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MD Research News

Issue 208

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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Drug treatment

Ophthalmologica. 2014 Nov 19. [Epub ahead of print]

Intravitreal Ranibizumab for Patients with Neovascular Age-Related Macular Degeneration with Good Baseline Visual Acuity.

Kato A, Yasukawa T, Suga K, Hirano Y, Nozaki M, Yoshida M, Ogura Y.

Purpose: To report the 1-year results of intravitreal ranibizumab (IVR) injections for neovascular age-related macular degeneration (nAMD) in patients with good baseline visual acuity (VA).

Methods: Thirty-six eyes of 36 patients with nAMD with best-corrected VAs (BCVAs) >0.6 (equal to 0.22 in the logarithm of the minimum angle of resolution unit) were enrolled. IVR was the primary treatment; additional treatment was administered as needed. BCVAs and central retinal thickness (CRT) were measured periodically.

Results: The mean number of injections at month 12 was 3.3. The mean BCVAs were 0.11 ± 0.02 at baseline and 0.12 ± 0.03 at month 12, which did not significantly differ. The mean CRT significantly improved from 320 ± 15 to 254 ± 12 μm at month 12 ($p < 0.01$). Photodynamic therapy was applied in 2 cases because of frequent recurrences.

Conclusions: IVR maintained VA and improved morphological changes in wet AMD with good baseline VA.

PMID: 25412682 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2014 Nov 17. [Epub ahead of print]

Combined effects of genetic and non-genetic risk factors affect response to ranibizumab in exudative age-related macular degeneration.

Piermarocchi S, Miotto S, Colavito D, Leon A, Segato T.

PURPOSE: To investigate whether genetic and non-genetic risk factors influence 12-month response to ranibizumab treatment for exudative age-related macular degeneration (AMD).

METHODS: A cohort of 94 Caucasian patients with unilateral exudative AMD received intravitreal ranibizumab. After a three-injection loading phase, a PRN regimen was followed. Patients were genotyped for three single-nucleotide polymorphisms: CFH rs1061170, ARMS2 rs10490924 and C3 rs2230199. Non-genetic risk factors [choroidal neovascularization (CNV) phenotype, smoking habit, hypertension and body mass index] were considered. The selected end-point was the 12-month variation of number of ETDRS

letters.

RESULTS: Complement factor H (CFH) risk alleles, smoking history and arterial hypertension each independently influenced treatment response, with worse 12-month BCVA outcomes (p = 0.036, 0.037, 0.043, respectively). A significant cumulative effect of these risk factors was also observed: patients homozygous for the CFH risk alleles and with a positive smoking history showed a mean loss of 8.0 ETDRS letters (p = 0.010). Patients with CFH risk alleles, smoking history and hypertension had a mean loss of 13.9 ETDRS letters (p = 0.013). CNV phenotypes did not influence visual outcomes, nor were they associated with other genetic/non-genetic risk factors.

CONCLUSIONS: Complement factor H risk alleles, smoking history and hypertension affect the mid-term response to ranibizumab in exudative AMD.

PMID: 25402348 [PubMed - as supplied by publisher]

Ophthalmologica. 2014 Nov 19. [Epub ahead of print]

Intravitreal Ranibizumab and/or Dexamethasone Implant for Macular Edema Secondary to Retinal Vein Occlusion.

Nghiem-Buffet S, Fajnkuchen F, Buffet M, Ayrault S, Le Gloahec-Lorcy A, Grenet T, Delahaye-Mazza C, Quentel G, Cohen SY.

Purpose: To investigate the outcome of intravitreal ranibizumab and/or dexamethasone implant treatment for treatment of macular edema (ME) secondary to central or branch retinal vein occlusion (CRVO or BRVO) in a clinical setting.

Methods: Retrospective analysis of consecutive patients followed for at least 6 months. Data recorded included the type of occlusion, initial and final visual acuity, and number of injections.

Results: Sixty-five patients were included, 26 had CRVO and 39 BRVO. Mean (±SD) follow-up duration was 16 (±7.7) months. Twenty-four (36.9%) patients received ranibizumab in monotherapy, 19 patients (29.3%) dexamethasone in monotherapy, and 22 patients (33.8%) received successively both treatments. In dexamethasone-treated patients, mean (±SD) visual acuity gain was 5.8 ± 10.7 letters for BRVO and 16.8 ± 15.6 letters for CRVO. In ranibizumab-treated patients, mean (±SD) visual acuity gain was 9.2 ± 10 letters for BRVO and 18.2 ± 20.5 letters for CRVO.

