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MD Research News

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Drug treatment

Ophthalmology. 2014 Jan 23. pii: S0161-6420(13)01153-6. doi: 10.1016/j.ophtha.2013.11.031. [Epub ahead of print]

The Neovascular Age-Related Macular Degeneration Database: Multicenter Study of 92 976 Ranibizumab Injections: Report 1: Visual Acuity.

Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group.

PURPOSE: To study real-world ranibizumab therapy for treatment-naïve eyes with neovascular age-related macular degeneration (nAMD) and to benchmark standards of care.

DESIGN: Multicenter, national nAMD database study.

PARTICIPANTS: A total of 92 976 treatment episodes from 12 951 eyes of 11 135 patients.

METHODS: Up to 5 years of routinely collected, anonymized data were extracted remotely from 14 United Kingdom centers to a central database using an electronic medical record (EMR) system. Participating centers used ranibizumab to treat nAMD using a loading phase of 3 monthly injections and a pro re nata retreatment regimen. The minimum data set defined before first patient data entry and mandated by the EMR system included age, Early Treatment Diabetic Retinopathy Study visual acuity (VA) at all visits, and injection episodes.

MAIN OUTCOME MEASURES: Baseline VA, change in VA, number of treatments and clinic visits, and baseline characteristics affecting VA change.

RESULTS: Information from more than 300 000 clinic visits (2.8 million data points) were collated. Mean age at first treatment was 79.1 years, with a female preponderance of 1.7:1. Mean VA (letters) for eyes followed up for at least 3 years from a baseline of 55 letters was 57 (+2) letters at 1 year, 56 (+1) letters at 2 years, and 53 (-2) letters at 3 years. The proportion of eyes that avoided moderate vision loss at years 1, 2, and 3 were 90%, 84%, and 82%, respectively. The proportion of eyes with VA of 20/40 or better were: baseline, 16%; year 1, 30%; year 2, 30%; and year 3, 29%. The median number of treatments for eyes followed up for at least 3 years in years 1, 2 and 3 was 5, 4, and 4, respectively, and the median number of outpatient visits was 9.2, 8.2, and 8.2, respectively. Baseline VA was related inversely to mean vision gain at 3 months. Older age was associated with lower presenting VA.

CONCLUSIONS: Real-world visual outcomes achieved at a large number of centers across the United Kingdom do not match the results achieved in most randomized trials, but they were delivered with substantially fewer injections and hospital visits. This study provides important benchmark results that should be of interest to patients, retina specialists, and commissioners of health care. This study

demonstrates the EMR system's potential usefulness for future phase 4 and 5 clinical trials.

PMID: 24461586 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Eur J Ophthalmol. 2014 Jan 27:0. doi: 10.5301/ejo.5000433. [Epub ahead of print]

Imaging of sub-retinal pigment epithelial linear structures in patients with age-related macular degeneration.

Inoue M, Arakawa A, Yamane S, Kadonosono K.

Purpose: To evaluate hyperreflective linear structures (HLS), as assessed using spectral-domain optical coherence tomography (SD-OCT), identified under the retinal pigment epithelium (RPE) in patients with age -related macular degeneration (AMD).

Methods: This retrospective observational case study was conducted on 427 eyes of 408 consecutive patients who were scheduled to undergo anti-vascular endothelial growth factor (anti-VEGF) therapy for AMD. Patients with HLS under the RPE were investigated based on the SD-OCT findings at baseline or during the follow-up period. The associations between HLS and the lesion subtypes, localization in SD-OCT, clinical findings, and structural change after anti-VEGF treatment were also investigated.

Results: HLS were identified in 18 eyes of 16 patients. From the eyes with HLS, 12 eyes (66.7%) were diagnosed with retinal angiomatous proliferation (RAP), 4 eyes (22.2%) were diagnosed with occult choroidal neovascularization, and the remaining 2 eyes (11.1%) were diagnosed with polypoidal choroidal vasculopathy. HLS were multifocal and exhibited multilocalization under the RPE in all the eyes. Although it was difficult to identify these structures in the clinical findings at baseline, crystalline deposits correlated with the linear bands were observed during the follow-up period in 16 eyes (88.9%). After the anti-VEGF treatments, the HLS remained between the Bruch membrane and RPE or combined with the fibrovascular component.

Conclusions: HLS are rare SD-OCT findings found in patients with AMD, found in only 4.2% of the patients examined in this study. HLS were found especially in RAP lesions.</p>

PMID: 24474382 [PubMed - as supplied by publisher]

Int J Mol Sci. 2014 Jan 27;15(2):1865-86. doi: 10.3390/ijms15021865.

Antioxidant drug therapy approaches for neuroprotection in chronic diseases of the retina.

Payne AJ1, Kaja S2, Naumchuk Y3, Kunjukunju N4, Koulen P5.

