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# MD Research News

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## Drug treatment

**Eur J Ophthalmol. 2014 Jun 28:0. doi: 10.5301/ejo.5000480. [Epub ahead of print]**

**Switching intravitreal anti-VEGF treatment in neovascular age-related macular degeneration.**

Küçükerdönmez C, Gelisken F, Yoeruek E, Bartz-Schmidt KU, Leitritz MA.

PURPOSE: To compare the outcomes after switching between bevacizumab and ranibizumab therapy due to poor treatment effect in neovascular age-related macular degeneration (AMD).

METHODS: This is a retrospective review of patients with neovascular AMD with first treatment using intravitreal bevacizumab (group 1) or ranibizumab (group 2) who switched to the other drug due to poor treatment effect. Primary outcome measures were change in mean best-corrected visual acuity (BCVA) and mean central retinal thickness (CRT) at 1 year and last visit.

RESULTS: Eighty-seven eyes met the inclusion criteria. In group 1 (43 eyes), the mean BCVA decreased from 20/94 to 20/100 at 1 year after being switched ($p = 0.573$) and to 20/150 ($p = 0.015$) at final visit (mean 29.2 months, range 12-53). In group 2 (44 eyes), mean BCVA decreased from 20/72 to 20/90 ($p = 0.401$) and 20/100 ($p = 0.081$) at 1 year after switch and at final visit (mean 20.1 months, range 10-40), respectively. The mean CRT at switch, 1 year after switch, and at final visit were 344.4 ± 140 µm (mean ± SD), 286.26 ± 155 µm ($p = 0.019$), and 290.58 ± 196 µm ($p = 0.009$) in group 1 and 329.36 ± 144 µm, 302.0 ± 179 µm ($p = 0.215$), and 309.5 ± 220 µm ($p = 0.154$) in group 2, respectively.

CONCLUSIONS: The mean BCVA decreased over time in both groups; however, nearly 30% of the eyes in each group showed vision improvement after switching. Mean CRT decreased in both groups, which was more pronounced after being switched from bevacizumab to ranibizumab. In neovascular AMD, a switch between ranibizumab and bevacizumab can be considered as a further therapy option if poor treatment effect is seen with the initial therapy.

PMID: 24980110 [PubMed - as supplied by publisher]

**PLoS One. 2014 Jun 30;9(6):e101057. doi: 10.1371/journal.pone.0101057. eCollection 2014.**

**A prospective study of treatment patterns and 1-year outcome of asian age-related macular degeneration and polypoidal choroidal vasculopathy.**

Cheung CM, Li X, Mathur R, Lee SY, Chan CM, Yeo I, Loh BK, Williams R, Wong EY, Wong D, Wong TY.

OBJECTIVE: To study the treatment patterns and visual outcome over one year in Asian patients with choroidal neovascular membrane secondary to age-related macular degeneration (AMD-CNV) and polypoidal choroidal vasculopathy (PCV).

DESIGN: Prospective cohort, non-interventional study.

METHODS: 132 treatment-naïve patients who received treatment for AMD-CNV and PCV were included. All patients underwent standardized examination procedures including retinal imaging at baseline and follow-up. AMD-CNV and PCV were defined on fundus fluorescein angiography and indocyanine green angiography at baseline. Patients were treated according to standard of care.We report the visual acuity (VA) and optical coherence tomography (OCT) measurements at baseline, month 3 and month 12 The factors influencing month 12 outcomes were analyzed.

MAIN OUTCOME MEASURE: Type of treatment, number of Anti-vascular endothelial growth factor (VEGF) treatments, visual outcome over one year.

RESULTS: Anti-VEGF monotherapy was the initial treatment in 89.1% of AMD-CNV, but only 15.1% of PCV. The mean number of anti-VEGF injections up to month 12 was 3.97 (4.51 AMD-CNV, 3.43 PCV, p= 0.021). Baseline OCT, month 3 OCT and month 3 VA were significant in determining continuation of treatment after month 3. At month12, mean VA improved from 0.82 (~20/132) at baseline to 0.68 (~20/96) at month 12 (mean gain 6.5 ETDRS letters, p=0.002). 34.2% of eyes (38/113 eyes) gained ≥15 ETDRS letters and 14.4% (16/113 eyes) lost ≥15 ETDRS letters. There were no significant differences in visual outcome between AMD-CNV and PCV (p=0.51). Factors predictive of month 12 visual outcome were baseline VA, baseline OCT central macular thickness, month 3 VA and age.

CONCLUSIONS: There is significant variation in treatment patterns in Asian eyes with exudative maculopathy. There is significant visual improvement in all treatment groups at one year. These data highlight the need for high quality clinical trial data to provide evidence-based management of Asian AMD.

PMID: 24978485 [PubMed - in process] PMCID: PMC4076260

**Retina. 2014 Jun 20. [Epub ahead of print]**

**RANIBIZUMAB FOR MACULAR TELANGIECTASIA TYPE 2 IN THE ABSENCE OF SUBRETINAL NEOVASCULARIZATION.**

Do DV, Bressler SB, Cassard SD, Gower EW, Tabandeh H, Jefferys JL, Bressler NM.

PURPOSE: To evaluate the effects of 0.3 mg or 0.5 mg of ranibizumab in eyes with macular telangiectasia type 2 without subretinal neovascularization.

METHODS: Ten eyes were randomized to either 0.3 mg or 0.5 mg ranibizumab group in 1 eye only. Study eye received ranibizumab at baseline and at Months 1 and 2. Injections at Months 3, 4, and 5 were at investigator's discretion. Participants were followed monthly through 6 months with best-corrected visual acuity, fluorescein angiography, and optical coherence tomography.

RESULTS: For study eyes at baseline, median best-corrected visual acuity letter score was 60 (20/64 Snellen equivalent) and central subfield retinal thickness was 181.5 μm. Median number of injections was six. Median change in best-corrected visual acuity at Month 3 was 4 letters (range: -5 to 9 letters) at both doses in the study eye and 3 letters (range: -10 to 5 letters) in the untreated fellow eye. At Month 3, retinal leakage decreased 0.87 disk area and 0.76 disk area for 0.3 mg and 0.5 mg ranibizumab, respectively. Median change in central subfield retinal thickness was 1 μm and -11 μm for 0.3 mg and 0.5 mg ranibizumab, respectively.

CONCLUSION: Ranibizumab (0.3 mg or 0.5 mg) decreases leakage secondary to macular telangiectasia type 2, but accompanying improvements in best-corrected visual acuity appear similar to improvements in

the untreated fellow eye where retinal thickness is relatively unchanged.

PMID: 24978428 [PubMed - as supplied by publisher]

**Retina. 2014 Jun 20. [Epub ahead of print]**

**POLYPOIDAL CHOROIDAL VASCULOPATHY IN WHITE PATIENTS.**

Davis SJ, Lauer AK, Flaxel CJ.

PURPOSE: To report on a series of white patients in the United States with polypoidal choroidal vasculopathy (PCV).

METHODS: This is a retrospective chart review of 27 patients at a single center with PCV.

RESULTS: The mean age was 74.3 with 48% being male. The most common presenting diagnosis was exudative age-related macular degeneration in 59%, and it took 17.5 months to diagnose PCV. During this time, patients received one antivascular endothelial growth factor injection every 1.3 months. The most common reason for suspecting PCV was a large retinal pigment epithelial detachment or a poor response to antivascular endothelial growth factor therapy. Once PCV was diagnosed, most underwent photodynamic therapy. In those who received photodynamic therapy, the fluid and/or age-related macular degeneration decreased in 86%. The vision improved in 41% with 36% maintaining stable vision. Patients received only one additional injection every 3.95 months after photodynamic therapy.

CONCLUSION: This is one of the larger series of PCV in an entirely white population. It emphasizes the importance of diagnosis in whites as PCV can masquerade as recalcitrant exudative age-related macular degeneration. Common findings were a temporal or peripapillary location and the presence of lipid. After photodynamic therapy, the patients still required antivascular endothelial growth factor therapy, but the injection burden was decreased by 67% and vision was found to be improved or maintained in 77% of patients.

