

MDFA Research update

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FEATURED ARTICLE

Long-term Outcomes of Adding Lutein/Zeaxanthin and ω -3 Fatty Acids to the AREDS Supplements on Age-Related Macular Degeneration Progression: AREDS2 Report 28.

JAMA Ophthalmology. 2022 Jun 2

Chew EY, Clemons TE, Agrón E, Domalpally A, Keenan TDL, Vitale S, Weber C, Smith DC, Christen W; AREDS2 Research Group.

Importance: After the Age-Related Eye Disease Study 2 (AREDS2) study, the beta carotene component was replaced by lutein/zeaxanthin for the development of the revised AREDS supplement. However, it is unknown if the increased risk of lung cancer observed in those assigned beta carotene persists beyond the conclusion of the AREDS2 trial and if there is a benefit of adding lutein/zeaxanthin to the original AREDS supplement that can be observed with long-term follow-up. **Objective:** To assess 10-year risk of developing lung cancer and late age-related macular degeneration (AMD).

Design, Setting, and Participants: This was a multicenter epidemiologic follow-up study of the AREDS2 clinical trial, conducted from December 1, 2012, to December 31, 2018. Included in the analysis were participants with bilateral or unilateral intermediate AMD for an additional 5 years after clinical trial. Eyes/participants were censored at the time of late AMD development, death, or loss to follow-up. Data were analyzed from November 2019 to March 2022.

Interventions: During the clinical trial, participants were randomly assigned primarily to lutein/zeaxanthin and/or ω -3 fatty acids or placebo and secondarily to no beta carotene vs beta carotene and low vs high doses of zinc. In the epidemiologic follow-up study, all participants received AREDS2 supplements with lutein/zeaxanthin, vitamins C and E, and zinc plus copper. Outcomes were assessed at 6-month telephone calls. Analyses of AMD progression and lung cancer development were conducted using proportional hazards regression and logistic regression, respectively.

Main Outcomes And Measures: Self-reported lung cancer and late AMD validated with medical records. **RESULTS:** This study included 3882 participants (mean [SD] baseline age, 72.0 [7.7] years; 2240 women [57.7%]) and 6351 eyes. At 10 years, the odds ratio (OR) of having lung cancer was 1.82 (95% CI, 1.06-3.12; $P = .02$) for those randomly assigned to beta carotene and 1.15 (95% CI, 0.79-1.66; $P = .46$) for lutein/zeaxanthin. The hazard ratio (HR) for progression to late AMD comparing lutein/zeaxanthin with no lutein/zeaxanthin was 0.91 (95% CI, 0.84-0.99; $P = .02$) and comparing ω -3 fatty acids with no ω -3 fatty acids was 1.01 (95% CI, 0.93-1.09; $P = .91$). When the lutein/zeaxanthin main effects analysis was restricted to those randomly assigned to beta carotene, the HR was 0.80 (95% CI, 0.68-0.92; $P = .002$). A direct analysis of lutein/zeaxanthin vs beta carotene showed the HR for late AMD was 0.85 (95% CI, 0.73-0.98; $P = .02$). The HR for low vs high zinc was 1.04 (95% CI, 0.94-1.14; $P = .49$), and the HR for no beta carotene vs beta carotene was 1.04 (95% CI, 0.94-1.15; $P = .48$).

Conclusions and Relevance: Results of this long-term epidemiologic follow-up study of the AREDS2 cohort suggest that lutein/zeaxanthin was an appropriate replacement for beta carotene in AREDS2 supplements. Beta carotene usage nearly doubled the risk of lung cancer, whereas there was no statistically significant increased risk with lutein/zeaxanthin. When compared with beta carotene, lutein/zeaxanthin had a potential beneficial association with late AMD progression.

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DRUG TREATMENTS

Patterns of treatment discontinuation in patients receiving anti-vascular endothelial growth factor for neovascular age-related macular degeneration.

Indian Journal of Ophthalmology. 2022 Jun

Dhingra N, Upasani D, Ghanchi FD

Purpose: To report the reasons for treatment discontinuation within 5 years in patients receiving intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for neovascular age-related macular degeneration (nAMD).

Methods: A retrospective case-notes review of patients commenced on anti-VEGF for nAMD who failed to complete 5 years of follow-up was undertaken. The reasons for treatment discontinuation, baseline age, baseline visual acuity (VA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters, and the VA change at the last follow-up were recorded. Age-specific all-cause mortality was calculated for deceased patients.