Abstract: The molecular pathways contributing to visual signal transduction in the retina generate a high energy demand that has functional and structural consequences such as vascularization and high metabolic rates contributing to oxidative stress. Multiple signaling cascades are involved to actively regulate the redox state of the retina. Age-related processes increase the oxidative load, resulting in chronically elevated levels of oxidative stress and reactive oxygen species, which in the retina ultimately result in pathologies such as glaucoma or age-related macular degeneration, as well as the neuropathic complications of diabetes in the eye. Specifically, oxidative stress results in deleterious changes to the retina through dysregulation of its intracellular physiology, ultimately leading to neurodegenerative and potentially also vascular dysfunction. Herein we will review the evidence for oxidative stress-induced contributions to each of the three major ocular pathologies, glaucoma, age-related macular degeneration, and diabetic retinopathy. The premise for neuroprotective strategies for these ocular disorders will be

discussed in the context of recent clinical and preclinical research pursuing novel therapy development approaches.

PMID: 24473138 [PubMed - in process]

Acta Ophthalmol. 2014 Jan 25. doi: 10.1111/aos.12350. [Epub ahead of print]

Precursor stage of retinal pigment epithelial tear in age-related macular degeneration.

Mukai R, Sato T, Kishi S.

PMID: 24460708 [PubMed - as supplied by publisher]

Pathogenesis

Invest Ophthalmol Vis Sci. 2014 Jan 28. pii: iovs.13-12903v1. doi: 10.1167/iovs.13-12903. [Epub ahead of print]

The association of retinal structure and macular pigment distribution.

Meyer Zu Westrup VK, Dietzel M, Pauleikhoff D, Hense HW.

Introduction: Macular pigment optical density (MPOD) and age-related macular degeneration (AMD) are thought to be associated; however, the details are not yet clearly understood. This study aimed at investigating how retinal anatomical structures relate with the spatial MPOD distribution in single eyes.

Study setting and methods: In a subgroup of the third follow-up examination of the Münster Aging and Retina Study (MARS) cohort (mean age 78.4 years), 124 single eyes of 79 participants were examined. MPOD was assessed using 2-wavelength autofluorescence (AF). Retinal thickness (RT) and fovea pit profile slopes were measured using optical coherence tomography (OCT). The results were analyzed for interocular correlation in 58 pairs of eyes, and for the association of MPOD distribution patterns with RT using uni- and multivariate statistical methods.

Results: The interocular correlations for several measures of RT and RT layers were high ($p < 0.001$). RT was inversely and significantly related to MPOD at 1.0° and at 2.0° from the foveal center but not to central MPOD. After controlling for sex, age, smoking and spherical equivalent, RT was significantly thinner (-39.7 micrometers, $p < 0.001$) in eyes with ring-like as compared to normal MPOD distribution. In particular, a thinner layer between internal and external limiting membrane showed strong associations with ring-like structures.

Conclusion: Higher values of MPOD at 1° and 2° as well as a ring-like distribution of MPOD were significantly associated with thinner maculae, due to thinner inner retinal layers. The MPOD distribution was unrelated to the slope of the foveal pit or the choroidal thickness. Our results suggest that the retinal section between the internal and external limiting membrane is involved in the spatial distribution of MPOD.

PMID: 24474270 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2014 Jan 30. doi: 10.1001/jamaophthalmol.2013.7664. [Epub ahead of print]

Serum Carboxymethyllysine, an Advanced Glycation End Product, and Age-Related Macular Degeneration: The Age, Gene/Environment Susceptibility-Reykjavik Study.

Semba RD1, Cotch MF2, Gudnason V3, Eiríksdottir G4, Harris TB5, Sun K1, Klein R6, Jonasson F7, Ferrucci L8, Schaumberg DA9.

IMPORTANCE: Advanced glycation end products have been implicated in the pathogenesis of age-related macular degeneration (AMD).

OBJECTIVE: To investigate the relationship between serum carboxymethyllysine (CML), a major circulating advanced glycation end product, and AMD in older adults.

DESIGN, SETTING, AND PARTICIPANTS: Cross-sectional study of a population-based sample of 4907 older adults (aged ≥66 years) in the Age, Gene/Environment Susceptibility-Reykjavik Study in Iceland.

EXPOSURES: Serum CML and risk factors for AMD.

MAIN OUTCOMES AND MEASURES: Early or late AMD, assessed through fundus images taken through dilated pupils using a 45° digital camera and grading for drusen size, type, area, increased retinal pigment, retinal pigment epithelial depigmentation, neovascular lesions, and geographic atrophy using the modified Wisconsin Age-Related Maculopathy Grading System.