PMID: 24978430 [PubMed - as supplied by publisher]

**Eye (Lond). 2014 Jul 4. doi: 10.1038/eye.2014.141. [Epub ahead of print]**

**25th RCOphth Congress, President's Session paper: 25 years of progress in medical retina.**

Gibson JM.

Abstract: The quarter century since the foundation of the Royal College of Ophthalmologists has coincided with immense change in the subspecialty of medical retina, which has moved from being the province of a few dedicated enthusiasts to being an integral, core part of ophthalmology in every eye department. In age-related macular degeneration, there has been a move away from targeted, destructive laser therapy, dependent on fluorescein angiography to intravitreal injection therapy of anti-growth factor agents, largely guided by optical coherence tomography. As a result of these changes, ophthalmologists have witnessed a marked improvement in visual outcomes for their patients with wet age-related macular degeneration (AMD), while at the same time developing and enacting entirely novel ways of delivering care. In the field of diabetic retinopathy, this period also saw advances in laser technology and a move away from highly destructive laser photocoagulation treatment to gentler retinal laser treatments. The introduction of intravitreal therapies, both steroids and anti-growth factor agents, has further advanced the treatment of diabetic macular oedema. This era has also seen in the United Kingdom the introduction of a coordinated national diabetic retinopathy screening programme, which offers an increasing hope that the burden of blindness from diabetic eye disease can be lessened. Exciting future advances in retinal imaging, genetics, and pharmacology will allow us to further improve outcomes for our patients and for ophthalmologists

specialising in medical retina, the future looks very exciting but increasingly busy.

PMID: 24993325 [PubMed - as supplied by publisher]

**Expert Opin Drug Deliv. 2014 Jun 30:1-14. [Epub ahead of print]**

**Advances in ocular drug delivery: emphasis on the posterior segment.**

Kang-Mieler JJ, Osswald CR, Mieler WF.

Introduction: Recent advances in pharmacological therapies to treat ocular diseases such as glaucoma, age-related macular degeneration, diabetic macular edema and retinal vascular occlusions have greatly improved the prognosis for these diseases. Due to these advances in pharmacological therapy, there is a great deal of interest in minimally invasive delivery methods, which has generated rapid developments in the field of ocular drug delivery.

Areas covered: This review will summarize currently available and recent developments for ocular drug delivery to both the anterior and posterior segments. Modes of delivery, including topical, systemic, transcleral/periocular and intravitreal, will be discussed and corresponding examples will be given. This review will highlight the advantages and disadvantages of each mode of delivery and discuss strategies to address these issues.

Expert opinion: An ideal therapy should maintain effective levels of drug for the intended duration of treatment following a single application, yet a significant number of months of therapy may be required. There are numerous approaches under investigation to improve treatment options. From the use of novel biomaterial implants and depots for sustained release, to prodrug formations, to iontophoresis to improve drug delivery, the main emphasis will continue to be placed on less invasive, longer acting, sustained release formulations in the treatment of numerous ocular disorders.

PMID: 24975820 [PubMed - as supplied by publisher]

**Nat Rev Drug Discov. 2014 Jul 1;13(7):487. doi: 10.1038/nrd4375.**

**Deal watch: Novartis eyes vision-enhancing therapy for macular degeneration.**

Cully M.

PMID: 24981352 [PubMed - in process]

## Other treatment & diagnosis

**Br J Ophthalmol. 2014 Jul 1. pii: bjophthalmol-2014-305455. doi: 10.1136/bjophthalmol-2014-305455. [Epub ahead of print]**

**Appearance of medium-large drusen and reticular pseudodrusen on adaptive optics in age-related macular degeneration.**

Querques G, Kamami-Levy C, Blanco-Garavito R, Georges A, Pedinielli A, Capuano V, Poulon F, Souied EH.

PURPOSE: To investigate the appearance of medium-large drusen and reticular pseudodrusen on adaptive optics (AO).

METHODS: In 14 consecutive patients, AO infrared (IR) images were overlaid with confocal scanning-laser

-ophthalmoscope IR reflectance images and IR-referenced spectral-domain optical coherence tomography.

RESULTS: In eight eyes of six patients, a total of 19 images of medium-large drusen were investigated by AO imaging. En face AO revealed medium-large drusen as highly hyper-reflective round/oval lesions, always centred and/or surrounded by a continuous/discontinuous hyporeflectivity. Cone photoreceptors were detected overlying drusen, appearing either as continuous 'bright' hyper-reflective dots over a 'dark' hyporeflective background, or as continuous 'dark' hyporeflective dots over a 'bright' hyper-reflective background. In eight eyes from eight patients, a total of 14 images of pseudodrusen were investigated by AO imaging. En face AO revealed reticular pseudodrusen as isoreflective lesions, always surrounded by a continuous/discontinuous hyporeflectivity. Cone photoreceptors were detected overlying pseudodrusen as 'bright' hyper-reflective dots over either a hyporeflective or isoreflective background. No 'dark' hyporeflective dots were detected in eyes with reticular pseudodrusen only. Cone photoreceptors were counted on the border of the drusen and pseudodrusen, respectively, and in a visibly healthy zone in its absolute vicinity. A similar decrease in cone appearance was observed for drusen and pseudodrusen (15.7% vs 16.2%).

CONCLUSIONS: AO allows differences in reflectivity between medium-large drusen and reticular pseudodrusen to be appreciated. The cone mosaics may be detected as continuous 'bright' hyper-reflective dots overlying/on the border of drusen and pseudodrusen deposits, and possibly as continuous 'dark' hyporeflective dots overlying drusen only.

PMID: 24985725 [PubMed - as supplied by publisher]

**Ophthalmic Res. 2014 Jun 27;52(2):53-59. [Epub ahead of print]**

**Geographic Atrophy Progression in Eyes with Age-Related Macular Degeneration: Role of Fundus Autofluorescence Patterns, Fellow Eye and Baseline Atrophy Area.**

Batıoğlu F, Gedik Oğuz Y, Demirel S, Ozmert E.

Background/Objective: To evaluate if fundus autofluorescence (FAF) patterns around geographic atrophy (GA) and the status of the fellow eye have an impact on GA progression.

Methods: We included 54 eyes of 35 patients with GA. Areas of GA were quantified by RegionFinder software.

Results: GA progression rates in eyes with a diffuse trickling pattern (median 1.42 mm2/year) were significantly higher than in normal eyes (median 0.22 mm2/year) and eyes with other diffuse FAF patterns (median 0.46 mm2/year). Eyes with a banded pattern had a significantly higher progression rate (median 0.81 mm2/year) than those without any FAF abnormalities ($p = 0.038$). The group with baseline total atrophy of the eyes <1 disk area (DA; median 0.42 mm2) had an inverse relation with GA progression compared to the groups with baseline atrophy >1 DA ($p < 0.05$).

Conclusion: Diffuse trickling and banded patterns may have an impact on GA progression and may serve as prognostic factors.

PMID: 24993093 [PubMed - as supplied by publisher]

**Am J Ophthalmol. 2014 Jun 28. pii: S0002-9394(14)00382-1. doi: 10.1016/j.ajo.2014.06.021. [Epub ahead of print]**

**Optical Coherence Tomography-Based Measurement of Drusen Load Predicts Development of Advanced Age-Related Macular Degeneration.**

Nathoo NA, Or C, Young M, Chui L, Fallah N, Kirker AW, Albiani DA, Merkur AB, Forooghian F.

PURPOSE: To determine whether baseline drusen load, as measured using spectral domain optical coherence tomography (SD-OCT), is a useful predictor of development of advanced age-related macular degeneration (AMD).

DESIGN: Retrospective cohort study METHODS, SETTING: Academic clinical practice STUDY POPULATION: All patients with non-neovascular AMD and no retinal pigment epithelial (RPE) atrophy at baseline who were seen between 2007 and 2012 in a single academic retina practice. A minimum of one year of follow-up was required.

OBSERVATION: Drusen load (area and volume) was assessed using automated SD-OCT software algorithms.

MAIN OUTCOME MEASURE: RPE atrophy area, assessed using an automated SD-OCT software algorithm, and the development of neovascular AMD.

RESULTS: 83 patients met the inclusion criteria with a mean age of 80 years and a mean follow-up time of 2.8 years. Repeated measures ANOVA showed an association between drusen area (p=0.005) and drusen volume (p=0.001) and the development of RPE atrophy. We also found an association between drusen area (p=0.001) and drusen volume (p=0.001) and the development of neovascular AMD.

