence of AMD is predicted to increase substantially with increase in the ageing population.

## Retina, Oxidative damage and Ageing

Pathogenesis of AMD is multifactorial involving complex interplay between environmental and genetic factors

leading to oxidative stress and chronic inflammation, eventually resulting in neovascularization and fibrosis.<sup>5</sup> Retina is especially liable to oxidative stress due to its high vascularization resulting in high oxygen tension, light induced stress in the fovea and its high content of unsaturated fatty acids and photosensitizing compounds.<sup>6</sup> Action of light on retina generates free radicals or reactive oxygen species (ROS) which act as prooxidants and lead to chain reactions with cellular and molecular damage. Oxidative stress in the outer segment of photoreceptors and RPE triggers the changes leading to the formation of drusen. Oxidative stress is therefore the factor that can be most efficiently modified by food components.

## Antioxidants and AREDS

To maintain cellular homeostasis a balance must be maintained between the production and consumption of ROS. Several factors like ageing, inflammation, exposure to ultraviolet and ionizing radiation, smoking, ischemia and reperfusion injury results in significant increase in the production of ROS resulting in oxidative damage.<sup>2</sup> The retina's defenses to such processes include enzymes, such as selenium-dependent glutathione (GSH) peroxidases and catalases, and antioxidant nutrients such as vitamins E and C and carotenoids.<sup>7</sup> Zinc functions as a cofactor for many of these enzymes. Role of these vitamins and micronutrients in preventing or delaying the progression of AMD has been reported by several epidemiological studies, but results were not consistent.<sup>2,5,6</sup> Given the lack of hard clinical data from a randomized interventional trial and the growing concern of widespread use of unproven, high dose supplements, US National Eye institute initiated the age related eye disease

**Table 1- Showing the ingredients and daily dose of AREDS formulation and recommended daily allowance (RDA)**

|               |        |               |
|---------------|--------|---------------|
| Vitamin C     | 500 mg | 75 – 90 mg    |
| Vitamin E     | 400 IU | 15 mg         |
| Beta carotene | 15 mg  | 700 – 900 mcg |
| Zinc          | 80 mg  | 8 – 11 mg     |
| Copper        | 2 mg   | 900 mcg       |

study (AREDS). AREDS<sup>1</sup> was the first large multicentric placebo controlled randomized clinical trial done to investigate the benefit of high dose supplementation with vitamin C, E, beta-carotene and zinc or its combination in preventing the progression of AMD. These nutrients were chosen based on the best nutritional knowledge of eye disease in the 1980's when AREDS study was conceived. Daily dosage of the nutrients in AREDS 1 formulation, recommended daily allowance (RDA) and their source is shown in Table 1. It is obvious that AREDS dosage of these micronutrients and vitamins are much higher than RDA and it would be difficult to achieve such high doses through a normal diet, thus making supplementation of antioxidants essential.<sup>8</sup> Copper was included in the formulation to prevent anemia due to high dose of zinc.

Participants in the AREDS 1 study were enrolled in 4 AMD categories determined by the size and extent of drusen and RPE abnormalities in each eye as shown in Table 2.<sup>9</sup> Category 1 with no signs of AMD was not included in the AMD trial analysis. Those who were in categories 2 to 4 were randomly assigned to receive daily oral tablets containing antioxidants, zinc, antioxidants plus zinc or placebo. After a mean follow up of 6.3 years data from AREDS demonstrated that treatment with zinc alone or in combination with antioxidants reduced the risk of progression to advanced AMD by 25% and risk of vision loss by 19% in patients in categories 3 and 4. The authors concluded that persons older than 55 years should undergo dilated eye examination to determine the risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or visual loss due to AMD in 1 eye, and

without contraindications such as smoking, should consider taking a supplementation of antioxidants plus zinc.