Results: Of the 1177 patients, 551 patients (46.8%) failed to complete the 5-year follow-up. The reasons for treatment discontinuation were death (251), early discharge due to stable disease (110), further treatment deemed futile (100), failure to attend (15), ill health (14), patient choice (7), and transfer of care (1). In 53 patients, no reason was documented. The mean baseline age of those who completed the 5-year follow-up (77.4 ± 7.8 years, 95% confidence interval (CI): 76.8-77.9) was significantly lower than those who discontinued the treatment for any reason (82 ± 7.7 years, 95% CI: 81.4-82.6) ($P < 0.0001$). Survival analysis showed that baseline VA was not a factor in treatment discontinuation; however, visual stability (± 5 letters from baseline) was associated with treatment continuation. The age-

specific all-cause mortality in deceased patients was lower than that in the general population.

Conclusion: At 5 years, only 53% of patients remained in active care, and death was the most common reason for treatment discontinuation. Lower baseline age and VA stability during therapy were associated with treatment continuation.

DOI: [10.4103/ijo.IJO_3066_21](https://doi.org/10.4103/ijo.IJO_3066_21)

Intravitreal aflibercept for diabetic macular edema in real-world clinical practice in Japan: 24-month outcomes.

Graefes Archive of Clinical and Experimental Ophthalmology. 2022 Jun 2.

Sugimoto M, Handa C, Hirano K, Sunaya T, Kondo M.

Purpose: To report the safety and effectiveness of intravitreal aflibercept (IVT-AFL) for diabetic macular edema (DME) in the real-world clinical practice setting in Japan.

Methods: In this prospective, multicenter, observational, post-marketing surveillance, patients with DME newly receiving IVT-AFL were enrolled. During a 24-month follow-up, the primary outcome was the occurrence of safety events. Other pre-specified endpoints were effectiveness indicators, such as best-corrected visual acuity (BCVA), central retinal thickness, and injection frequency.

Results: In total, 646 patients administered at least one IVT-AFL injection were included in the safety analysis. During the follow-up period, adverse events occurred in 42 patients (6.50%), whereas adverse drug reactions occurred in 12 (1.86%). In the 12 patients who had adverse drug reactions, seven events occurred in seven patients within the first month of the most recent injection. In addition, 622 patients were included in the effectiveness analysis set. The number of injections over 24 months was 3.6 ± 3.0 (mean \pm standard deviation [SD]). BCVA (logarithm of the minimum angle of resolution) was 0.437 ± 0.362 (mean \pm SD) ($n = 622$) at baseline and 0.321 ± 0.348 ($n = 177$) after 24 months of treatment with IVT-AFL. Central retinal thickness was $440.8 \pm 134.2 \mu\text{m}$ (mean \pm SD) ($n = 444$) at baseline and $355.5 \pm 126.4 \mu\text{m}$ ($n = 140$) at 24 months.

Conclusion: Routine administration of IVT-AFL for DME was not associated with new safety concerns, and BCVA outcomes were maintained over 24 months in the real-world setting. Nonetheless, patients in this real-world setting received fewer injections than those in clinical trials, suggesting that a margin for improvement exists in clinical practice. TRIAL REGISTRATION: ClinicalTrials.gov: NCT02425501.

DOI: [10.1007/s00417-022-05703-9](https://doi.org/10.1007/s00417-022-05703-9)

OTHER TREATMENTS

Real World Data Comparison of Standard Care vs SDM Laser Vision Protection Therapy for Prevention of Neovascular AMD.

Clinical Ophthalmology. 2022 May 24

Luttrull JK, Gray G.

Purpose: To assess the impact of regular periodic subthreshold diode micropulse

laser (SDM) as Vision Protection Therapy on the rate of neovascular conversion of dry age-related macular degeneration (AMD).

Methods: Patient unidentified clinical data aggregated by Vestrum Health, LLC (VH) from 300 retina specialists across the United States was analyzed to examine the effect of a program of regular periodic panmacular low-intensity/high-density subthreshold diode micropulse laser as vision protection therapy (VPT) compared to standard care alone, on the incidence of neovascular conversion in patients with dry age-related macular degeneration (AMD), between January 4, 2016, and September 30, 2020, producing 392,250 eyes for study.

Results: After applying inclusion and exclusion criteria, eyes were matched by propensity scoring for key risk factors. This produced 830 eyes managed by standard care plus VPT, performed on average every 108 days per eye; and 8300 eyes managed with standard care alone (SCA) in a 1/10 ratio for comparison. Comparison found that VPT eyes had a markedly lower rate of neovascular conversion than SCA eyes (hazard ratio 13.04) overall, and for each propensity score matched quintile. VA worsened over time in the SCA group but improved in the VPT group.