Conclusion: Both intravitreal ranibizumab and dexamethasone intravitreal implant could be used as first-line therapy for patients with ME secondary to retinal vein occlusion.

PMID: 25413000 [PubMed - as supplied by publisher]

Wien Klin Wochenschr. 2014 Nov 20. [Epub ahead of print]

Endogenous endophthalmitis after carotid endarterectomy due to exudative macular degeneration.

Ivastinovic D, El-Shabrawi Y, Ardjomand N.

Abstract: A 78-year-old male patient with unilateral exudative macular degeneration developed endogenous endophthalmitis 11 days after carotid endarterectomy. The endophthalmitis could not be treated by intravitreal application of antibiotics. The patient underwent vitrectomy and systemic application of vancomycin. Six days later, the eye was quiet and the patient was discharged with a visual acuity of 0.9 logMAR. Patients with exudative macular degeneration have a higher risk for developing endogenous endophthalmitis after vascular surgery of the carotid arteries and prolonged postoperative application of systemic antibiotics might be considered in these patients.

PMID: 25409946 [PubMed - as supplied by publisher]

Ophthalmic Res. 2014 Nov 14;52(4):234-238. [Epub ahead of print]

Anterior Chamber Paracentesis Might Prevent Sustained Intraocular Pressure Elevation after Intravitreal Injections of Ranibizumab for Age-Related Macular Degeneration.

Ichiyama Y, Sawada T, Kakinoki M, Sawada O, Nakashima T, Saishin Y, Kawamura H, Ohji M.

Background/Aims: To evaluate the efficacy of anterior chamber paracentesis for preventing sustained intraocular pressure (IOP) elevation after intravitreal ranibizumab (IVR) injections for age-related macular degeneration (AMD).

Methods: The medical records for all cases of exudative AMD treated with IVR injections and followed monthly for 12 months or longer were reviewed retrospectively. Anterior chamber paracentesis was performed just before IVR injections. A sustained IOP elevation was defined as 22 mm Hg or higher during 2 consecutive visits with an increase exceeding 6 mm Hg from baseline.

Results: One hundred and eleven eyes met the inclusion criteria, and none of these eyes had a sustained IOP elevation.

Conclusions: Anterior chamber paracentesis before IVR injections may prevent sustained IOP elevations.

PMID: 25401265 [PubMed - as supplied by publisher]

JAMA. 2014 Nov 19;312(19):2045.

Drugs for macular degeneration--reply.

Silver J.

Comment on

Drugs for macular degeneration, price discrimination, and Medicare's responsibility not to overpay. [JAMA. 2014]

Drugs for macular degeneration. [JAMA. 2014]

PMID: 25399292 [PubMed - in process]

JAMA. 2014 Nov 19;312(19):2044-5.

Drugs for macular degeneration.

Stoilov I, Fung AE, Rubio RG.

Comment in

Drugs for macular degeneration--reply. [JAMA. 2014]

Comment on

Drugs for macular degeneration, price discrimination, and Medicare's responsibility not to overpay. [JAMA. 2014]

PMID: 25399288 [PubMed - in process]

BMJ. 2014 Nov 18;349:g6887.

What is stopping the NHS from using bevacizumab for macular degeneration and other retinal disorders?

Lotery A, MacEwen C.

PMID: 25406142 [PubMed - in process]

Other treatment & diagnosis

Ophthalmologica. 2014 Nov 19. [Epub ahead of print]

Longitudinal Analysis of Reticular Drusen Associated with Age-Related Macular Degeneration Using Combined Confocal Scanning Laser Ophthalmoscopy and Spectral-Domain Optical Coherence Tomography Imaging.

Steinberg JS, Auge J, Fleckenstein M, Holz FG, Schmitz-Valckenberg S.

Purpose: To evaluate longitudinal variations of reticular drusen (RDR) in age-related macular degeneration using confocal scanning laser ophthalmoscopy (cSLO), near-infrared reflectance (NIR) and spectral-domain optical coherence tomography (SD-OCT) imaging.