### Why AREDS 2?

AREDS formulation became the standard of care following the publication of AREDS report in 2001. However it did not contain lutein and zeaxanthin, the important carotenoids in the macular pigment due to the commercial unavailability at that time. These natural occurring blue light screening antioxidants are the only carotenoids in the fovea of human retina.<sup>10</sup> It was also observed that increased intake of beta carotene may be associated with increased risk of lung cancer in smokers. This led to the suggestion that beta carotene should be replaced with lutein and Zeaxanthin. Another recommendation was to include omega-3 long chain poly unsaturated fatty acids namely docosahexanoic acid (DHA) and eicosapentanoic acid (EPA). It helps to prevent the oxidative, inflammatory and age-related retinal damage that occurs during AMD development. Retina has high concentration of DHA and is constantly shed during the visual cycle. Diet is the only source of these fatty acids as it is not synthesized in the human retina. Hence the AREDS 2 trial was planned with the purpose of improving the efficacy and reducing the side effects of AREDS 1 formulation. Patients were randomized to receive oral tablets containing lutein 10mg + zeaxanthin 2mg, and/or EPA 650 mg + DHA 350mg. A secondary randomization was done to evaluate the effects of lower doses of zinc (25 mg versus 80 mg) as high dose of zinc supplementation was found to be associated with increased incidence of genitourinary disorders. The results of AREDS 2 revealed that the expected 25% improvement over the original AREDS study was not obtained. Addition of lutein and zeaxanthin reduced advanced AMD by 10%, which was increased to 18% when beta-carotene was removed possibly due to amelioration of competitive absorption effects of different carotenoids. Those who had the maximum benefit with the addition of lutein/zeaxanthin were those in the lowest quintile of dietary intake.<sup>10</sup> However, addition of omega-3 fatty acids was neither harmful nor beneficial. Also, there was no significant difference of low dose versus high dose zinc and it was recommended to retain the original dose of 80 mg

**Table 2- Showing the AMD categories in the AREDS Study**

| Category                | Grading of AMD   | Fundus features              | Visual acuity  | Average 5 year risk of visual loss |
|-------------------------|--|------------------------------|--|------------------------------------|
| No AMD                  | Total drusen area < 5 small drusen (< 63µm)  | Disc haemorrhage             | 20/32 or better in both eyes   | Not available                      |
| Early AMD               | Multiple small drusen, single or non extensive intermediate drusen (63-124µm), pigment abnormalities or any combination in one or both eyes  | Sub conjunctival haemorrhage | 20/32 or better in both eyes   | 1.3%                               |
| Intermediate AMD        | 1 large druse (125µm), extensive intermediate drusen or geographic atrophy (GA) not involving centre of macula or any combination of these   | Macular edema                | 20/32 or better in at least 1 eye                                      | 18.3%                              |
| Advanced AMD Unilateral | No advanced AMD (GA involving the center of macula or choroidal neovascularization) in the study eye. Fellow eye had advanced AMD or AMD abnormalities sufficient to explain reduced visual acuity | Uveitis                      | 20/32 or better in the study eye and less than 20/32 in the fellow eye | 42.9%                              |