CONCLUSIONS: Drusen load, as measured using SD-OCT, is associated with the development of RPE atrophy and neovascular AMD. SD-OCT assessments of drusen load are simple and practical measurements that may be useful in stratifying the risk of developing advanced AMD. These measurements have potential applications in both routine clinical care and in clinical trials.

PMID: 24983793 [PubMed - as supplied by publisher]

**Optom Vis Sci. 2014 Jul 1. [Epub ahead of print]**

**Visual-Function Tests for Self-monitoring of Age-Related Macular Degeneration.**

Liu L, Wang YZ, Bedell HE.

Abstract: Age-related macular degeneration (AMD) is one of the leading causes of severe visual impairment in the United States. Changes in lifestyle can slow the progression of AMD, and new therapies that arrest choroidal neovascularization can preserve vision in patients who progress to the neovascular form of advanced AMD. Appropriate timing is required for these interventions to be optimally effective, which, in turn, depends critically on early diagnosis. Because annual or semiannual eye examinations may not be sufficient to ensure an early diagnosis, the preferred practice for AMD management must include self-monitoring by patients for disease onset or progression. In this review, we discuss a number of visual functions that have been shown to be impaired in eyes with AMD and specify desirable characteristics of visual-function tests that can be used for self-monitoring by populations at risk for AMD.

PMID: 24987816 [PubMed - as supplied by publisher]

**Optom Vis Sci. 2014 Jul 1. [Epub ahead of print]**

**Autofluorescence Patterns as a Predictive Factor for Neovascularization.**

Batoğlu F, Demirel S, Ozmert E, Oguz YG, Ozyol P.

PURPOSE: To investigate fundus autofluorescence (FAF) patterns in patients with nonexudative age-related macular degeneration (AMD) and to test if FAF patterns affect the development of choroidal neovascularization (CNV).

METHODS: One hundred one patients with early AMD underwent a detailed ophthalmological examination. Fundus autofluorescence imaging was performed with a confocal scanning laser ophthalmoscope following a standard protocol. The classification of the International Fundus Autofluorescence Classification Group was used for the description of the FAF patterns.

RESULTS: One hundred seventy-eight eyes of 101 patients (59 women, 42 men) with a mean (±SD) age of 66.4 (±6.1) years were included. The mean (±SD) follow-up was 41.3 (±27) months. One hundred seventy-eight eyes presented various types of drusen with or without hyperpigmentation or hypopigmentation at initial examination. During follow-up, a total of 22 (12.3%) eyes developed CNV. The most frequent pattern for CNV development was the patchy pattern in 30.4%, followed by linear in 25%, and reticular pattern in 20.8% of eyes.

CONCLUSIONS: Fundus autofluorescence imaging using a confocal scanning laser ophthalmoscope is a useful technique to identify FAF characteristics in patients with nonexudative AMD. Different patterns of FAF abnormalities can be obtained in these eyes. Our results indicate that patchy, linear, and reticular patterns are the specific patterns associated with CNV development in nonexudative AMD.

PMID: 24987815 [PubMed - as supplied by publisher]

**Optom Vis Sci. 2014 Jul 1. [Epub ahead of print]**

**Multifocal Pupillography in Early Age-Related Macular Degeneration.**

Sabeti F, Maddess T, Essex RW, Saikal A, James AC, Carle CF.

PURPOSE: To investigate the potential of multifocal pupillographic objective perimetry to assess changes in retinal function with clinical severity of age-related macular degeneration (AMD).

METHODS: Pupil responses were recorded from 40 subjects with AMD and 23 normal control subjects (mean ± SD age, 71.3 ± 5.1 years). Age-related macular degeneration subjects were classified according to the Age-Related Eye Disease Study (AREDS) classification system and allocated into one of four AMD severity groups. Three multifocal pupillographic objective perimetry stimulus variants that were identical in luminance but varied in spatiotemporal sequence were used. In one of the three protocols, stimuli were presented with a pedestal flicker for 266 milliseconds at 15 Hz.

RESULTS: On average, response amplitudes demonstrated a significant change in sensitivity with progression from early-stage (0.32 ± 0.08 dB, t = 3.88) to late-stage (-1.60 ± 0.12 dB, t = -12.7) age-related macular degeneration. Response delays followed a similar trend with the longest delays in AREDS4 (57.2 ± 1.9 milliseconds, t = 29.5). Ring analysis identified the largest mean effect on responses within the central 6 degrees of fixation. The NewStimuli protocol achieved the best diagnostic accuracy across all severity groups with area under the curve values of 0.85 ± 0.066 (AREDS1), 0.908 ± 0.085 (AREDS2), 0.929 ± 0.040 (AREDS3), and 1.0 ± 0.0 (AREDS4).

CONCLUSIONS: The mean effect of AMD on contraction amplitudes and response delays reflected the severity of disease, and the NewStimuli protocol achieved good diagnostic accuracy across all AMD severity groups. Multifocal pupillographic objective perimetry may potentially be a useful method in monitoring progression of AMD and assessing change in retinal function with novel interventions in early AMD. Longitudinal studies are required to identify biomarkers that predict eyes at risk of progression.

PMID: 24987814 [PubMed - as supplied by publisher]

**Curr Eye Res. 2014 Jun 30:1-9. [Epub ahead of print]**

**The ARPE-19 Cell Line: Mortality Status and Utility in Macular Degeneration Research.**

Kozlowski MR.

Abstract Purpose: The present report examines several subcultures of a single sample of ARPE-19 cells to determine their status with respect to cell mortality. If a transformation from mortal to immortal has occurred in these cells, it may impact their characteristics and, thereby, their utility for modeling natural retinal pigment epithelial (RPE) cells.

Methods: Five separate subcultures of ARPE-19 cells were grown as recommended by the supplier. During the course of culture, they were periodically monitored for signs of mortality including erosion of telomeres, increased senescence-associated beta-galactosidase (SABG) staining, altered morphology and reduced viability with an increased population doubling level (PDL). There were also observed for signs of immortality including continuous growth to very high population doubling levels and maintenance of short telomere lengths.

Results: Each of the subcultures showed both mortal and immortal characteristics. Telomere erosion, increased SABG staining, changes in cell morphology and a modest drop in cell viability took place within a range of population doublings (59-77) in which cell senescence would be expected to occur. The cultures, however, continued to proliferate even after signs of senescence had appeared, with one subculture propagating to 257 population doublings. In addition, little further telomere erosion occurred at high PDL.

Conclusion: These results suggest that the ARPE-19 subcultures contained both mortal and immortal cells. Since no transformation event was witnessed during the study, it appears likely that both types of cells were present in the original sample. Based on the proportion of cells demonstrating senescence-related changes, the mortal cells were estimated to comprise approximately 27% of the total culture. Because of the differences that can exist between normal and immortalized cells, and given the large proportion of ARPE-19 cells that are immortalized, discretion should be exercised when using ARPE-19 cells to model native RPE cells for the study of retinal diseases such as AMD.

PMID: 24977298 [PubMed - as supplied by publisher]

**Stem Cell Rev. 2014 Jun 29. [Epub ahead of print]**

**Ethics of iPSC-Based Clinical Research for Age-Related Macular Degeneration: Patient-Centered Risk-Benefit Analysis.**

Nakano-Okuno M, Borah BR, Nakano I.

Abstract: The opportunity to undergo an induced pluripotent stem cell-based autologous transplant can strike patients as a chance for a cure from a debilitating condition with few options for respite. However, when clinical studies of this caliber present themselves, patients and researchers, each with their own set of motives, may find it difficult to take a balanced approach to evaluating them. We present a patient-centered risk-benefit analysis of the iPSC-based clinical research currently underway in Japan, including a survey of in vitro and in vivo tests that support this project, an in-depth discussion of risks, and further elucidation of considerations patients may wish to consider. The arguments presented will assist patients in undertaking a more informed decision-making process.

PMID: 24974102 [PubMed - as supplied by publisher]

**Optom Vis Sci. 2014 Jun 26. [Epub ahead of print]**

**An Evaluation of Two Candidate Functional Biomarkers for Age-Related Macular Degeneration.**

McKeague C, Binns AM, Margrain TH.

