


Management of Age-Related Macular Degeneration (AMD) with AREDS2 Supplementation

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ABSTRACT

Age-related macular degeneration (AMD) is a degenerative disease of the macula that is the leading cause of blindness in the over-50 population. AMD is divided into non-exudative (dry) and exudative (wet) types, with the dry type accounting for 90% of cases. The main clinical features of dry AMD include drusen, hyperpigmentation or hypopigmentation of the retinal pigment epithelium (RPE), and geographic atrophy in advanced stages. Management of dry AMD focuses on preventing disease progression, one of which is through antioxidant supplementation based on the Age-Related Eye Disease Study (AREDS) and AREDS2 studies. AREDS2 supplementation, which contains vitamin C, E, zinc, copper, lutein and zeaxanthin, was shown to slow the progression of dry AMD by 55% over three years in cases of geographic atrophy beyond the fovea. In addition to nutritional supplementation, appropriate management includes early diagnosis, regular ophthalmic follow-up, and modification of risk factors such as smoking cessation and maintaining a healthy lifestyle to reduce the risk of disease progression. Early recognition and timely intervention are essential to preserve visual function and improve patients' quality of life. This review aims to outline the pathophysiology, risk factors and management of AMD with an emphasis on the role of AREDS2 supplementation in preventing disease progression.

Keywords: Age-related macular degeneration, antioxidants, AREDS2 supplementation, dry AMD.

ABSTRAK

Age-related macular degeneration (AMD) merupakan penyakit degeneratif pada makula yang menjadi penyebab utama kebutaan pada populasi berusia di atas 50 tahun. AMD terbagi menjadi tipe non-eksudatif (*dry*/kering) dan eksudatif (*wet*/basah), dengan tipe *dry* mencakup sekitar 90% dari seluruh kasus. Gambaran klinis utama *dry* AMD meliputi drusen, hiperpigmentasi atau hipopigmentasi epitel pigmen retina (*retinal pigment epithelium*/RPE), serta atrofi geografik pada stadium lanjut. Penatalaksanaan *dry* AMD berfokus pada pencegahan progresi penyakit, salah satunya melalui suplementasi antioksidan berdasarkan studi Age-Related Eye Disease Study (AREDS) dan AREDS2. Suplementasi AREDS2, yang mengandung vitamin C, E, *zinc*, tembaga, *lutein*, dan *zeaxanthin*, terbukti dapat memperlambat progresi *dry* AMD hingga 55% dalam periode tiga tahun pada kasus atrofi geografik di luar fovea. Selain suplementasi nutrisi, penatalaksanaan yang optimal juga mencakup diagnosis dini, pemantauan oftalmologis secara berkala, serta modifikasi faktor risiko, seperti berhenti merokok dan menerapkan gaya hidup sehat, untuk mengurangi risiko progresi penyakit. Pengenalan dini dan intervensi yang tepat sangat penting untuk mempertahankan fungsi penglihatan serta meningkatkan kualitas hidup pasien. Tinjauan ini bertujuan menguraikan patofisiologi, faktor risiko, dan penatalaksanaan AMD dengan penekanan pada peran suplementasi AREDS2 dalam mencegah progresi penyakit. **Andhika Guna Dharma**. **Penatalaksanaan *Age-Related Macular Degeneration* (AMD) dengan Suplementasi AREDS2.**

Kata Kunci: *Age-related macular degeneration*, antioksidan, suplementasi AREDS2, AMD kering.

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INTRODUCTION

Age-related macular degeneration (AMD) is a progressive degenerative condition affecting the macula, the central region of the retina responsible for sharp central vision. AMD is a major cause of irreversible vision loss among individuals aged over 50 years worldwide.[1,2] Based on global data, approximately 285 million people experience visual impairment, including 39 million individuals who are blind, and around 65% of them are over the age of 50 years. In the United States, the prevalence of AMD was estimated to increase from 2.07 million cases in 2010 to approximately 3.7 million cases by 2030, with around 71,000 new cases of exudative AMD occurring annually in North America.[3]

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AMD is classified into two main types: non-exudative (dry) and exudative (wet). Dry AMD accounts for 90% of cases and is characterized by drusen (yellowish deposits beneath the RPE), RPE hyperpigmentation or hypopigmentation, and geographic atrophy in advanced stages. Geographic atrophy causes irreversible central vision loss and is found bilaterally in 20%–25% of patients.[4–6] Wet AMD is characterized by choroidal neovascularization (CNV), which leads to fluid or blood leakage, accelerating vision loss.[7]

One significant innovation in AMD management is the development of supplement formulations in the Age-Related Eye Disease Study (AREDS) and its updated version, AREDS2.[3,4] These studies demonstrate that a combination of antioxidants and minerals can slow AMD progression in high-risk individuals. AREDS2 refined the formulation by replacing beta-carotene with lutein and zeaxanthin and adding omega-3 fatty acids, which have been shown to reduce the progression of geographic atrophy by up to 55% over three years for extrafoveal lesions.[8–10] This review aims to outline the pathophysiology, risk factors, and management of dry AMD, emphasizing the role of AREDS2 supplementation in preventing disease progression.