**Table 3: Showing comparison of ingredients in the antioxidants available in the Indian market to AREDS formulation**

| Sl no | Product name<br>Manufacturer                 | Vit C           | Vit E          | Lutein        | Zeaxanthin   | Zinc           | Copper       | Other ingredients   | Cost/ 10<br>tab.(Rs) |
|-------|--|-----------------|----------------|---------------|--------------|----------------|--------------|---|----------------------|
| 1     | AREDS<br>Cap. Astador<br>Salvador visiontech | 500 mg<br>50 mg | 400 IU<br>5 mg | 10 mg<br>5 mg | 2 mg<br>1 mg | 80 mg<br>40 mg | 2 mg<br>2 mg | Astaxanthin, Vit A, Se  | 160                  |
| 2     | Cap. Astagold<br>Sunways                     | 50 mg           | 5 mg           | 5 mg          | 1 mg         | 40 mg          | 2 mg         | Astaxanthin, Vit A,Se   | 175                  |
| 3     | Tab. Fiteye<br>Cipla                         | 150 mg          | 50 IU          | 2.5 mg        | 0.5 mg       | 40 mg          | 2 mg         | $\beta$ carotene, Vit B2, Se,<br>L-Glutathione, Mn,<br>Rutin                | 166.50               |
| 4     | Tab. Gloeye<br>Sun Pharma                    |                 |                |               |              |                |              | Billberry extract<br>Pycnogenol   | 237                  |
| 5     | Cap. I-site/<br>Sun Pharma                   | 150 mg          | 50 IU          | 3.2 mg        | 256 $\mu$ g  | 40 mg          | 2 mg         | $\beta$ carotene, Se<br>L-Glutathione, Mn                                   | 165                  |
| 6     | Tab. I-site plus<br>Sun Pharma               |                 |                | 3.2 mg        |              |                |              | Astaxanthin<br>Glutathione  | 195                  |
| 7     | Cap. Lutivit<br>Microvision                  |                 | 25 mg          | 7 mg          | 256 $\mu$ g  | 7.5 mg         | 1 mg         | $\beta$ carotene, Mn<br>L-arginine, Lycopene                                | 58                   |
| 8     | Cap. Macuchek<br>Indoco Remedies             |                 |                | 3.2 mg        |              | 40 mg          | 2 mg         | $\beta$ carotene, L-glutamic<br>acid  | 270                  |
| 9     | Cap.<br>Novoret Allergan                     |                 |                | 5 mg          | 1 mg         |                |              | Omega-3 fatty acids   | 312                  |
| 10    | Cap. Novoret Neo<br>Allergan                 |                 |                | 5 mg          | 1 mg         | 12 mg          | 2 mg         | Astaxanthin,<br>Resveratrol,<br>Tocotrienol                                 | 220                  |
| 11    | Tab. Nu-Eye<br>Intas                         |                 |                |               |              |                | 7.5 mg       | Billberry extract<br>Curcumin, Piperine, Se                                 | 142                  |
| 12    | Tab.Ocugold<br>Ajanta                        |                 |                | 3.2 mg        |              |                |              | $\beta$ carotene, mixed<br>carotene   | 96                   |
| 13    | Tab.Ocugold Plus<br>Ajanta                   |                 |                |               |              |                |              | $\beta$ carotene,<br>Astaxanthin, Lycopene                                  | 175                  |
| 14    | Cap.Omegared<br>Alembic                      | 250 mg          | 400 IU         | 5 mg          | 1 mg         | 12.5 mg        | 1 mg         | Omega-3 fatty acids   | 257                  |
| 15    | Cap.Omegasite<br>Sapient Labs                |                 |                |               |              | 15 mg          |              | Omega-3 fatty acids,<br>bioflavonoids, Ca,<br>Cr, Mg, Mn, Mixed<br>carotene | 150                  |
| 16    | Cap.Retinox<br>Ajanta                        |                 |                | 10 mg         | 2 mg         |                |              | Astaxanthin, Omega-3<br>fatty acids   | 164                  |
| 17    | Cap.Vesoret<br>Micro labs                    |                 |                | 7 mg          |              |                |              | Astaxanthin, DHA,<br>L-glutamic acid  | 258                  |
| 18    | Cap.Visionguard<br>Shrey Neutraceuticals     | 40 mg           | 10 mg          | 10 mg         | 5 $\mu$ g    | 1 mg           | 0.75 mg      | Billberry extract, Mn,<br>Se  | 140                  |
| 19    | Cap. Vitakind-I<br>Mankind Pharma            |                 |                | 4 mg          | 0.8 mg       | 40 mg          | 2 mg         | Lycopene, Se, Vit. B12  | 132                  |
| 20    | Cap. Vitakind-Zit<br>Mankind Pharma          | 40 mg           | 10 mg          |               |              | 10 mg          |              | D-Salina extract, Cr, Se,<br>silymarin                                      | 115                  |
| 21    | Tab.<br>Vitalux plus<br>Alcon                | 300 $\mu$ g     | 100 mg         | 4 mg          |              | 40 mg          | 2 mg         | $\beta$ carotene, Se, Vit. B2   | 306                  |

zinc in the AREDS formulation. Furthermore, beta carotene was found to increase the risk of lung cancer even among former smokers which was clinically relevant as more than 50% of the study participants were former smokers. To summarize, new formulation based on AREDS 2 contained

vitamin C 500mg, vitamin E 400 IU, lutein 10 mg, zeaxanthin 2 mg, zinc 80 mg and copper 2 mg. Though AREDS 2 did not provide evidence to support the inclusion of omega-3 fatty acids, there are several studies that has demonstrated its benefit and so clinicians are left to individually counsel

the patients regarding omega-3 supplementation.<sup>10</sup> There are several ongoing trials involving other therapies for preventing dry AMD.<sup>11,12</sup> These therapeutic agents are being developed to target the key features of the disease, including inhibiting the complement pathway and other inflammatory pathways, reducing oxidative stress and protecting RPE cells, inhibiting lipofuscin and visual cycle, regenerating RPE cells from stem cells and restoring choroidal blood flow.<sup>13</sup> Some of these therapeutic options, especially the stem-cell based therapy seem to have the potential for visual stability and recovery. Only with time we will know if they are viable options for the treatment of this chronic progressive blinding disease.

#### Cost effectiveness

AREDS formulation has been found to be not only clinically effective, but also cost effective in preventing the progression to advanced AMD.<sup>14</sup> There are very few studies which have done a cost-effectiveness analysis for vitamin therapy in AMD.<sup>14-16</sup> All these studies have concluded that vitamin therapy improves quality of life at a reasonable cost and these observations have implications on ophthalmic practice and health care planning.