Conclusion: Our findings suggest that, compared to standard care alone, VPT may markedly reduce the rate of neovascular conversion in AMD, the main cause of irreversible visual loss worldwide.

DOI: [10.2147/OPHTH.S366150](https://doi.org/10.2147/OPHTH.S366150)

DIAGNOSIS AND IMAGING

Correlating the patterns of diabetic macular edema, optical coherence tomography biomarkers and grade of diabetic retinopathy with stage of renal disease.

International Ophthalmology. 2022 May 28.

Agarwal M, Sachdeva M, Shah S, Raman R, Rani PK, Rajalakshmi R, Sivaprasad S, Vignesh TP, Ramasamy K, Madharia A, Sen A, Sugumar S, Behera UC, Rodrigues AM, Anantharaman G, Priya S, Majumdar A; India Retinal Disease Study group.

Purpose: To correlate optical coherence tomography (OCT)-based morphological patterns of diabetic macular edema (DME), biomarkers and grade of diabetic retinopathy (DR) in patients with various stages of chronic kidney disease (CKD) secondary to diabetes.

Design: Multicentric retrospective cross-sectional study was conducted at seven centers across India.

Methods: Data from medical records of patients with DME and CKD were entered in a common excel sheet across all seven centers. Staging of CKD was based on estimated glomerular filtration rate (eGFR).

Results: The most common morphological pattern of DME was cystoid pattern (42%) followed by the mixed pattern (31%). The proportion of different morphological patterns did not significantly vary across various CKD stages ($p = 0.836$). The presence of external limiting membrane-ellipsoid zone (ELM-EZ) defects ($p < 0.001$) and foveal sub-field thickness ($p = 0.024$) showed a direct correlation with the stage of CKD which was statistically significant. The presence of hyperreflective dots (HRD) and disorganization of inner retinal layers (DRIL) showed no significant correlation with the stage of CKD. Sight threatening DR was found to increase from 70% in CKD

stage 3 to 82% in stages 4 and 5 of CKD, and this was statistically significant ($p = 0.03$).

Conclusion: Cystoid morphological pattern followed by mixed type was the most common pattern of DME on OCT found in patients suffering from stage 3 to 5 of CKD. However, the morphological patterns of DME did not significantly vary across various CKD stages. ELM-EZ defects may be considered as an important OCT biomarker for advanced stage of CKD.

DOI: [10.1007/s10792-022-02332-3](https://doi.org/10.1007/s10792-022-02332-3)

NUTRITION AND LIFESTYLE

The effects of vitamin E on non-proliferative diabetic retinopathy in type 2 diabetes mellitus: Are they sustainable with 12 months of therapy.

SAGE Open Med. 2022 May 26

Ho JI, Ng EY, Chiew Y, Koay YY, Chuar PF, Phang SCW, Ahmad B, Kadir KA.

Introduction: Prolonged uncontrolled hyperglycaemia has shown to cause oxidative stress, inflammation, thrombosis and upregulation of angiogenesis in diabetics, which all contributes to diabetic retinopathy development and progression. Vitamin E is found to have anti-inflammatory, anti-oxidative, anti-thrombogenic and anti-angiogenesis which could play an important role in early treatment of diabetic retinopathy. This study aims to investigate the effect of Tocotrienol-rich vitamin E (Tocovid) on the progression of retinal microhaemorrhages and diabetic macular oedema in patients with diabetic retinopathy.

Method: This is a multi-centred, randomized, double-blinded, placebo-controlled trial which involved 55 eligible participants. The participants in the treatment group ($n = 22$) received Tocovid 200 mg twice daily while those in the placebo group ($n = 23$) would receive placebo twice daily. Both groups will be on the treatment for a total duration of 12 months. Both retinal signs will be assessed at baseline, 2 months, 6 months and 12 months of treatment to determine the progression of diabetic retinopathy. Serum vascular endothelial growth factor which reflects on the angiogenesis process in the eye was analysed as well at similar time points as the retinal findings.

Results: After 12 months of treatment, the placebo group had a significant increase of 23.42% in retinal microhaemorrhages ($p < 0.05$), but the Tocovid group had no significant changes. Moreover, the Tocovid group showed a significant decrease of 48.38% in area of diabetic macular oedema over the 12 months period ($p < 0.05$), but the placebo group had no significant changes. Meanwhile, there was no significant difference in serum vascular endothelial growth factor level when comparing between both groups.

Conclusion: These findings could indicate that Tocovid has an important role in preventing early diabetic retinopathy progression.