RESULTS: Of the 4907 participants, 1025 (20.9%) had early AMD and 276 (5.6%) had late AMD. Mean (SD) serum CML concentrations among adults with no AMD, early AMD, and late AMD (exudative AMD and pure geographic atrophy) were 618.8 (195.5), 634.2 (206.4), and 638.4 (192.0) ng/mL, respectively (to convert to micromoles per liter, multiply by 0.00489; P = .07). Log serum CML (per 1-SD increase) was not associated with any AMD (early and late AMD) (odds ratio = 0.97; 95% CI, 0.90-1.04; P = .44) or with late AMD (odds ratio = 0.94; 95% CI, 0.82-1.08; P = .36) in respective multivariable logistic regression models adjusting for age, sex, body mass index, smoking, and renal function.

CONCLUSIONS AND RELEVANCE: Higher serum CML concentration had no significant cross-sectional association with prevalent AMD in this large population-based cohort of older adults in Iceland.

PMID: 24481410 [PubMed - as supplied by publisher]

Biochim Biophys Acta. 2014 Jan 23. pii: S0925-4439(14)00022-2. doi: 10.1016/j.bbadis.2014.01.010. [Epub ahead of print]

Regulation of the cholesterol efflux transporters ABCA1 and ABCG1 in retina in hemochromatosis and by the endogenous siderophore 2,5-dihydroxybenzoic acid.

Ananth S1, Gnana-Prakasam JP1, Bhutia YD1, Veeranan-Karmegam R1, Martin PM1, Smith SB2, Ganapathy V3.

Abstract: Hypercholesterolemia and polymorphisms in the cholesterol exporter ABCA1 are linked to age-related macular degeneration (AMD). Excessive iron in retina also has a link to AMD pathogenesis. Whether these findings mean a biological/molecular connection between iron and cholesterol is not known. Here we examined the relationship between retinal iron and cholesterol using a mouse model (Hfe-/-) of hemochromatosis, a genetic disorder of iron overload. We compared the expression of the cholesterol efflux transporters ABCA1 and ABCG1 and cholesterol content in wild type and Hfe-/- mouse retinas. We also investigated the expression of Bdh2, the rate-limiting enzyme in the synthesis of the endogenous siderophore 2,5-dihydroxybenzoic acid (2,5-DHBA) in wild type and Hfe-/- mouse retinas, and the influence of this siderophore on ABCA1/ABCG1 expression in retinal pigment epithelium. We found that ABCA1 and ABCG1 were expressed in all retinal cell types, and that their expression was decreased in Hfe-/- retina. This was accompanied with an increase in retinal cholesterol content. Bdh2 was also expressed in all retinal cell types, and its expression was decreased in hemochromatosis. In ARPE-19 cells, 2,5-DHBA increased ABCA1/ABCG1 expression and decreased cholesterol content. This was not due to depletion of free iron because 2,5-DHBA (a siderophore) and deferiprone (an iron chelator) had opposite effects on transferrin receptor expression and ferritin levels. We conclude that iron is a regulator of cholesterol homeostasis in retina and that removal of cholesterol from retinal cells is impaired in hemochromatosis. Since excessive cholesterol is pro-inflammatory, hemochromatosis might promote retinal inflammation via

cholesterol in AMD.

PMID: 24462739 [PubMed - as supplied by publisher]

AAPS J. 2014 Jan 28. [Epub ahead of print]

Novel Endogenous Glycan Therapy for Retinal Diseases: Safety, In Vitro Stability, Ocular Pharmacokinetic Modeling, and Biodistribution.

Swaminathan S, Li H, Palamoor M, de Obarrio WT, Madhura D, Meibohm B, Jablonski MM.

Abstract: Asialo, tri-antennary oligosaccharide (NA3 glycan) is an endogenous compound, which supports proper folding of outer segment membranes, promotes normal ultrastructure, and maintains protein expression patterns of photoreceptors and Müller cells in the absence of retinal pigment epithelium support. It is a potential new therapeutic for atrophic age-related macular degeneration (AMD) and other retinal degenerative disorders. Herein, we evaluate the safety, in vitro stability, ocular pharmacokinetics and biodistribution of NA3. NA3 was injected into the vitreous of New Zealand white rabbits at two concentrations viz. 1 nM (minimum effective concentration (MEC)) and 100 nM (100XMEC) at three time points. Safety was evaluated using routine clinical and laboratory tests. Ocular pharmacokinetics and biodistribution of [3H]NA3 were estimated using scintillation counting in various parts of the eye, multiple peripheral organs, and plasma. Pharmacokinetic parameters were estimated by non-compartmental modeling. A 2-aminobenzamide labeling and hydrophilic interaction liquid interaction chromatography were used to assess plasma and vitreous stability. NA3 was well tolerated by the eye. The concentration of NA3 in eye tissues was in the order: vitreous > retina > sclera/choroid > aqueous humor > cornea > lens. Area under the curve (0 to infinity) (AUC∞) was the highest in the vitreous thereby providing a positive concentration gradient for NA3 to reach the retina. Half-lives in critical eye tissues ranged between 40 and 60 h. NA3 concentrations were negligible in peripheral organs. Radioactivity from [3H]NA3 was excreted via urine and feces. NA3 was stable at 37°C in vitreous over a minimum of 6 days, while it degraded rapidly in plasma. Collectively, these results document that NA3 shows a good safety profile and favorable ocular pharmacokinetics.