PATHOPHYSIOLOGY OF AMD

The pathophysiology of AMD involves oxidative processes in the macula that generate reactive oxygen species (ROS), such as free radicals and peroxides. This process is exacerbated by aging, which causes the thickening of Bruch's membrane due to basal laminar deposits (BLamD) and basal linear deposits (BLinD) as seen on **Figure 1**. BLamD consists of abnormal material and collagen between the RPE cytoplasmic membrane and its basal lamina, while BLinD consists of granular material containing phospholipids between the RPE basal lamina and the collagenous layer of Bruch's membrane. The accumulation of these deposits causes the separation of the RPE from Bruch's membrane, reducing permeability and impairing photoreceptor nutrition.[7,11]

The aging process leads to a decline in the integrity of the macular elastic layer and the choriocapillaris, which reduces oxygen supply to the retina. This hypoxia can trigger the activation of vascular endothelial growth factor (VEGF), which stimulates CNV growth in wet AMD. In dry AMD, progression to geographic atrophy is characterized by the loss of photoreceptor cells, RPE, and the choriocapillaris, resulting in irreversible central scotoma.[7,13,14]

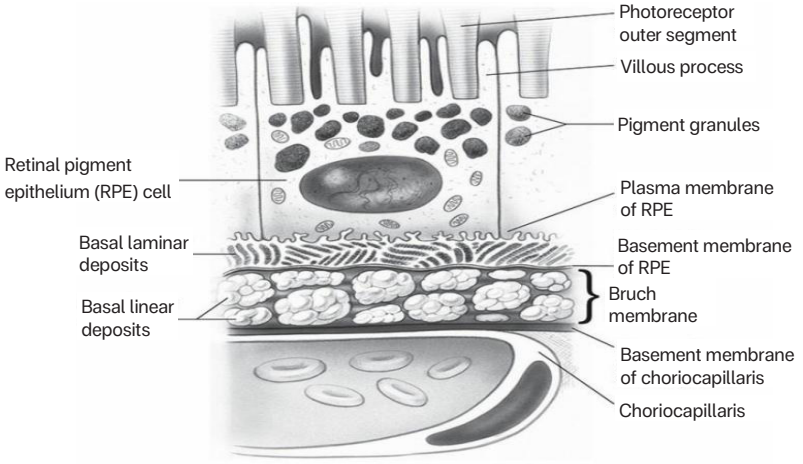

Figure 1. Schematic illustration of basal laminar deposits and basal linear deposits causing thickening of the inner collagenous layer of Bruch's membrane.[12]

RISK FACTORS FOR AMD

Risk factors for AMD include age, gender, genetics, race, family history, and environmental conditions. The prevalence of AMD increases with age, with an incidence of 2% at age 70 and 6% at age 80 (Framingham Eye Study). Women have a higher risk than men, with odds ratios of 1.15–1.39 for soft drusen (Beaver Dam Eye Study; NHANES-III).[12] Genetic factors account for 55% of AMD risk, with CFH and ARMS2/HTRA1 genes as the primary contributors. The CFH Y402H polymorphism increases risk 4.6 times (heterozygous) to 7.4 times (homozygous).[15,16]

White individuals have a prevalence of AMD twice as high as that of colored races, possibly because melanin acts as an antioxidant. A family history increases the risk of AMD, with an odds ratio of 2.17 for early-stage AMD and 3.92 for advanced-stage AMD (Blue Mountains Eye Study).[10,11] Environmental factors such as smoking increase the risk of AMD by up to 3.6 times for geographic atrophy, while sun exposure triggers photo-oxidative damage to the retina.[3]

Systemic conditions such as hypertension, hypercholesterolemia, and diabetes can also increase the risk of AMD.[12] Body mass index (BMI) outside the normal range (20–25 kg/m²) and a large waist circumference are correlated with AMD progression.[7,14] Low macular pigment optical density (MPOD), especially in smokers and women, also increases the risk of AMD.[17]