Methods: Eighteen eyes of 12 patients with RDR (median observational time 5 months, range 3-10) were included. Changes over time in the en face cSLO NIR images, the identical SD-OCT B scan (simple approach) and the dense SD-OCT volume scans (11 µm between B scans, detailed approach) for 5 preselected RDR lesions were analysed, respectively.

Results: Nineteen of 90 (21%) lesions were no longer detectable at the follow-up examination with the simple SD-OCT approach (increase 7/decrease 48/unchanged 15/not gradable 1). By contrast, no disappearance of single lesions was noted for both cSLO (3/8/61/18) and detailed SD-OCT image analysis (67/22/1/0). Within the dense SD-OCT volume scan, a median change of individual lesion height of 10 µm/year was determined.

Conclusions: The findings indicate a recordable progression of RDR lesions in lateral and vertical dimensions. Using dense SD-OCT volume scans, individual RDR lesion progression can be quantified and may be applied in future longitudinal studies. © 2014 S. Karger AG, Basel.

PMID: 25413846 [PubMed - as supplied by publisher]

Stem Cells Transl Med. 2014 Nov 19. [Epub ahead of print]

Polarized Human Embryonic Stem Cell-Derived Retinal Pigment Epithelial Cell Monolayers Have Higher Resistance to Oxidative Stress-Induced Cell Death Than Nonpolarized Cultures.

Hsiung J, Zhu D, Hinton DR.

Abstract: Oxidative stress-mediated injury to the retinal pigment epithelium (RPE) is a major factor involved in the pathogenesis of age-related macular degeneration (AMD), the leading cause of blindness in the elderly. Human embryonic stem cell (hESC)-derived RPE cells are currently being evaluated for their potential for cell therapy in AMD patients through subretinal injection of cells in suspension and subretinal placement as a polarized monolayer. To gain an understanding of how transplanted RPE cells will respond to the highly oxidatively stressed environment of an AMD patient eye, we compared the survival of polarized and nonpolarized RPE cultures following oxidative stress treatment. Polarized, nonpolarized/confluent, nonpolarized/subconfluent hESC-RPE cells were treated with H2O2. Terminal deoxynucleotidyl transferase dUTP nick end labeling stains revealed the highest amount of cell death in subconfluent hESC-RPE cells and little cell death in polarized hESC-RPE cells with H2O2 treatment. There were higher levels of proapoptotic factors (phosphorylated p38, phosphorylated c-Jun NH2-terminal kinase, Bax, and cleaved caspase 3 fragments) in treated nonpolarized RPE-particularly subconfluent cells-relative to polarized cells. On the other hand, polarized RPE cells had constitutively higher levels of cell survival and antiapoptotic signaling factors such as p-Akt and Bcl-2, as well as antioxidants superoxide dismutase 1 and catalase relative to nonpolarized cells, that possibly contributed to polarized cells' higher tolerance to oxidative stress compared with nonpolarized RPE cells. Subconfluent cells were particularly sensitive to oxidative stress-

induced apoptosis. These results suggest that implantation of polarized hESC-RPE monolayers for treating AMD patients with geographic atrophy should have better survival than injections of hESC-RPE cells in suspension.

PMID: 25411476 [PubMed - as supplied by publisher]

Ophthalmologica. 2014 Nov 15. [Epub ahead of print]

Stereotactic Radiotherapy for Polypoidal Choroidal Vasculopathy: A Pilot Study.

Introini U, Casalino G, Triolo G, O'Shaughnessy D, Shusterman EM, Chakravarthy U, Slakter JS, Bandello F.

Purpose: To evaluate low-voltage X-ray stereotactic radiotherapy (SRT) delivered in conjunction with intravitreal ranibizumab for the treatment of active macular polypoidal choroidal vasculopathy (PCV).

Methods: At baseline, all eyes received an intravitreal injection of ranibizumab, followed by 16-Gy X-ray SRT to the macula. Further ranibizumab injections were given pro re nata. The primary outcome measure was regression of the polyps assessed by indocyanine green angiography. Secondary outcome measures were best-corrected visual acuity (BCVA) and central foveal thickness (CFT) changes on optical coherence tomography. Local or systemic adverse events were evaluated as well.