PMID: 24470212 [PubMed - as supplied by publisher]

Protein Cell. 2014 Jan 29. [Epub ahead of print]

Direct conversion of human fibroblasts into retinal pigment epithelium-like cells by defined factors.

Zhang K, Liu GH, Yi F, Montserrat N, Hishida T, Esteban CR, Izpisua Belmonte JC.

Abstract: The generation of functional retinal pigment epithelium (RPE) is of great therapeutic interest to the field of regenerative medicine and may provide possible cures for retinal degenerative diseases, including age-related macular degeneration (AMD). Although RPE cells can be produced from either embryonic stem cells or induced pluripotent stem cells, direct cell reprogramming driven by lineage-determining transcription factors provides an immediate route to their generation. By monitoring a human RPE specific Best1::GFP reporter, we report the conversion of human fibroblasts into RPE lineage using defined sets of transcription factors. We found that Best1::GFP positive cells formed colonies and exhibited morphological and molecular features of early stage RPE cells. Moreover, they were able to obtain pigmentation upon activation of Retinoic acid (RA) and Sonic Hedgehog (SHH) signaling pathways. Our study not only established an ideal platform to investigate the transcriptional network regulating the RPE cell fate determination, but also provided an alternative strategy to generate functional RPE cells that complement the use of pluripotent stem cells for disease modeling, drug screening, and cell therapy of retinal degeneration.

PMID: 24474194 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmic Epidemiol. 2014 Feb;21(1):14-23. doi: 10.3109/09286586.2013.867512.

Harmonizing the Classification of Age-related Macular Degeneration in the Three-Continent AMD Consortium.

Klein R, Meuer SM, Myers CE, Buitendijk GH, Rochtchina E, Choudhury F, de Jong PT, McKean-Cowdin R, Iyengar SK, Gao X, Lee KE, Vingerling JR, Mitchell P, Klaver CC, Wang JJ, Klein BE.

Abstract Purpose: To describe methods to harmonize the classification of age-related macular degeneration (AMD) phenotypes across four population-based cohort studies: the Beaver Dam Eye Study (BDES), the Blue Mountains Eye Study (BMES), the Los Angeles Latino Eye Study (LALES), and the Rotterdam Study (RS).

Methods: AMD grading protocols, definitions of categories, and grading forms from each study were compared to determine whether there were systematic differences in AMD severity definitions and lesion categorization among the three grading centers. Each center graded the same set of 60 images using their respective systems to determine presence and severity of AMD lesions. A common 5-step AMD severity scale and definitions of lesion measurement cutpoints and early and late AMD were developed from this exercise.

Results: Applying this severity scale changed the age-sex adjusted prevalence of early AMD from 18.7% to 20.3% in BDES, from 4.7% to 14.4% in BMES, from 14.1% to 15.8% in LALES, and from 7.5% to 17.1% in RS. Age-sex adjusted prevalences of late AMD remained unchanged. Comparison of each center's grades of the 60 images converted to the consortium scale showed that exact agreement of AMD severity among centers varied from 61.0-81.4%, and one-step agreement varied from 84.7-98.3%.

Conclusion: Harmonization of AMD classification reduced categorical differences in phenotypic definitions across the studies, resulted in a new 5-step AMD severity scale, and enhanced similarity of AMD prevalence among the four cohorts. Despite harmonization it may still be difficult to remove systematic differences in grading, if present.

PMID: 24467558 [PubMed - in process]

JAMA Ophthalmol. 2014 Jan 30. doi: 10.1001/jamaophthalmol.2013.7671. [Epub ahead of print]

Markers of Inflammation, Oxidative Stress, and Endothelial Dysfunction and the 20-Year Cumulative Incidence of Early Age-Related Macular Degeneration: The Beaver Dam Eye Study.

Klein R1, Myers CE2, Cruickshanks KJ3, Gangnon RE4, Danforth LG2, Sivakumaran TA5, Iyengar SK6, Tsai MY7, Klein BE2.

IMPORTANCE: Modifying levels of factors associated with age-related macular degeneration (AMD) may decrease the risk for visual impairment in older persons.

OBJECTIVE: To examine the relationships of markers of inflammation, oxidative stress, and endothelial dysfunction to the 20-year cumulative incidence of early AMD.