PURPOSE: To evaluate the intersession repeatability of the Colour Assessment and Diagnosis (CAD) test

and a novel 14-Hz flicker test in a population of healthy participants to provide benchmark data for their use as functional biomarkers for age-related macular degeneration (AMD).

METHODS: Visual function was assessed using both techniques in 30 healthy adults (mean [standard deviation] age 36.3 [14.1] years) on two separate days. Intersession repeatability of RG and YB CAD thresholds and 14-Hz flicker thresholds was assessed by determining their coefficient of repeatability (CoR).

RESULTS: The CoR was calculated to be 0.39 CAD units (17.0%) for RG thresholds, 0.43 CAD units (31.1%) for YB thresholds, and 0.015 (53.4%) for 14-Hz flicker contrast thresholds. On average, thresholds improved by 4.72% (RG), 6.33% (YB), and 13.3% (14-Hz flicker) between visits 1 and 2, suggesting a small but consistent learning effect. The CoR for all parameters was relatively small compared to the mean thresholds obtained (RG: mean 2.27 [4.58], CoR 0.39; YB: mean 1.37 [0.55], CoR 0.43; 14-Hz flicker: mean 0.028 [0.01], CoR 0.015).

CONCLUSIONS: This study has described the repeatability of the CAD and 14-Hz flicker tests. These data can help clinicians decide if the results from repeated measures are of clinical significance. Despite pretest training, there was some evidence of a learning effect. Therefore, clinical trials using these techniques should ensure training is sufficient to minimize these effects.

PMID: 24978867 [PubMed - as supplied by publisher]

**Br J Ophthalmol. 2014 Jul 4. pii: bjophthalmol-2014-305673. doi: 10.1136/bjophthalmol-2014-305673. [Epub ahead of print]**

**Quantitative assessment of central retinal thickness in recurrent neovascular age-related macular degeneration.**

Chee Yee C, Papakostas TD, Vavvas DG.

PMID: 24997184 [PubMed - as supplied by publisher]

## Pathogenesis

**Clin Experiment Ophthalmol. 2014 Jul 3. doi: 10.1111/ceo.12376. [Epub ahead of print]**

**HIF1A as a major VEGF regulator: Do its polymorphisms have an association with AMD?**

Okur V, Cetin O, Cetin E, Tepeli E, Bulgu Y, Yilidirim C.

BACKGROUND: To investigate the association between age-related macular degeneration (AMD) and the polymorphisms of HIF1A, a major VEGF regulator under hypoxic conditions. The associations of AMD and polymorphisms of genes CFH, SKIV2L and MYRIP were also studied.

DESIGN: Prospective study.

PARTICIPANTS: 87 AMD patients and 80 healthy subjects admitted to the Department of Ophthalmology at Pamukkale University Hospital, Denizli, Turkey, were included: 45 (52%) had wet type AMD and 42 (48%) had dry type AMD.

METHODS: Polymorphisms rs1061170 (CFH), rs429608 (SKIV2L), rs2679798 (MYRIP), and both rs11549465 and rs11549467 (HIF1A) were investigated in DNA isolated from peripheral blood samples of the cases and controls by dye-termination DNA sequencing.

MAIN OUTCOME MEASURES: Genotype distribution of rs1061170 (CFH), rs429608 (SKIV2L), rs2679798

(MYRIP), and both rs11549465 and rs11549467 (HIF1A) in AMD cases and healthy controls; association between genotypes, and AMD subtypes.

RESULTS: Given the significant difference between the mean age of case and control groups (72.13 ± 5.77 vs 62.80 ± 5.22, respectively) (p=.000), subsequent analyses were adjusted for age. We found that having at least one C allele for polymorphism rs1061170 increases AMD risk independent of age (OR= 2.42, 95% CI, 1.22-4.81). The ancestral T allele for polymorphism rs1061170 has a protective effect for AMD (OR=0.53, 95%CI, 0.34-0.83). No statistically significant difference for distributions of other SNPs emerged between patients and healthy subjects.

CONCLUSIONS: No associations appeared between HIF1A SNPs and AMD, which were studied here for the first time; however polymorphism rs1061170 of the CFH gene is associated with AMD in our population.

PMID: 24995509 [PubMed - as supplied by publisher]

**Invest Ophthalmol Vis Sci. 2014 Jul 1. pii: IOVS-14-14311. doi: 10.1167/iovs.14-14311. [Epub ahead of print]**

**Detection of Esterified Cholesterol in Murine Bruch's Membrane Wholemounts with a Perfringolysin O-based Cholesterol Marker.**

Rudolf M, Mohi A, Dettbarn MC, Miura Y, Aherrahrou Z, Ranjbar M, Mutus B, Knobloch JK.

Purpose: To investigate the effects of Bruch's membrane (BrM) neutral lipid deposition in mouse models and its significance to aging and age-related macular degeneration it is essential to reliable detect small quantities of neutral lipids including esterified cholesterol (EC). In chorioretinal sections and BrM wholemounts we tested a novel fluorescent cholesterol marker based on the bacterial toxin Perfringolysin O (PFO) and compared results to those obtained with the classic cholesterol dye filipin.

Methods: An engineered plasmid containing the specific cholesterol binding domain (D4) of PFO fused to green fluorescent protein (GFP) was expressed in cultured E. coli, isolated, purified, and concentrated. A total of 150 BrM-choroid wholemounts and chorioretinal sections of 11 to 13-month-old ApoEnull mice were prepared and stained with PFO/D4-GFP or filipin for EC. Samples were examined by epifluorescence microscopy.

Results: The fluorescence intensity of PFO/D4-GFP was strong, stable, and if small quantities of EC were present superior to filipin. In all specimens we could sharply locate the PFO/D4-GFP signal to BrM. A semi-quantitative evaluation of BrM lipid deposition is possible by measuring PFO/D4-GFP fluorescence intensity.

Conclusions: PFO/D4-GFP allowed a robust and direct detection of EC in aged murine BrM. In wholemount samples its strong and stable fluorescence facilitated a semi-quantitative evaluation of BrM's EC content over a large area. The patterns of EC deposition in murine BrM wholemounts are comparable to findings in human BrM wholemounts. PFO/D4-GFP could be an important tool for investigating the effects of BrM lipid deposition in mouse models.

PMID: 24985479 [PubMed - as supplied by publisher]

**Invest Ophthalmol Vis Sci. 2014 Jul 1. pii: IOVS-14-14633. doi: 10.1167/iovs.14-14633. [Epub ahead of print]**

**Mitochondrial Oxidative Stress in the Retinal Pigment Epithelium Leads to Localized Retinal Degeneration.**

Mao H, Seo S, Biswal MR, Li H, Conners M, Nandyala A, Jones K, Le YZ, Lewin AS.

Purpose: Oxidative stress in the retinal pigment epithelium (RPE) is a contributing factor to age related macular degeneration (AMD). To develop a mouse model of mitochondrial oxidative stress, we used a conditional knockout of the Sod2 gene (encoding manganese superoxide dismutase) in the RPE.

Methods: Mice, in which exon 3 of Sod2 was flanked by loxP sites, were transgenic for PVMD2-rtTA and tetO-PhCMV cre, so that cre recombinase was expressed only in the RPE after doxycycline (dox) treatment. Controls included mice not treated with dox and dox-treated Sod2flox/flox mice lacking cre. Mice were followed over a period of nine months by spectral domain optical coherence tomography (SD-OCT), digital fundus imaging and electoretinography (ERG). Following sacrifice, retinas were examined by microscopy or by immunohistochemistry. Contour length of rod outer segments and thickness of the RPE layer were measured by unbiased stereology.

Results: Following dox-induction of cre, Sod2flox/flox cre mice demonstrated increased oxidative stress autofluorescent material in the RPE. They showed a decline in the ERG response and thinning of the ONL that were statistically significant by siax months. At this time, the choroid appeared distended. Fundus micrographs displayed pigmentary and vascular abnormalities. By nine months following deletion of Sod2 mice, the RPE was thicker the rod outer segments were significantly longer over most of the retina, though localized atrophy of photoreceptors was apparent in some eyes.