Results: We examined 12 eyes of 12 patients with PCV. At month 12, an angiographic regression of the polyps was observed in 10 of the 12 eyes. The mean BCVA improved by 7.6 letters: from 65.08 ± 11.4 to 72.7 ± 14.75 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The mean CFT decreased from 372.3 ± 79.6 to 215.9 ± 57.9 μm ($p < 0.01$). No local or systemic adverse events were reported.

Conclusions: The preliminary data support the safety of low-voltage X-ray SRT for the treatment of macular PCV and show polyp closure, reduction in CFT and improvement in the mean BCVA. Additional research is warranted to confirm the efficacy and longer-term safety of this therapy in this population.

PMID: 25402871 [PubMed - as supplied by publisher]

Biomed Sci Instrum. 2014;50:265-84.

Enduring eye care with smartphones aiding real time diagnosis.

Sudhakar MS, Bhoopathy BK.

Abstract: In todays world, eye defects are more common among people of all ages. Most serious disorders of the eye include retinal detachment, macular degeneration. Technology is ever emergent and improving the way that assists in analyzing fundal images. Smart phones deployed with android applications leads to promising means for significant enrichment in eye care aids. In this paper an, add-on for effective detection of such eye defects is presented that can be incorporated in smartphones. The developed add-on initially acquires L*a*b* triplets of the given fundus image. The resulting L*a*b* triplets is then contrast enhanced for further fundus examination as the image is captured under non-uniform illumination environment. Subsequent steps involve feature extraction and defect classification with Artificial neural network based Back Propagation Algorithm. Performance analysis of the proposed system is evaluated using fundus images attained from DRIVE, MESSIDOR and STARE database. The ROC analysis depicts a consistent performance and 90% classification accuracy for images of different database. Hence, this application improves efficacy of retinal diagnosis and aids in timely assessment of retinal disorders. This application is developed in android platform and is compatible with existing smartphones, augmenting its features. A step by step procedure for installation and operation of the add-on in smartphones is also presented in the paper.

PMID: 25405434 [PubMed - in process]

Pathogenesis

Proteomics. 2014 Nov 19. [Epub ahead of print]

The proteome of human retina.

Zhang P, Dufresne C, Turner R, Ferri S, Venkatraman V, Karani R, Lutty GA, Eyk JE, Semba RD.

Abstract: The retina is a delicate tissue that detects light, converts photochemical energy into neural signals, and transmits the signals to the visual cortex of the brain. A detailed protein inventory of the proteome of the normal human eye may provide a foundation for new investigations into both the physiology of the retina and the pathophysiology of retinal diseases. To provide an inventory, proteins were extracted from five retinas of normal eyes and fractionated using SDS-PAGE. After in-gel digestion, peptides were analyzed in duplicate using LC-MS/MS on an Orbitrap Elite mass spectrometer. A total of 3436 non-redundant proteins were identified in the human retina, including 20 unambiguous protein isoforms, of which 8 have not previously been demonstrated to exist at the protein level. The proteins identified in the retina included most of the enzymes involved in the visual cycle and retinoid metabolism. One hundred and fifty-eight proteins that have been associated with age-related macular degeneration were identified in the retina. The MS proteome database of the human retina may serve as a valuable resource for future investigations of retinal biology and disease. The mass spectrometry proteomics data have been deposited to the Proteome Xchange Consortium via the PRIDE partner repository with the dataset identifier PXD001242.

PMID: 25407473 [PubMed - as supplied by publisher]

Science. 2014 Nov 21;346(6212):1000-3.

Nucleoside reverse transcriptase inhibitors possess intrinsic anti-inflammatory activity.

Fowler BJ, Gelfand BD, Kim Y, et al

Abstract: Nucleoside reverse transcriptase inhibitors (NRTIs) are mainstay therapeutics for HIV that block retrovirus replication. Alu (an endogenous retroelement that also requires reverse transcriptase for its life cycle)-derived RNAs activate P2X7 and the NLRP3 inflammasome to cause cell death of the retinal pigment epithelium in geographic atrophy, a type of age-related macular degeneration. We found that NRTIs inhibit P2X7-mediated NLRP3 inflammasome activation independent of reverse transcriptase inhibition. Multiple approved and clinically relevant NRTIs prevented caspase-1 activation, the effector of the NLRP3 inflammasome, induced by Alu RNA. NRTIs were efficacious in mouse models of geographic atrophy, choroidal neovascularization, graft-versus-host disease, and sterile liver inflammation. Our findings suggest that NRTIs are ripe for drug repurposing in P2X7-driven diseases.