DESIGN, SETTING, AND PARTICIPANTS: This longitudinal population-based cohort study involved a random sample of 975 persons in the Beaver Dam Eye Study without signs of AMD who participated in the baseline examination in 1988-1990 and up to 4 follow-up examinations in 1993-1995, 1998-2000, 2003-2005, and 2008-2010.

EXPOSURES: Serum markers of inflammation (high-sensitivity C-reactive protein, tumor necrosis factor-α receptor 2, interleukin-6, and white blood cell count), oxidative stress (8-isoprostane and total carbonyl

content), and endothelial dysfunction (soluble vascular cell adhesion molecule-1 and soluble intercellular adhesion molecule-1) were measured. Interactions with complement factor H (rs1061170), age-related maculopathy susceptibility 2 (rs10490924), complement component 3 (rs2230199), and complement component 2/complement factor B (rs4151667) were examined using multiplicative models. Age-related macular degeneration was assessed from fundus photographs.

MAIN OUTCOMES AND MEASURES: Early AMD defined by the presence of any size drusen and the presence of pigmentary abnormalities or by the presence of large-sized drusen (≥125-μm diameter) in the absence of late AMD.

RESULTS: The 20-year cumulative incidence of early AMD was 23.0%. Adjusting for age, sex, and other risk factors, high-sensitivity C-reactive protein (odds ratio comparing fourth with first quartile, 2.18; P = .005), tumor necrosis factor-α receptor 2 (odds ratio, 1.78; P = .04), and interleukin-6 (odds ratio, 1.78; P = .03) were associated with the incidence of early AMD. Increased incidence of early AMD was associated with soluble vascular cell adhesion molecule-1 (odds ratio per SD on the logarithmic scale, 1.21; P = .04).

CONCLUSIONS AND RELEVANCE: We found modest evidence of relationships of serum high-sensitivity C-reactive protein, tumor necrosis factor-α receptor 2, interleukin-6, and soluble vascular cell adhesion molecule-1 to the 20-year cumulative incidence of early AMD independent of age, smoking status, and other factors. It is not known whether these associations represent a cause and effect relationship or whether other unknown confounders accounted for the findings. Even if inflammatory processes are a cause of early AMD, it is not known whether interventions that reduce systemic inflammatory processes will reduce the incidence of early AMD.

PMID: 24481424 [PubMed - as supplied by publisher]

J Cataract Refract Surg. 2014 Feb;40(2):173-4. doi: 10.1016/j.jcrs.2013.11.022.

Age-related macular degeneration and cataract surgery. Editorial

Rosen ES.

PMID: 24461495 [PubMed - in process]

J Cataract Refract Surg. 2014 Feb;40(2):184-91. doi: 10.1016/j.jcrs.2013.07.036.

Changes in choroidal thickness after cataract surgery.

Ohsugi H1, Ikuno Y2, Ohara Z2, Imamura H2, Nakakura S2, Matsuba S2, Kato Y2, Tabuchi H2.

PURPOSE: To evaluate changes in choroidal thickness before and after cataract surgery and factors affecting the changes.

SETTING: Tsukazaki Hospital, Himeji, Japan.

DESIGN: Prospective interventional study.

METHODS: Patients having cataract surgery without other eye pathology were studied. The corrected distance visual acuity (CDVA), intraocular pressure (IOP), axial length (AL), and enhanced-depth-imaging optical coherence tomography (OCT) were measured preoperatively. The choroidal thickness was measured at 5 points (subfoveal and 1.5 mm nasal, temporal, superior, and inferior to the fovea) using the OCT device's software. Enhanced-depth-imaging OCT and IOP measurements were obtained 3 days, 1 and 3 weeks, and 3 and 6 months postoperatively and compared with the baseline values. Stepwise analysis determined which factors (ie, age, CDVA, preoperative IOP, AL, operative time, changes in IOP) were associated with changes in choroidal thickness.

RESULTS: One hundred eyes were analyzed. The postoperative IOP significantly decreased at 3 weeks, 3 months, and 6 months. The postoperative choroidal thickness significantly increased at the foveal and inferior regions throughout the follow-up; at the nasal region at 3 days, 1 week, and 6 months; at the temporal region at 1 week; and at the superior region at 6 months. These changes negatively correlated with those in IOP early after surgery. The changes in choroidal thickness later negatively correlated with the AL in all regions.

CONCLUSION: Cataract surgery caused changes in choroidal thickness. The AL and changes in the IOP are critical for evaluating the changes in choroidal thickness.

Acta Ophthalmol. 2014 Jan 28. doi: 10.1111/aos.12357. [Epub ahead of print]

Relationship between breast arterial calcifications seen on screening mammograms and age-related macular degeneration.