DOI: [10.1177/20503121221095324](https://doi.org/10.1177/20503121221095324)

Recent Advances and the Mechanism of Astaxanthin in Ophthalmological Diseases.

Journal Ophthalmology. 2022 May 20

Yang M, Wang Y.

Astaxanthin (AST) is a naturally occurring carotenoid that has strong antioxidant, anti-inflammatory, and antiapoptosis effects and is used for the prevention of cancer. There is growing evidence that AST has multiple protective effects against various eye diseases. This article reviews the function and the potential mechanism of AST in dry eye syndrome, keratitis, cataract, diabetic retinopathy, age-related macular degeneration, high intraocular pressure, and other ocular diseases. It provides a theoretical basis for the clinical application of AST as a potential nutraceutical.

DOI: [10.1155/2022/8071406](https://doi.org/10.1155/2022/8071406)

REVIEW

Adherence to the Mediterranean-Style Eating Pattern and Macular Degeneration: A Systematic Review of Observational Studies.

Nutrients. 2022 May 12

Gastaldello A, Giampieri F, Quiles JL, Navarro-Hortal MD, Aparicio S, García Villena E, Tutusaus Pifarre K, De Giuseppe R, Grosso G, Cianciosi D, Forbes-Hernández TY, Nabavi SM, Battino M.

Age-related macular degeneration (AMD) is a serious degenerative disease affecting the eyes, and is the main cause of severe vision loss among people >55 years of age in developed countries. Its onset and progression have been associated with several genetic and lifestyle factors, with diet appearing to play a pivotal role in the latter. In particular, dietary eating patterns rich in plant foods have been shown to lower the risk of developing the disease, and to decrease the odds of progressing to more advanced stages in individuals already burdened with early AMD. We systematically reviewed the literature to analyse the relationship between the adherence to a Mediterranean diet, a mainly plant-based dietary pattern, and the onset/progression of AMD. Eight human observational studies were analysed. Despite some differences, they consistently indicate that higher adherence to a Mediterranean eating pattern lowers the odds of developing AMD and decreases the risk of progression to more advanced stages of the disease, establishing the way for preventative measures emphasizing dietary patterns rich in plant-foods.

DOI: [10.3390/nu14102028](https://doi.org/10.3390/nu14102028)

Metabolism Dysregulation in Retinal Diseases and Related Therapies.

Antioxidants (Basel). 2022 May 11

Chen Y, Coorey NJ, Zhang M, Zeng S, Madigan MC, Zhang X, Gillies MC, Zhu L, Zhang T.

The human retina, which is part of the central nervous system, has exceptionally high

energy demands that requires an efficient metabolism of glucose, lipids, and amino acids. Dysregulation of retinal metabolism disrupts local energy supply and redox balance, contributing to the pathogenesis of diverse retinal diseases, including age-related macular degeneration, diabetic retinopathy, inherited retinal degenerations, and Macular Telangiectasia. A better understanding of the contribution of dysregulated metabolism to retinal diseases may provide better therapeutic targets than we currently have.

DOI: [10.3390/antiox11050942](https://doi.org/10.3390/antiox11050942)

Do Oral Pathogens Inhabit the Eye and Play a Role in Ocular Diseases?

Journal of Clinical Medicine. 2022 May 23

Arjunan P, Swaminathan R.

Fascinatingly, the immune-privileged healthy eye has a small unique population of microbiota. The human microbiome project led to continuing interest in the ocular microbiome. Typically, ocular microflorae are commensals of low diversity that colonize the external and internal sites of the eye, without instigating any disorders. Ocular commensals modulate immunity and optimally regulate host defense against pathogenic invasion, both on the ocular surface and neuroretina. Yet, any alteration in this symbiotic relationship culminates in the perturbation of ocular homeostasis and shifts the equilibrium toward local or systemic inflammation and, in turn, impaired visual function. A compositional variation in the ocular microbiota is associated with surface disorders such as keratitis, blepharitis, and conjunctivitis. Nevertheless, innovative studies now implicate non-ocular microbial dysbiosis in glaucoma, age-related macular degeneration (AMD), uveitis, and diabetic retinopathy. Accordingly, prompt identification of the extra-ocular etiology and a methodical understanding of the mechanisms of invasion and host-microbial interaction is of paramount importance for preventative and therapeutic interventions for vision-threatening conditions. This review article aims to explore the current literature evidence to better comprehend the role of oral pathogens in the etiopathogenesis of ocular diseases, specifically AMD.

DOI: [10.3390/jcm11102938](https://doi.org/10.3390/jcm11102938)