Conclusions: Tissue-specific reduction in MnSOD induced oxidative stress leading to RPE dysfunction and death of photoreceptor cells and injury to Bruch's membrane and the choroid.

PMID: 24985474 [PubMed - as supplied by publisher]

**Optom Vis Sci. 2014 Jun 26. [Epub ahead of print]**

**Studying Age-Related Macular Degeneration Using Animal Models.**

Fletcher EL, Jobling AI, Greferath U, Mills SA, Waugh M, Ho T, de Iongh RU, Phipps JA, Vessey KA.

Abstract: Over the recent years, there have been tremendous advances in our understanding of the genetic and environmental factors associated with the development of age-related macular degeneration (AMD). Examination of retinal changes in various animals has aided our understanding of the pathogenesis of the disease. Notably, mouse strains, carrying genetic anomalies similar to those affecting humans, have provided a foundation for understanding how various genetic risk factors affect retinal integrity. However, to date, no single mouse strain that develops all the features of AMD in a progressive age-related manner has been identified. In addition, a mutation present in some background strains has clouded the interpretation of retinal phenotypes in many mouse strains. The aim of this perspective was to describe how animals can be used to understand the significance of each sign of AMD, as well as key genetic risk factors.

PMID: 24978866 [PubMed - as supplied by publisher]

**Ocul Immunol Inflamm. 2014 Jul 2:1-4. [Epub ahead of print]**

**Assessment of Neutrophil/Lymphocyte Ratio in Patients with Age-related Macular Degeneration.**

Ilhan N, Daglioglu MC, Ilhan O, Coskun M, Tuzcu EA, Kahraman H, Keskin U.

Abstract Purpose: To investigate the neutrophil/lymphocyte ratio (NLR) as an indicator of inflammation in patients with age-related macular degeneration (AMD).

Methods: Patients were evaluated by a review of records. The study included 81 patients with dry AMD (group 1), 84 patients with wet AMD (group 2), and 80 healthy age- and sex-matched controls (group 3). The NLR of the patients was obtained from the hospital laboratory archive and was measured by dividing the neutrophil count by the lymphocyte count.

Results: A significant difference was found in NLR values between groups 1 and 2 ($p = 0.017$), groups 2 and 3 ($p < 0.001$), and groups 1 and 3 ($p < 0.001$). In correlation analyses, NLR was correlated positively with age ($r = 0.22$, $p < 0.001$) and disease severity ($r = 0.40$, $p < 0.001$).

Conclusions: Patients with AMD have higher NLR compared with controls, and NLR correlates with disease severity. NLR may be used as a biomarker of inflammation in AMD.

PMID: 24987927 [PubMed - as supplied by publisher]

**J Ophthalmic Vis Res. 2014 Jan;9(1):44-9.**

**Safety of Intravitreal Zoledronic Acid, an Anti-angiogenic Bisphosphonate, in a Rat Model.**

Nourinia R, Ahmadieh H, Rezaei-Kanavi M, Shoeibi N, Kamrava K, Karimi S.

PURPOSE: To determine the safety of intravitreal zoledronic acid (ZA) in the rat eye.

METHODS: Twenty eyes of 20 pigmented rats were randomized into five groups to receive an intravitreal injection of 8, 4, 2 and 1 micrograms (mcg) of ZA, or balanced salt solution (BSS). One week and one month after the injections, all eyes were evaluated for intraocular inflammation. Electroretinography (ERG) was performed before, and one week and one month after the injections. All eyes were enucleated one month after the injection for histologic examination.

RESULTS: No significant inflammatory response was observed in any eye. No significant decrease in ERG amplitude (a & b waves) was observed one week and one month after intravitreal ZA injection, as compared to baseline, BSS-treated eyes or non-injected fellow eyes. Histologic examination of the retinal pigment epithelium and neurosensory retina were unremarkable in all groups. Additionally, no significant increase in immune reactivity for glial fibrillary acidic protein was noted in any eye.

CONCLUSION: Based on clinical, histopathologic and ERG findings in this experimental study, up to 8 mcg of intravitreal zoledronic acid seems to be safe in the rat eye.

PMID: 24982731 [PubMed] PMCID: PMC4074473

**Optom Vis Sci. 2014 Jun 26. [Epub ahead of print]**

**Reorganization of Visual Processing in Macular Degeneration Depends on Foveal Loss.**

Dilks DD, Julian JB, Peli E, Kanwisher N.

PURPOSE: When individuals with central vision loss due to macular degeneration (MD) view stimuli in the periphery, most of them activate the region of retinotopic cortex normally activated only by foveal stimuli-a process often referred to as reorganization. Why do some show this reorganization of visual processing whereas others do not? We reported previously that six individuals with complete bilateral loss of central vision showed such reorganization, whereas two with bilateral central vision loss but with foveal sparing did not, and we hypothesized that the effect occurs only after complete bilateral loss of foveal vision. Here, we conduct a stronger test of the dependence of reorganization of visual processing in MD on complete loss of foveal function, by bringing back one (called MD6) of the two participants who previously did not show reorganization and who showed foveal sparing. MD6 has now lost all foveal function, and we predicted that if large-scale reorganization of visual processing in MD individuals depends on complete loss of foveal input, then we will now see such reorganization in this individual.

METHODS: MD6 and two normally sighted control subjects were scanned. Stimuli were gray-scale photographs of objects presented at either the fovea or a peripheral retinal location (i.e., the MD participant's preferred retinal locus or the control participants' matched peripheral location).

RESULTS: In MD6, visual stimulation at the preferred retinal locus significantly activated not only the expected "peripheral" retinotopic cortex but also the deprived "foveal" cortex. Crucially, MD6 exhibited no such large-scale reorganization 5 years earlier when she had some foveal sparing. By contrast, in the control participants, stimulation at the matched peripheral location produced significant activation in peripheral retinotopic cortex only.

CONCLUSIONS: We conclude that complete loss of foveal function may be a necessary condition for large-scale reorganization of visual processing in individuals with MD.

PMID: 24978868 [PubMed - as supplied by publisher]

**Proc Natl Acad Sci U S A. 2014 Jul 1;111(26):9603-8. doi: 10.1073/pnas.1401191111. Epub 2014 Jun 16.**

**Cytochrome P450-generated metabolites derived from ω-3 fatty acids attenuate neovascularization.**

Yanai R, Mulki L, Hasegawa E, Takeuchi K, Sweigard H, Suzuki J, Gaissert P, Vavvas DG, Sonoda KH, Rothe M, Schunck WH, Miller JW, Connor KM.

Abstract: Ocular neovascularization, including age-related macular degeneration (AMD), is a primary cause of blindness in individuals of industrialized countries. With a projected increase in the prevalence of these blinding neovascular diseases, there is an urgent need for new pharmacological interventions for their treatment or prevention. Increasing evidence has implicated eicosanoid-like metabolites of long-chain polyunsaturated fatty acids (LCPUFAs) in the regulation of neovascular disease. In particular, metabolites generated by the cytochrome P450 (CYP)-epoxygenase pathway have been shown to be potent modulators of angiogenesis, making this pathway a reasonable previously unidentified target for intervention in neovascular ocular disease. Here we show that dietary supplementation with ω-3 LCPUFAs promotes regression of choroidal neovessels in a well-characterized mouse model of neovascular AMD. Leukocyte recruitment and adhesion molecule expression in choroidal neovascular lesions were down-regulated in mice fed ω-3 LCPUFAs. The serum of these mice showed increased levels of anti-inflammatory eicosanoids derived from eicosapentaenoic acid and docosahexaenoic acid. 17,18-epoxyeicosatetraenoic acid and 19,20-epoxydocosapentaenoic acid, the major CYP-generated metabolites of these primary ω-3 LCPUFAs, were identified as key lipid mediators of disease resolution. We conclude that CYP-derived bioactive lipid metabolites from ω-3 LCPUFAs are potent inhibitors of intraocular neovascular disease and show promising therapeutic potential for resolution of neovascular AMD.

PMID: 24979774 [PubMed - in process]

**J Clin Exp Ophthalmol. 2013 Feb 26;Suppl 2:0071-76.**

**Immuno-modulatory Effect of IFN-gamma in AMD and its Role as a Possible Target for Therapy.**

Jiang K, Cao S, Cui JZ, Matsubara JA.