#### Antioxidants in the Indian market

Antioxidants prescribed to our patients should not only be cost effective but also contain the constituents in the AREDS formula in the correct dosage. Several antioxidants are available in the Indian market at widely ranging cost and often the clinician is confused as to how to choose an appropriate antioxidant. A comparison of the modified AREDS formulation to some of the currently available antioxidants along with its cost is listed in Table 3. This information is obtained from an INTERNET search under the category of antioxidants/ nutrients for ocular use. It may be noted that there is not a single product which exactly matches the newer AREDS formulation. Only 6 out of the 21 (28.57%) products contain all the 6 ingredients included in the AREDS formulation, but in significantly lower doses. There are 2 products which do not contain any of the ingredients recommended by AREDS and another 4 which contain only one ingredient. Despite strong evidence supporting the benefits of lutein and zeaxanthin there are many products that have not included the same. Still they are marketed and prescribed as ocular antioxidants. These products are recommended for single daily usage by the manufacturers. Instead, advising patients to take these tablets twice or thrice daily or combining 2 products might provide a more optimal dose of AREDS ingredients but it will be at the cost of over dosage of some constituents which can be harmful in the long term. 33.33% (7 out of 21) of these products have not eliminated beta carotene, of which 3 also contain lutein and zeaxanthin and another 3 contain only lutein. These combinations not only have the disadvantage of competitive absorption effects of different carotenoids but also have the risk of increasing the propensity for lung cancer in susceptible individuals. Another factor is that the antioxidants evaluated in various trials contained a synthetic beta carotene and there is no proof that naturally

occurring beta carotenes (as in carrot) may have a similar risk.<sup>17</sup> Also, it is not known whether higher or lower dosages of these constituents than used in the AREDS would have any different effect, as AREDS is the only study to have shown a treatment benefit.<sup>8</sup>

There are no previous reports either from India or in other countries which have compared the ingredients of ocular antioxidants to the modified AREDS recommendations. A comparison of commercially available antioxidants to the AREDS1 formulation done in UK found that 75% of the products contained ingredients recommended by AREDS1.<sup>8</sup> However, another study in Australia found that only 1% of patients were taking the formulations in the correct dosage.<sup>17</sup> Compliance with treatment is also an important issue considering the chronicity of the disease. Few reports which have studied the vitamin usage patterns in AMD patients have shown poor adherence to the AREDS recommendations.<sup>18,19</sup> A study done at John Hopkins university school of medicine found that more than one-third of the potential candidates for AREDS supplements were not using it, while one fifth of the participants who had only early AMD and unlikely to benefit by treatment were on high dose supplements. The latter group is thus unnecessarily exposed to the potential adverse effects of chronic use of high dose supplements. This emphasizes the need for increasing awareness regarding AREDS recommendations and proper selection of patients.

Other factors: Genetic risk and life style

AMD is a complex disease with numerous genetic risk factors, of which 2 most widely studied and important loci are complement factor H (CFH) region in chromosome 1 and age related maculopathy susceptibility2/ high temperature requirement A serine peptidase1 (ARMS2/HTRA1) region on chromosome<sup>10,20,21</sup> Evidence suggests that risk alleles in specific genes may influence the development of AMD and the likely response to treatment. However, various retrospective analyses of genetic associations with treatment outcomes of original AREDS study have reported conflicting results. The significant associations that some investigators have identified from the AREDS study could not be validated in a second study population. Therefore, use of genetic information to guide treatment decisions is not currently recommended, until it is proved by a randomized clinical trial. AMD is also associated with several non-generic risk factors like advancing age, body mass index, cigarette smoking and lack of physical activity.<sup>6,22</sup> Implementing a healthy life style can have a direct effect in preventing AMD and also an indirect effect by preventing various metabolic and vascular diseases which in turn can facilitate progression of AMD. Patients with known genetic risk or those with a family history of AMD might benefit more by adopting a healthy life style at an early age. It may be hoped that individualized prevention and treatment strategies will soon become a reality.

#### Conclusions

AREDS based supplements should be recommended for those with moderate or advanced AMD. Since an ideal

formulation is not yet available in our market, one option would be to consider combination of drugs. It is important to evaluate the individual needs of the patient before recommending the supplementation. It is preferable to include lutein/zeaxanthin in the formulation especially in those with low dietary intake. The list of antioxidants included in this article is fairly comprehensive, though not a complete one and will serve as a reference for ophthalmologists in selecting the appropriate supplement. Clinicians should be equipped with the essential knowledge on eye nutrient products to assess and educate patients properly. Patients may be counseled regarding life style modifications like increasing consumption of green leafy vegetables and fish and avoidance of smoking and sedentary life style. Patient education is also important to improve compliance, reduce the risk of unnecessary drug related toxicity and expense. Finally, the regulatory agencies like foods safety and standards authority of India (FSSAI) can bring legislation to ensure all the nutritional supplements manufactured for use in AMD patients comply with the AREDS recommendations.

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