DIAGNOSIS OF DRY AMD

The diagnosis of dry AMD is established through anamnesis, clinical examination, and supporting tests. Clinical symptoms include metamorphopsia, decreased visual acuity, central scotoma, difficulty with light-dark adaptation, and color vision disturbances. Clinical examination using magnifying lenses (60, 90, or 78 diopters) identifies drusen (diameter ≥ 63 µm), RPE hyperpigmentation or hypopigmentation, reticular pseudodrusen, and geographic atrophy. Drusen are classified as hard drusen (diameter < 50 µm) and soft drusen (larger, confluent) as shown on **Figure 2**; soft drusen increase the risk of AMD progression.[5,6,18]

Geographic atrophy (GA) of the RPE is a clinical feature of advanced non-exudative AMD associated with a gradual and progressive decline in central visual acuity. GA areas are generally bilateral and contribute to 20% of blindness in AMD cases, with a prevalence of 3.5% in populations over 75 years of age, increasing to 22% in populations over 90 years of age.[7,14] Peripapillary atrophy is also found in up to 40% of eyes with macular GA. Other ophthalmological findings

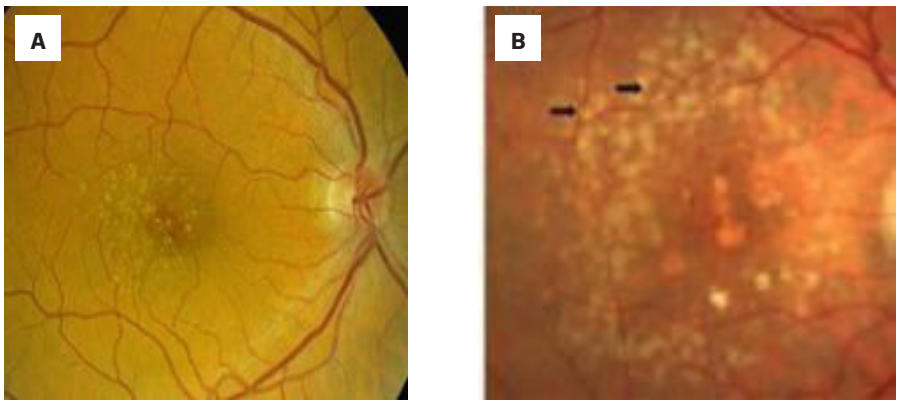

Figure 2. Types of drusen: A) Hard drusen, B) Soft drusen.[7,14]

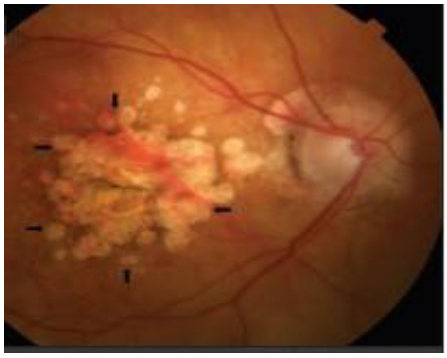

Figure 3. Geographic atrophy of the macula accompanied by peripapillary atrophy and visualized choroidal blood vessels.[7]

include pigmentation changes, such as hypopigmentation or hyperpigmentation, around the macular atrophy **(Figure 3)**.[7]

Supporting tests such as fundus autofluorescence (FAF) show hypoautofluorescence in geographic atrophy, while optical coherence tomography (OCT) identifies drusen, RPE detachment, and retinal thickening. Fundus fluorescein angiography (FFA) helps detect leakage in wet AMD but is less specific for dry AMD.[7,14,18]

The Age-Related Eye Disease Study (AREDS) classifies AMD into four categories: Category I (no AMD), Category II (early stage), Category III (intermediate stage), and Category IV (advanced stage). The risk of progression to the advanced stage is 18% for Category III and 35%–50% for Category IV in the fellow eye within five years.[14, 18,19]

MANAGEMENT OF DRY AMD

Management of dry AMD aims to slow disease progression through observation, antioxidant supplementation, and, if signs of exudative type AMD are found, alternative therapies: anti-VEGF injections, photodynamic therapy, and laser photocoagulation.[20–22]

a. Early Detection

Patients with early-stage AMD and/or a family history of AMD should be educated on how to monitor monocular vision independently (e.g., using an Amsler grid) and the importance of scheduled eye examinations with dilated pupils to detect AMD worsening. Antioxidant supplementation according to AREDS recommendations is suggested for patients with AMD progression in at least one eye.[18,19] Patients with high-risk AMD phenotypes who are at risk of progressive AMD should be educated to independently detect new symptoms arising from the onset of CNV. Patients should also be educated on the importance of reporting new symptoms to clinicians.[13,19]

b. Antioxidant and Zinc Supplementation

The AREDS study, conducted by the National Eye Institute, showed that a combination of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc (80 mg), and copper (2 mg) reduced the risk of progression from intermediate to advanced AMD by 25% and lowered the risk of further vision loss (≥ 3 lines in 5 years), but offered no benefit for patients with early-stage AMD or no AMD. Beta-carotene administration has also been reported to potentially trigger lung cancer in patients with a history of smoking; therefore, AREDS recommends new antioxidant supplementation in the AREDS2 study.[14,20]