Saá J, Fernández-Guinea O, García-Pravia P, Fernandez-Garcia B, Eiró N, Del Casar JM, Venta R, Baamonde B, Vizoso FJ.

PMID: 24472216 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Jan 30. pii: iovs.13-13204v1. doi: 10.1167/iovs.13-13204. [Epub ahead of print]

Macular pigment spatial profiles in South Asian and White subjects.

Huntjens B, Asaria TS, Dhanani SD, Konstantakopoulou E, Ctori I.

Purpose: Variability in central macular pigment optical density (MPOD) has been reported amongst healthy individuals. These variations seem to be related to risk factors of age-related macular degeneration, such as female gender, smoking, and ethnicity. This study investigates the variations in MPOD spatial profiles amongst ethnicities.

Methods: Using heterochromatic flicker photometry (HFP), MPOD was measured at 7 retinal locations in 54 healthy young South Asian and 19 White subjects of similar age. Macular pigment spatial profiles were classified as either typical 'exponential', atypical 'ring-like' or atypical 'central dip'.

Results: Central MPOD was significantly greater in South Asian (0.56 ± 0.17) compared to White subjects (0.45 ± 0.18; P = 0.015). Integrated MPOD up to 1.8° i.e. MPODav(0-1.8) was also significantly increased in Asian (0.34 ± 0.09) versus White subjects (0.27 ± 0.10; P = 0.003). MPODav(0-1.8) was significantly increased in all subjects presenting a ring-like profile (0.35 ± 0.08) or central dip profile (0.39 ± 0.09), compared to typical exponential profiles (0.28 ± 0.09; P < 0.0005). We found a statistically significant association between ethnicity and spatial profile type (P = 0.008), whereby an exponential profile was present in 79% of White compared to 41% of the South Asian subjects.

Conclusion: Central MPOD, MPODav(0-1.8), and the prevalence of atypical spatial profiles were significantly increased in South Asian compared to White subjects. Atypical profiles resulted in increased integrated MPOD up to 1.8° and may therefore offer enhanced macular protection from harmful blue light.

PMID: 24481263 [PubMed - as supplied by publisher]

Trop Med Int Health. 2014 Jan 31. doi: 10.1111/tmi.12276. [Epub ahead of print]

Posterior segment eye disease in sub-Saharan Africa: review of recent population-based studies.

Bastawrous A, Burgess PI, Mahdi AM, Kyari F, Burton MJ, Kuper H.

OBJECTIVE: To assess the burden of posterior segment eye diseases (PSEDs) in sub-Saharan Africa (SSA).

METHODS: We reviewed published population-based data from SSA and other relevant populations on the leading PSED, specifically glaucoma, diabetic retinopathy and age-related macular degeneration, as causes of blindness and visual impairment in adults. Data were extracted from population-based studies conducted in SSA and elsewhere where relevant.

RESULTS: PSEDs, when grouped or as individual diseases, are a major contributor to blindness and visual impairment in SSA. PSED, grouped together, was usually the second leading cause of blindness after cataract, ranging as a proportion of blindness from 13 to 37%.

CONCLUSIONS: PSEDs are likely to grow in importance as causes of visual impairment and blindness in SSA in the coming years as populations grow, age and become more urban in lifestyle. African-based cohort studies are required to help estimate present and future needs and plan services to prevent avoidable blindness.

PMID: 24479434 [PubMed - as supplied by publisher]

Genetics

PLoS One. 2014 Jan 21;9(1):e86538. doi: 10.1371/journal.pone.0086538. eCollection 2014.

Loss of CD34 Expression in Aging Human Choriocapillaris Endothelial Cells.

Sohn EH1, Flamme-Wiese MJ1, Whitmore SS1, Wang K2, Tucker BA1, Mullins RF1.

Abstract: Structural and gene expression changes in the microvasculature of the human choroid occur during normal aging and age-related macular degeneration (AMD). In this study, we sought to determine the impact of aging and AMD on expression of the endothelial cell glycoprotein CD34. Sections from 58 human donor eyes were categorized as either young (under age 40), age-matched controls (> age 60 without AMD), or AMD affected (>age 60 with early AMD, geographic atrophy, or choroidal neovascularization). Dual labeling of sections with Ulex europaeus agglutinin-I lectin (UEA-I) and CD34 antibodies was performed, and the percentage of capillaries labeled with UEA-I but negative for anti-CD34 was determined. In addition, published databases of mouse and human retinal pigment epithelium-choroid were evaluated and CD34 expression compared between young and old eyes. Immunohistochemical studies revealed that while CD34 and UEA-I were colocalized in young eyes, there was variable loss of CD34 immunoreactivity in older donor eyes. While differences between normal aging and AMD were not significant, the percentage of CD34 negative capillaries in old eyes, compared to young eyes, was highly significant ($p=3.8\times10(-6)$). Endothelial cells in neovascular membranes were invariably CD34 positive. Published databases show either a significant decrease in Cd34 (mouse) or a trend toward decreased CD34 (human) in aging. These findings suggest that UEA-I and endogenous alkaline phosphatase activity are more consistent markers of aging endothelial cells in the choroid, and suggest a possible mechanism for the increased inflammatory milieu in the aging choroid.