Abstract: Age-related macular degeneration (AMD) is a neurodegenerative disease characterized by retinal cell atrophy, and/or choroidal neovascularization in the macula and constitutes the most common cause of blindness among the elderly in industrialized countries. The management of AMD is constrained by our insufficient knowledge of its underlying mechanisms. Recent studies point towards an emerging involvement of interferon-gamma (IFN-γ), a soluble cytokine associated with innate and adaptive immunity. IFN-γ promotes proinflammatory responses by activating proinflammatory cytokines and chemokines, thereby recruiting immune cells such as macrophages and T cells. On the other hand, IFN-γ modulates inflammatory response by upregulating anti-inflammatory factors or inhibiting development of immune cells related to autoimmune response. The complex role of IFN-γ in AMD pathogenesis is intriguing and worth further investigation in terms of therapeutic development.

PMID: 24977104 [PubMed] PMCID: PMC4071053

**J Ophthalmic Vis Res. 2014 Jan;9(1):1-2.**

**Macrophages and macular degeneration.**

Jager MJ.

PMID: 24982724 [PubMed] PMCID: PMC4074466

## Epidemiology

**PLoS One. 2014 Jun 30;9(6):e101072. doi: 10.1371/journal.pone.0101072. eCollection 2014.**

**Estimated cases of blindness and visual impairment from neovascular age-related macular degeneration avoided in Australia by ranibizumab treatment.**

Mitchell P, Bressler N, Doan QV, Dolan C, Ferreira A, Osborne A, Rochtchina E, Danese M, Colman S, Wong TY.

Abstract: Intravitreal injections of anti-vascular endothelial growth factor agents, such as ranibizumab, have significantly improved the management of neovascular age-related macular degeneration. This study used patient-level simulation modelling to estimate the number of individuals in Australia who would have been likely to avoid legal blindness or visual impairment due to neovascular age-related macular degeneration over a 2-year period as a result of intravitreal ranibizumab injections. The modelling approach used existing data for the incidence of neovascular age-related macular degeneration in Australia and outcomes from ranibizumab trials. Blindness and visual impairment were defined as visual acuity in the better-seeing eye of worse than 6/60 or 6/12, respectively. In 2010, 14 634 individuals in Australia were estimated to develop neovascular age-related macular degeneration who would be eligible for ranibizumab therapy. Without treatment, 2246 individuals would become legally blind over 2 years. Monthly 0.5 mg intravitreal ranibizumab would reduce incident blindness by 72% (95% simulation interval, 70-74%). Ranibizumab given as needed would reduce incident blindness by 68% (64-71%). Without treatment, 4846 individuals would become visually impaired over 2 years; this proportion would be reduced by 37% (34-39%) with monthly intravitreal ranibizumab, and by 28% (23-33%) with ranibizumab given as needed. These data suggest that intravitreal injections of ranibizumab, given either monthly or as needed, can substantially lower the number of cases of blindness and visual impairment over 2 years after the diagnosis of neovascular age-related macular degeneration.

PMID: 24979237 [PubMed - in process] PMCID: PMC4076243

**Optom Vis Sci. 2014 Jun 26. [Epub ahead of print]**

**Early Signs of Exudative Age-Related Macular Degeneration in Asians.**

Sasaki M, Kawasaki R, Uchida A, Koto T, Shinoda H, Tsubota K, Wong TY, Ozawa Y.

PURPOSE: To investigate the relationship between the early signs of age-related macular degeneration (AMD) and the risk of developing exudative AMD (typical AMD or polypoidal choroidal vasculopathy [PCV]) in the fellow eye of Japanese patients with unilateral exudative AMD, focusing particularly on eyes with only pigmentary abnormality.

METHODS: This study is a retrospective observational consecutive case series. We retrospectively reviewed the medical charts of patients who revisited the AMD clinic from 2010 to 2011 and confirmed 129

cases with unilateral exudative AMD at their first visit (baseline). The non-affected eyes at baseline (the second eye) were categorized by the presence of early signs of AMD. The incidence of exudative AMD (typical AMD or PCV) in the fellow eye was confirmed by fluorescein and indocyanine green angiography.

RESULTS: Of the 129 patients, 14 (10.9%) developed exudative AMD in the fellow eye (median follow-up, 3.2 years; n = 7 typical AMD and n = 7 PCV). Eyes with both pigmentary abnormalities and large drusen were more likely to develop typical AMD (age- and sex-adjusted odds ratio = 9.46, 95% confidence interval = 1.05 to 85.0), whereas pigmentary abnormalities without large drusen were associated with PCV (age- and sex-adjusted odds ratio = 15.9, 95% confidence interval = 1.8 to 140.5).

CONCLUSIONS: There was a difference in the association between early signs of AMD and incident development of either typical AMD or PCV. Further research is warranted to determine whether pigmentary abnormalities alone may be an important risk factor for PCV in Asians.

PMID: 24978864 [PubMed - as supplied by publisher]

**Ophthalmic Epidemiol. 2014 Jul 1:1-7. [Epub ahead of print]**

**A Follow-Up Survey on the Knowledge of Age-Related Macular Degeneration and its Risk Factors among Singapore Residents after 5 Years of Nation-Wide Awareness Campaigns.**

Sanjay S, Chin YC, Teo HT, Ong SX, Toh SH, Khong MH, Yeo AC, Au Eong KG.

Abstract Purpose: To re-evaluate the awareness of age-related macular degeneration (AMD) and knowledge of its risk factors among Singapore residents after 5 years of awareness campaigns.

Methods: Cross-sectional, questionnaire-based telephone survey (modified from the AMD Alliance International Global Report), conducted in Singapore in 2011. Participants were randomly selected using the Global Yellow Pages Singapore residential listings 2009/2010. Awareness of AMD and its risk factors was assessed among participants.

Results: Of 1773 Singapore residents contacted over the telephone, 559 participated (31.5% response rate). The mean age of participants was 43.1 years (range 21-85 years). A total of 157 participants (28.1%) were familiar with AMD. Among these, the number who correctly identified the risk factors were: smoking, n = 132 (84.1%); ageing, n = 123 (78.3%); lack of vitamins/nutrients, n = 121 (77.1%); genetics, n = 101 (64.3%); unprotected light exposure, n = 100 (63.7%) and; sex, n = 62 (39.5%). Participants aged >50 years (prevalence rate ratio, PRR 2.23, confidence interval, CI, 1.31-3.81) or who had undergone an eye test within the previous year (PRR 2.61, 95% CI 1.79-3.82) were more familiar with AMD, while females (PRR 0.68, 95% CI 0.47-0.98) were less familiar.

Conclusion: Self-reported awareness of AMD among Singapore residents increased four-fold from 7.3% in 2006 to 28.1% in 2011 following 5 years of awareness campaigns. Participants who were >50 years or had undergone an eye test within the previous year were more aware of AMD while female participants were less aware of AMD.

PMID: 24983763 [PubMed - as supplied by publisher]

**Retina. 2014 Jun 20. [Epub ahead of print]**

**ASSOCIATIONS BETWEEN CARDIOVASCULAR RISK FACTORS AND EARLY AGE-RELATED MACULAR DEGENERATION IN A RURAL CHINESE ADULT POPULATION.**

Yang K, Wang FH, Liang YB, Wong TY, Wang JJ, Zhan SY, Wang NL.

BACKGROUND: There have been a limited number of population-based studies investigating the associations between cardiovascular disease risk factors and early age-related macular degeneration (AMD).

METHODS: A total of 7,557 eligible people aged 30 or older were recruited from 2006 to 2007. Cardiovascular risk factors and serum lipids including total cholesterol, total triglycerides, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and fasting plasma glucose, and urines were assessed. Digital photographs of the optic disk and macula fields (Early Treatment of Diabetic Retinopathy Study) were taken and graded after the modified Wisconsin Age-related Maculopathy Grading System. Logistic regression models were constructed to assess odds ratios and 95% confidence intervals. Cases of late AMD were excluded.