The AREDS2 study reported that lutein and zeaxanthin, which are carotenoids like beta-carotene, have a lower risk and are widely found as macular pigments (beta-carotene is not detected in the human retina), so both are used to replace beta-carotene. The administration of lutein and zeaxanthin can reduce the risk of AMD progression by 10% and the risk of GA incidence by 11%. This study also states that a zinc dose of 80 mg is the appropriate dose for AMD prophylaxis. AMD patients with AREDS category III and IV are advised to receive AREDS2 supplementation with the following composition: vitamin C 500 mg, vitamin E 400 IU, lutein 10 mg, zeaxanthin 2 mg, zinc oxide 80 mg (plus cupric oxide 20 mg).[17,20,23]

The AREDS2 study also investigated the effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on AMD progression. Both are major structures of omega-3 LCPUFA (long-chain polyunsaturated fatty acids) of the outer layer of retinal photoreceptors. EPA is a precursor to DHA, and both play a role in inflammation and the pathogenesis of retinal disorders. The doses in the AREDS2 study were 350 mg of DHA and 650 mg of EPA; however, the study results indicated no significant correlation between the administration of EPA and DHA and AMD progression.[20,21]

c. Risk Factor Control

Risk factor control for AMD is related to lifestyle. Patients need to be educated to modify their lifestyle as follows: (1) Stop smoking, as smoking is the strongest environmental risk factor for AMD incidence; the risk of AMD progression is higher in smokers than in non-smokers, and even passive smokers can be affected; (2) Maintain a normal body weight, as excess weight poses a risk for various systemic diseases that contribute to AMD incidence; (3) Physical activity: routine exercise for 30 minutes at least once a week reduces the risk of AMD; (4) A healthy diet: consuming a balanced diet (including fruits and vegetables) can lower the risk of AMD incidence by 46%; (5) Use protective eyewear when

outdoors.[21,24–26]

d. Follow up

Evaluation of dry AMD patients is performed periodically to detect clinical improvement or worsening. Evaluation includes the current disease course, such as: changes in symptoms (decreased visual acuity, metamorphopsia), changes in medication and supplementation, changes in lifestyle and risk factor control, and ocular and systemic conditions. Evaluation of ophthalmological status includes visual acuity examination and fundus examination. The American Academy of Ophthalmology provides recommendations regarding the periodic evaluation schedule for dry AMD patients, as presented in **Table**.[18,22,27]

CONCLUSION

Age-related macular degeneration (AMD) is a progressive degenerative disease that is the leading cause of blindness in the elderly population. Dry AMD, which dominates 90% of cases, is characterized by drusen, RPE pigment changes, and geographic atrophy in advanced stages. Management of dry AMD focuses on antioxidant supplementation based on AREDS2, which contains vitamin C, E, zinc, copper, lutein, and zeaxanthin, proven to slow the progression of geographic atrophy by up to 55% in three years. Other strategies include early detection with the Amsler grid, risk factor control through a healthy lifestyle, and periodic evaluation every 6–24 months. This approach helps minimize disease progression and improve the quality of life of AMD patients.

Table. Recommended therapy and follow-up for AMD patients.[18,22,27]

Recommendation	Diagnosis	Follow-Up Recommendation	
Observation without medication or surgery	Early-stage AMD/AREDS Category II	Re-evaluation within 6–24 months if asymptomatic, or immediate evaluation if symptoms suggestive of CNV occur	Fundus photography, FFA, or OCT as clinically indicated
	Advanced AMD with subfoveal geographic atrophy or bilateral disciform scar	Re-evaluation within 6–24 months if asymptomatic, or immediate evaluation if symptoms suggestive of CNV occur	Fundus photography, FFA, or OCT as clinically indicated
AREDS-based antioxidant supplementation	Intermediate AMD/AREDS Category III; or advanced AMD in one eye	Re-evaluation within 6–18 months if asymptomatic, or immediate evaluation if symptoms suggestive of CNV occur	• Self-monitoring of near monocular vision (reading test/Amsler grid) • Fundus photography and/or FAF as clinically indicated • FFA and/or OCT if CNV is suspected.

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