PMID: 24466138 [PubMed - in process] PMCID: PMC3897719

Hum Mol Genet. 2014 Jan 26. [Epub ahead of print]

Insights into the mechanisms of macular degeneration associated with the R172W mutation in RDS.

Conley SM, Stuck MW, Burnett JL, Chakraborty D, Azadi S, Fliesler SJ, Naash MI.

Abstract: Mutations in the photoreceptor tetraspanin gene peripherin-2/retinal degeneration slow (PRPH2/

RDS) cause both rod- and cone-dominant diseases. While rod-dominant diseases, such as autosomal dominant retinitis pigmentosa, are thought to arise due to haploinsufficiency caused by loss-of-function mutations, the mechanisms underlying PRPH2-associated cone-dominant diseases are unclear. Here we took advantage of a transgenic mouse line expressing an RDS mutant (R172W) known to cause macular degeneration (MD) in humans. To facilitate the study of cones in the heavily rod-dominant mouse retina, R172W mice were bred onto an Nrl-/- background (in which developing rods adopt a cone-like fate). In this model the R172W protein and the key RDS-binding partner, rod outer segment (OS) membrane protein 1 (ROM-1), were properly expressed and trafficked to cone OSs. However, the expression of R172W led to dominant defects in cone structure and function with equal effects on S- and M-cones. Furthermore, the expression of R172W in cones induced subtle alterations in RDS/ROM-1 complex assembly, specifically resulting in the formation of abnormal, large molecular weight ROM-1 complexes. Fundus imaging demonstrated that R172W mice developed severe clinical signs of disease nearly identical to those seen in human MD patients, including retinal degeneration, retinal pigment epithlium (RPE) defects and loss of the choriocapillaris. Collectively, these data identify a primary disease-causing molecular defect in cone cells and suggest that RDS-associated disease in patients may be a result of this defect coupled with secondary sequellae involving RPE and choriocapillaris cell loss.

PMID: 24463884 [PubMed - as supplied by publisher]

Diet & lifestyle

BMC Ophthalmol. 2014 Jan 28;14(1):10. [Epub ahead of print]

Fear of falling in age-related macular degeneration.

van Landingham SW, Massof RW, Chan E, Friedman DS, Ramulu PY.

BACKGROUND: Prior studies have shown age-related macular degeneration (AMD) to be associated with falls. The purpose of this study is to determine if age-related macular degeneration (AMD) and AMD-related vision loss are associated with fear of falling, an important and distinct outcome.

METHODS: Sixty-five persons with AMD with evidence of vision loss in one or both eyes and 60 glaucoma suspects with normal vision completed the University of Illinois at Chicago Fear of Falling questionnaire. Responses were Rasch analyzed. Scores were expressed in logit units, with lower scores demonstrating lesser ability and greater fear of falling.

RESULTS: Compared to glaucoma suspect controls, AMD subjects had worse visual acuity (VA) (median better-eye VA = 20/48 vs. 20/24, $p < 0.001$) and worse contrast sensitivity (CS) (binocular CS = 1.9 vs. 1.5 log units, $p < 0.001$). AMD subjects were also older, more likely to be Caucasian, and less likely to be employed ($p < 0.05$ for all), but were similar with regards to other demographic and health measures. In multivariable models controlling for age, gender, body habitus, strength, and comorbid illnesses, AMD subjects reported greater fear of falling as compared to controls (beta = -0.77 logits, 95% CI = -1.5 to -0.002, $p = 0.045$). In separate multivariable models, fear of falling increased with worse VA (beta = -0.15 logits/1 line decrement, 95% CI = -0.28 to -0.03, $p = 0.02$) and CS (beta = -0.20 logits/0.1 log unit decrement, 95% CI = -0.31 to -0.09, $p = 0.001$). Greater fear of falling was also associated with higher BMI, weaker grip, and more comorbid illnesses ($p < 0.05$ for all.)

CONCLUSIONS: AMD and AMD-related vision loss are associated with greater fear of falling in the elderly. Development, validation, and implementation of methods to address falls and fear of falling for individuals with vision loss from AMD are important goals for future work.

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Effectiveness of eccentric viewing training for daily visual activities for individuals with age-related macular degeneration: A systematic review and meta-analysis.

Hong SP1, Park H2, Kwon JS3, Yoo E4.