RESULTS: Of 6,577 subjects included in the analysis, there were 200 (3.04%) cases with early AMD. Multivariate analysis showed that higher age, untreated hypertension, coronary heart disease, and smoking were associated with an increased risk of early AMD. After adjusting for other variables in the final model, no variable was significantly associated with hyperpigmentation while smoking was significantly associated with an increased risk of hypopigmentation; higher age and any cardiovascular disease were associated with an increased risk of large drusen, and higher age, smoking, untreated hypertension, and coronary heart disease were associated with an increased risk of soft drusen.

CONCLUSION: Our findings support the associations between smoking, coronary heart disease, and early AMD.

PMID: 24978429 [PubMed - as supplied by publisher]

**PLoS One. 2014 Jul 1;9(7):e102216. doi: 10.1371/journal.pone.0102216. eCollection 2014.**

**Correction: age-related macular degeneration and the incidence of cardiovascular disease: a systematic review and meta-analysis.**

PLOS ONE Staff.

Abstract

[This corrects the article DOI: 10.1371/journal.pone.0089600.].

PMID: 24983447 [PubMed - in process] PMCID: PMC4077830

## Diet & lifestyle

**Ophthalmology. 2014 Jun 26. pii: S0161-6420(14)00428-X. doi: 10.1016/j.ophtha.2014.05.008. [Epub ahead of print]**

**No Clinically Significant Association between CFH and ARMS2 Genotypes and Response to Nutritional Supplements: AREDS Report Number 38.**

Chew EY, Klein ML, Clemons TE, Agrón E, Ratnapriya R, Edwards AO, Fritsche LG, Swaroop A, Abecasis GR; Age-Related Eye Disease Study Research Group.

OBJECTIVE: To determine whether genotypes at 2 major loci associated with late age-related macular degeneration (AMD), complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2), influence the relative benefits of Age-Related Eye Disease Study (AREDS) supplements.

DESIGN: Unplanned retrospective evaluation of a prospective, randomized, placebo-controlled clinical trial of vitamins and minerals for the treatment of AMD.

SUBJECTS: AREDS participants (mean age, 69 years) who were at risk of developing late AMD and who were randomized to the 4 arms of AREDS supplement treatment.

METHODS: Analyses were performed using the Cox proportional hazards model to predict progression to late AMD (neovascular or central geographic atrophy). Statistical models, adjusted for age, gender, smoking status, and baseline AMD severity, were used to examine the influence of genotypes on the response to therapy with 4 randomly assigned arms of AREDS supplement components: placebo, antioxidants (vitamin C, vitamin E, β-carotene), zinc or a combination.

MAIN OUTCOME MEASURES: The influence of the genotype on the relative treatment response to the randomized components of the AREDS supplement, measured as progression to late AMD.

RESULTS: Of the 1237 genotyped AREDS participants of white ethnicity, late AMD developed in 385 (31.1%) during the mean follow-up of 6.6 years. As previously demonstrated, CFH genotype (P = 0.005), ARMS2 (P< 0.0001), and supplement were associated individually with progression to late AMD. An interaction analysis found no evidence that the relative benefits of AREDS supplementation varied by genotype. Analysis of (1) CFH rs1061170 and rs1410996 combined with ARMS2 rs10490924 with the 4 randomly assigned arms of AREDS supplement and (2) analysis of the combination of CFH rs412852 and rs3766405 with ARMS2 c.372_815del443ins54 with the AREDS components resulted in no interaction (P = 0.06 and P = 0.45, respectively, before multiplicity adjustment).

CONCLUSIONS: The AREDS supplements reduced the rate of AMD progression across all genotype groups. Furthermore, the genotypes at the CFH and ARMS2 loci did not statistically significantly alter the benefits of AREDS supplements. Genetic testing remains a valuable research tool, but these analyses suggest it provides no benefits in managing nutritional supplementation for patients at risk of late AMD.

PMID: 24974817 [PubMed - as supplied by publisher]

**Acta Clin Croat. 2014 Mar;53(1):79-87.**

**Metabolic risk factors, coping with stress, and psychological well-being in patients with age-related macular degeneration.**

Cavar I, Lovrić S, Vukojević M, Sesar I, Petric-Vicković I, Sesar A.

Abstract: The aim of this study was to determine the relationship between the risk factors (age, obesity, hypertension, hyperlipidemia, smoking, consumption of alchohol and drugs, positive family history, and exposure to sunlight), coping with stress, psychological well-being and age-related macular degeneration (ARMD). Forty patients with ARMD (case group) and 63 presbyopes (control group) participated in the study. Patient data were collected through general information questionnaire including patient habits, the COPE questionnaire that showed the way the patients handling stress, and the GHQ that analyzed the psychological aspects of their quality of life. These questionnaires were administered to the patients during ophthalmologic examination. The study involved 46 (44.66%) men and 57 (55.33%) women. Statistical analysis showed that the major risks for the development of ARMD were elevated cholesterol, triglycerides and LDL cholesterol in plasma. A significantly higher number ofARMD patients had a positive family history when compared with presbyopes. This study showed presbyopes to cope with emotional problems significantly better and to have a lower level of social dysfunction when compared with ARMD patients. However, it is necessary to conduct further studies in a large number of patients to determine more accurately the pathophysiological mechanisms of metabolic factors as well as the impact of the disease on the quality of life in patients with ARMD.

PMID: 24974669 [PubMed - in process]

**Optom Vis Sci. 2014 Jun 26. [Epub ahead of print]**

**An Augmented-Reality Edge Enhancement Application for Google Glass.**

Hwang AD, Peli E.

PURPOSE: Google Glass provides a platform that can be easily extended to include a vision enhancement tool. We have implemented an augmented vision system on Glass, which overlays enhanced edge information over the wearer's real-world view, to provide contrast-improved central vision to the Glass wearers. The enhanced central vision can be naturally integrated with scanning.

METHODS: Google Glass' camera lens distortions were corrected by using an image warping. Because the camera and virtual display are horizontally separated by 16 mm, and the camera aiming and virtual display projection angle are off by 10 degrees, the warped camera image had to go through a series of three-dimensional transformations to minimize parallax errors before the final projection to the Glass' see-through virtual display. All image processes were implemented to achieve near real-time performance. The impacts of the contrast enhancements were measured for three normal-vision subjects, with and without a diffuser film to simulate vision loss.

RESULTS: For all three subjects, significantly improved contrast sensitivity was achieved when the subjects used the edge enhancements with a diffuser film. The performance boost is limited by the Glass camera's performance. The authors assume that this accounts for why performance improvements were observed only with the diffuser filter condition (simulating low vision).

CONCLUSIONS: Improvements were measured with simulated visual impairments. With the benefit of see-through augmented reality edge enhancement, natural visual scanning process is possible and suggests that the device may provide better visual function in a cosmetically and ergonomically attractive format for patients with macular degeneration.

PMID: 24978871 [PubMed - as supplied by publisher]

**Optom Vis Sci. 2014 Jun 26. [Epub ahead of print]**

**Smoking Deception and Age-Related Macular Degeneration.**

Swanson MW.

PURPOSE: Smoking has been identified as a major modifiable risk factor for age-related macular degeneration (AMD). Smoking deception or failing to self-report as a smoker is a recognized concern among studies of smoking-related disease. To date, no studies have evaluated the rates of smoking deception in macular degeneration.

METHODS: Data from the 2005 to 2008 National Health and Nutrition Examination Survey were used to produce estimates of smoking deception among three ethnic groups within the US population. Comparisons of self-reported rates of cigarette use, any nicotine product use, and serum cotinine levels were used to produce estimates of potential smoking deception among adults older than 40 years with any-level macular degeneration and those at risk of late-stage disease.

RESULTS: Any-level AMD was found to be present in 6.7% (95% confidence interval [CI] = 5.6% to 7.8%) of this cohort. Excluding those with late AMD, 9.7% (95% CI = 8.3% to 11.0%) were at risk of developing late-stage disease. Among individuals with any level of macular degeneration, 5.4% (95% CI = 2.1% to 8.6%) were potential smoking deceivers. A similar rate was seen among those at risk of late-stage disease at 5.0% (95% CI = 2.3% to 7.6%).

CONCLUSIONS: The rate of possible smoking deception seems higher for macular degeneration and those at risk of late-stage AMD than is generally reported in the US population. While the deception rate is

low at the individual level, as many as 450,000 adults in the US population at risk of late-stage AMD may misclassify their smoking status.