PMID: 25414314 [PubMed - in process]

Ophthalmic Res. 2014 Nov 12;52(4):224-233. [Epub ahead of print]

Expression of Endoplasmic Reticulum Stress Markers GRP78 and CHOP Induced by Oxidative Stress in Blue Light-Mediated Damage of A2E-Containing Retinal Pigment Epithelium Cells.

Feng J, Chen X, Sun X, Wang F, Sun X.

Aims: Age-related lipofuscin N-retinylidene-N-retinylethanolamine (A2E) accumulated in human retinal pigment epithelium (RPE) cells confers susceptibility to blue light-mediated damage, which represents one pathogenesis of age-related macular degeneration. This study investigated the expression of 2 best-characterized endoplasmic reticulum (ER) stress markers, glucose-related protein 78 (GRP78) and C/EBP homologous protein (CHOP), as well as their regulation by oxidative stress after blue light-mediated damage of A2E-containing RPE cells.

Methods: ARPE-19 cells were incubated with A2E (10, 25, 50 μM) for 2 h and exposed to blue light for 20

min. A2E distributions in RPE cells were assessed via laser scanning confocal microscope and liquid chromatography-mass spectrometry. Cell viability was measured by a Cell Titer 96 Aqueous One Solution cell proliferation assay. The quantity of intracellular reactive oxygen species (ROS) was detected by dihydroethidium fluorescence using flow cytometry. Expressions of GRP78 and CHOP were measured at both mRNA and protein levels. To examine the role of oxidative stress in regulating GRP78 and CHOP expression, RPE cells were pretreated with the antioxidant N-acetylcysteine (NAC) for 2 h. RNA interference of GRP78 performed by short hairpin RNA was used to evaluate the effect of GRP78 in blue light-mediated damage of RPE cells.

Results: After blue light exposure, A2E-treated RPE cells showed a gradual decrease in cell viability and a particular increase in ROS levels. Meanwhile, the expressions of GRP78 and CHOP in A2E-treated RPE cells were significantly increased at different time points after illumination. Pretreatment with NAC attenuated the expression of 2 ER stress markers, especially CHOP in A2E and blue light-treated RPE cells. Silencing of GRP78 by RNA interference upregulated CHOP and caspase-12 expression as well as aggravated the blue light-mediated damage of A2E-laden RPE cells.

Conclusion: RPE cells exhibited ROS accumulation and subsequent elevation of GRP78 and CHOP expression after A2E and blue light-induced damage. The ROS scavenger NAC diminished ER stress protein expression, suggesting a connection between ER and oxidative stress in blue light-mediated damage of A2E-containing RPE cells. Besides, GRP78 may play a protective role in it.

PMID: 25402962 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Nov 20. [Epub ahead of print]

Preparative and Biosynthetic Insights into PdA2E and IsopdA2E, Retinal-Derived Fluorophores of Retinal Pigment Epithelial Lipofuscin.

Zhao J, Yao K, Jin Q, Jiang K, Chen J, Liu Z, Li J, Wu Y.

PURPOSE: Retinal-derived fluorophores that accumulate as retinal pigment epithelial (RPE) lipofuscin are implicated in pathological mechanisms of age-related macular degeneration (AMD). One component of RPE lipofuscin has been characterized as pdA2E, a pyridinium adduct derived from all-trans-retinal and excess ethanolamine. One-step preparation and biosynthetic studies of pdA2E and its novel isomer called isopdA2E are reported.

METHODS. Biosynthetic reaction mixtures, RPE/choroids and neural retinas dissected from bovines, eyes harvested from Abca4-/-Rdh8-/- mice, irradiated samples, and enzyme-treated solutions were analyzed by high performance liquid chromatography, mass spectrometry, nuclear magnetic resonance spectroscopy, fluorescence spectrophotometry, and density functional theory (DFT).