BACKGROUND: Eccentric viewing training can be successfully applied in the clinical setting based on positive evidence. Nonetheless, published research should be integrated to provide a conclusive perspective of the efficacy of eccentric viewing training.

OBJECTIVE: Meta-analysis was conducted to examine effectiveness of eccentric viewing training on daily visual activities for individuals with age-related macular degeneration (AMD).

METHODS: The papers used in this study were located through PubMed, Ovid, ProQuest, EBSCOhost, RISS, and KMbase on studies published between January, 1990 and December, 2012. The keywords for searching were "age-related macular degeneration" and "eccentric viewing", "eccentric fixation", "peripheral vision" or "preferred retinal loci". The effect sizes were calculated using Comprehensive Meta-Analysis 2.0 and interpreted according to Cohen's criteria.

RESULTS: A total of 258 studies were found, among which five papers suited the main selection criteria for final analysis. The entire effect size was 0.660 (95% CI 0.232 ~ 1.088), indicating a "moderate effect size" of the eccentric viewing training for individuals with AMD in their daily visual activities ($p < .05$).

CONCLUSIONS: The results of this study demonstrated the clinical effectiveness of eccentric viewing training for individuals with AMD. This result should be interpreted cautiously, though, given the possibility of publication bias.

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Review of nutrient actions on age-related macular degeneration.

Zampatti S1, Ricci F2, Cusumano A2, Marsella LT1, Novelli G3, Giardina E4.

Abstract: The actions of nutrients and related compounds on age-related macular degeneration (AMD) are explained in this review. The findings from 80 studies published since 2003 on the association between diet and supplements in AMD were reviewed. Antioxidants and other nutrients with an effect on AMD susceptibility include carotenoids (lutein and zeaxanthin, β-carotene), vitamins (vitamin A, E, C, D, B), mineral supplements (zinc, copper, selenium), dietary fatty acids [monounsaturated fatty acids, polyunsaturated fatty acids (PUFA both omega-3 PUFA and omega-6 PUFA), saturated fatty acids and cholesterol], and dietary carbohydrates. The literature revealed that many of these antioxidants and nutrients exert a protective role by functioning synergistically. Specifically, the use of dietary supplements with targeted actions can provide minimal benefits on the onset or progression of AMD; however, this does not appear to be particularly beneficial in healthy people. Furthermore, some supplements or nutrients have demonstrated discordant effects on AMD in some studies. Since intake of dietary supplements, as well as exposure to damaging environmental factors, is largely dependent on population habits (including dietary practices) and geographical localization, an overall healthy diet appears to be the best strategy in reducing the risk of developing AMD. As of now, the precise mechanism of action of certain nutrients in AMD prevention remains unclear. Thus, future studies are required to examine the effects that nutrients have on AMD and to determine which factors are most strongly correlated with reducing the risk of AMD or preventing its progression.

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Cardiovascular risk factors associated with age-related macular degeneration: the Tromsø Study.

Erke MG, Bertelsen G, Peto T, Sjølie AK, Lindekleiv H, Njølstad I.

PURPOSE: To examine associations between cardiovascular risk factors and age-related macular degeneration (AMD).

METHODS: A population-based, cross-sectional study of Caucasians aged 65-87 years was conducted in Norway in 2007/2008. Retinal photographs were graded for AMD. Multivariable logistic regression analyses were performed based on questionnaires addressing habits of smoking, alcohol consumption, physical activity, health and medication; and physical examination comprising anthropometric measurements, blood pressure and blood sampling. Cardiovascular disease status was obtained from a validated end-point registry.

RESULTS: Gradable photographs were available for 2631 participants, of whom 92 (3.5%) subjects had late AMD. In the multivariable analysis of late AMD, significant interactions were found between sex and the variables age, triglyceride level, use of lipid-lowering drugs and physical exercise. Current daily smoking was significantly related to late AMD in both sexes (odds ratio (OR) 4.06, 95% confidence interval (CI) 1.69-9.76 and OR 3.59, 95% CI 1.17-11.04, women and men, respectively) compared with never smokers. Higher number of pack years was associated with the presence of large drusen (>125 μm) (OR 1.04, 95% CI 1.01-1.09 per 5 years). Higher systolic blood pressure (OR 1.06, 95% CI 1.01-1.12 per 5 mmHg), overweight (OR 2.87, 95% CI 1.13-7.29) and obesity (OR 2.92, 95% CI 1.06-8.03), physical exercise duration (OR 0.41, 95% 0.18-0.96 for 30 min or more compared with less) and frequency (OR 0.46, 95% CI 0.23-0.92 for weekly or more often compared to less) were associated with late AMD in women only.

CONCLUSIONS: Smoking was strongly associated with AMD, in line with results from other populations. Also, late AMD was related to higher systolic blood pressure, physical inactivity, overweight and obesity in women.

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