PMID: 24978870 [PubMed - as supplied by publisher]

**Optom Vis Sci. 2014 Jun 26. [Epub ahead of print]**

**Divergence in the Lived Experience of People with Macular Degeneration.**

McCloud C, Khadka J, Gilhotra JS, Pesudovs K.

PURPOSE: The aim of this study was to understand people's experience with age-related macular degeneration (AMD) in light of new treatment successes.

METHODS: An interpretive qualitative methodology was used to facilitate understanding of the experience of people with AMD. Rich in-depth data were collected using focus groups and individual interviews. Thematic analysis of the data occurred through the processes of line-by-line coding, aggregation, and theme development using the NVivo 10 software.

RESULTS: A total of 4 focus groups and 16 individual interviews were conducted with 34 people (median age = 81 years; range = 56 to 102 years; 19 females) with AMD. Four major themes arose from the narratives of the participants: cautious optimism, enduring, adaptation, and profound loss. Cautious optimism resonated for participants who had received successful treatment and stabilization of AMD. Enduring emerged as participants with exudative AMD described an ongoing need for invasive and frequent treatments (anti-vascular endothelial growth factor injections) that maintained their vision. Adaptation was evident in the narratives of all participants and was directly related to the physical and psychological limitations that were a consequence of visual disability. Profound loss encompassed both physical and emotional aspects of deteriorating vision and was most evident in patients for whom treatment had failed or had not been considered appropriate for their disease.

CONCLUSIONS: The findings of this study shed new light on the influence of underlying pathology, disease trajectory, and success of new treatments on quality of life of people living with AMD. Optimism toward maintaining vision in the presence of exudative AMD was described by participants, moderated by ongoing caution and a need for endurance of frequent and often problematic intravitreal treatments. These findings add a deeper understanding of this complex and life-changing experience.

PMID: 24978869 [PubMed - as supplied by publisher]

**J Nutr. 2014 Jul 2. pii: jn.114.195503. [Epub ahead of print]**

**Consuming a Buttermilk Drink Containing Lutein-Enriched Egg Yolk Daily for 1 Year Increased Plasma Lutein but Did Not Affect Serum Lipid or Lipoprotein Concentrations in Adults with Early Signs of Age-Related Macular Degeneration.**

van der Made SM, Kelly ER, Berendschot TT, Kijlstra A, Lütjohann D, Plat J.

Abstract: Dietary lutein intake is postulated to interfere with the development of age-related macular degeneration (AMD). Because egg yolk-derived lutein has a high bioavailability, long-term consumption of lutein-enriched eggs might be effective in preventing AMD development, but alternatively might increase cardiovascular disease risk. Here, we report the effect of 1-y daily consumption of a buttermilk drink containing 1.5 lutein-rich egg yolks on serum lipid, lipoprotein, and plasma lutein concentrations. Additionally, subgroups that could potentially benefit most from the intervention were identified. Men and women who had early signs of AMD in at least 1 eye, but were otherwise healthy, participated in a 1-y randomized, placebo-controlled parallel intervention trial. At the start of the study, 101 participants were

included: 52 in the experimental (Egg) group and 49 in the control (Con) group. Final analyses were performed with 45 participants in the Egg group and 43 participants in the Con group. As expected, the increase in plasma lutein concentrations in the Egg group was 83% higher than that in the Con group ($P < 0.001$). Changes in serum total cholesterol and HDL and LDL cholesterol, as well as the ratio of total cholesterol to HDL cholesterol, were not different between the 2 groups. Interestingly, participants classified as cholesterol absorbers had higher serum HDL cholesterol concentrations than participants classified as cholesterol synthesizers or participants with average campesterol-to-lathosterol ratios ($P < 0.05$) at baseline. In addition, cholesterol absorbers had a 229% higher increase in plasma lutein concentrations than participants who were classified as having an average campesterol-to-lathosterol ratio ($P < 0.05$) upon consumption of the lutein-enriched egg yolk drink. Moreover, the change in serum HDL cholesterol upon consumption was significantly different between these 3 groups ($P < 0.05$). We suggest that cholesterol absorbers particularly might benefit from the lutein-enriched buttermilk drink. This study was registered at clinicaltrials.gov as NCT00902408.

PMID: 24991045 [PubMed - as supplied by publisher]

**Optom Vis Sci. 2014 Jun 26. [Epub ahead of print]**

**Space Representation in Age-Related Macular Degeneration.**

Tran TH, Despretz P, Boucart M.

PURPOSE: To investigate the effect of age-related macular degeneration (AMD) on memory for spatial representations in realistic environments.

METHODS: Participants were 19 patients with AMD and 13 age-matched observers. In a short-term spatial memory task, observers were first presented with one view of a scene (the prime view), and their task was to change the viewpoint forward or backward to match the prime view. Memory performance was measured as the number of snapshots between the selected view and the prime view.

RESULTS: When selecting a match to the prime view, both people with AMD and those in the control group showed systematic biases toward the middle view of the range of snapshots. People with AMD exhibited a stronger middle bias after presentation of close and far prime views while navigating accurately after a middle prime view. No relation was found between visual acuity, visual field defect, or lesion size and the memory performance.

CONCLUSIONS: Memory tasks using indoor scenes can be accomplished when central vision is impoverished, as with AMD. Stronger center bias for a scene location suggests that people with AMD rely more on their memory of a canonical view.

PMID: 24978865 [PubMed - as supplied by publisher]

**Optom Vis Sci. 2014 Jul 1. [Epub ahead of print]**

**Effect of Ambient Light and Macular Degeneration on Precision Walking.**

Alexander MS, Lajoie K, Neima DR, Strath RA, Robinovitch SN, Marigold DS.

PURPOSE: To determine how age-related macular degeneration (AMD) and changes in ambient light affect the control of foot placement while walking.

METHODS: Ten older adults with AMD and 11 normal-sighted controls performed a precision walking task under normal (~600 lx), dim (~0.7 lx), and after a sudden reduction (~600 to 0.7 lx) of light. The precision walking task involved subjects walking and stepping to the center of a series of irregularly spaced, low-contrast targets. Habitual visual acuity and contrast sensitivity and visual field function were also assessed.

RESULTS: There were no differences between groups when performing the walking task in normal light ($p > 0.05$). In reduced lighting, older adults with AMD were less accurate and more variable when stepping across the targets compared to controls ($p < 0.05$). A sudden reduction of light proved the most challenging for this population. In the AMD group, contrast sensitivity and visual acuity were not significantly correlated with walking performance. Visual field thresholds in the AMD group were only associated with greater foot placement error and variability in the dim light walking condition ($r = -0.69$ to $-0.87$, $p < 0.05$).

CONCLUSIONS: While walking performance is similar between groups in normal light, poor ambient lighting results in decreased foot placement accuracy in older adults with AMD. Improper foot placement while walking can lead to a fall and possible injury. Thus, to improve the mobility of those with AMD, strategies to enhance the environment in reduced lighting situations are necessary.

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**The role of social deprivation in severe neovascular age-related macular degeneration.**

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BACKGROUND/AIMS: Advances in therapy have improved outcomes for patients with neovascular age-related macular degeneration (nAMD). Prompt access to treatment is a priority and may be used as a key performance indicator. In this study, we investigate how social deprivation may impact on access to services, treatment and visual impairment registration.

METHODS: Patients were identified retrospectively through the Certificate of Visual Impairment system for the University Hospitals Birmingham Medical Retina service. The Index of Multiple Deprivation (IMD) 2007 score was calculated for each patient. The impact of deprivation, age, gender and ethnicity on key stages in the care pathway was assessed.

RESULTS: 120 patients were identified. Patients with greater social deprivation were under-represented, had worse visual acuity at first presentation (correlation of the better-seeing eye with IMD 0.225 ($p=0.013$)) and had sight-impairment registration earlier (correlation -0.246; $p=0.007$). Deprivation did not affect time to first appointment, and was not associated with a higher rate of non-attendance.

CONCLUSIONS: The late presentation and under-representation of patients with greater social deprivation is a serious concern. Our study strongly suggests that this vulnerable group is encountering barriers in accessing treatment in nAMD, and that these occur prior to entry into the Hospital Eye Service.

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