RESULTS. Optimization of the in vitro synthesis of pdA2E resulted in a biomimetic preparation of this pigment in a yield of 15%; this protocol also allowed the identification of isopdA2E, a double-bond isomer of pdA2E at the C13C14 position in bovine RPE lipofuscin. Interconversion between these two molecules occurs when either pdA2E or isopdA2E is exposed to light. A phospholipase D-based assay demonstrated the possibility of pdA2-PE being formed in neural retina and served as a precursor of pdA2E in the biosynthetic pathway. DFT calculations revealed that the 492 nm absorbance was assigned to the long arm of pdA2E/isopdA2E and the 340/342 nm absorbance to the short arm. Fluorescence efficiency of pdA2E and isopdA2E is very similar, but is much weaker in comparison with A2E, isoA2E and iisoA2E.

CONCLUSIONS. Our results facilitate the understanding of compositions and biosynthetic pathways of adverse RPE lipofuscin.

PMID: 25414195 [PubMed - as supplied by publisher]

Genetics

Methods Mol Biol. 2015;1253:217-55.

Identification of Genome-Wide SNP-SNP and SNP-Clinical Boolean Interactions in Age-Related Macular Degeneration.

Riveros C, Vimieiro R, Holliday EG, Oldmeadow C, Wang JJ, Mitchell P, Attia J, Scott RJ, Moscato PA.

Abstract: We propose here a methodology to uncover modularities in the network of SNP-SNP interactions most associated with disease. We start by computing all possible Boolean binary SNP interactions across the whole genome. By constructing a weighted graph of the most relevant interactions and via a combinatorial optimization approach, we find the most highly interconnected SNPs. We show that the method can be easily extended to find SNP/environment interactions. Using a modestly sized GWAS dataset of age-related macular degeneration (AMD), we identify a group of only 19 SNPs, which include those in previously reported regions associated to AMD. We also uncover a larger set of loci pointing to a matrix of key processes and functions that are affected. The proposed integrative methodology extends and overlaps traditional statistical analysis in a natural way. Combinatorial optimization techniques allow us to find the kernel of the most central interactions, complementing current methods of GWAS analysis and also enhancing the search for gene-environment interaction.

PMID: 25403535 [PubMed - in process]

Diet & lifestyle

J Alzheimers Dis. 2014 Nov 18. [Epub ahead of print]

The Impact of Supplemental Macular Carotenoids in Alzheimer's Disease: A Randomized Clinical Trial.

Nolan JM, Loskutova E, Howard A, Mulcahy R, Moran R, Stack J, Bolger M, Coen RF, Dennison J, Akuffo KO, Owens N, Power R, Thurnham D, Beatty S.

Background: Patients with Alzheimer's disease (AD) exhibit significantly less macular pigment (MP) and poorer vision when compared to control subjects. Objective: To investigate supplementation with the macular carotenoids on MP, vision, and cognitive function in patients with AD versus controls.

Methods: A randomized, double-blind clinical trial with placebo and active arms. 31 AD patients and 31 age -similar control subjects were supplemented for six months with either Macushield (10 mg meso-zeaxanthin [MZ]; 10 mg lutein [L]; 2 mg zeaxanthin [Z]) or placebo (sunflower oil). MP was measured using dual-wavelength autofluorescence (Heidelberg Spectralis®). Serum L, Z, and MZ were quantified by high performance liquid chromatography. Visual function was assessed by best corrected visual acuity and contrast sensitivity (CS). Cognitive function was assessed using a battery of cognition tests, including the Cambridge Neuropsychological Test Automated Battery (CANTAB)).

Results: Subjects on the active supplement (for both AD and non-AD controls) exhibited statistically significant improvement in serum concentrations of L, Z, MZ, and MP ($p < 0.001$, for all) and also CS at 1.2 cpd ($p < 0.039$). Also, for subjects on the active supplement, paired samples t-tests exhibited four significant results (from five spatial frequencies tested) in the AD group, and two for the non-AD group, and all indicating improvements in CS. We found no significant changes in any of the cognitive function outcome variables measured ($p > 0.05$, for all).

Conclusion: Supplementation with the macular carotenoids (MZ, Z, and L) benefits patients with AD, in terms of clinically meaningful improvements in visual function and in terms of MP augmentation.

PMID: 25408222 [PubMed - as supplied by publisher]