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MD Research News

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Drug treatment

Am J Ophthalmol. 2014 Jun 17. pii: S0002-9394(14)00336-5. doi: 10.1016/j.ajo.2014.06.004. [Epub ahead of print]

Delayed Patchy Choroidal Filling in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

Gewaily DY, Grunwald JE, Pistilli M, Ying GS, Maguire MG, Daniel E, Ostroff CP, Fine SL; CATT Research Group.

PURPOSE: To determine the relationship between delayed patchy choroidal filling and morphologic and functional outcomes among eyes treated with ranibizumab or bevacizumab.

DESIGN: Cohort study.

METHODS: Comparison of Age-related Macular Degeneration Treatment Trials participants were randomly assigned to ranibizumab or bevacizumab on a monthly or as needed schedule. Presence of delayed patchy choroidal filling and morphologic and functional outcomes were evaluated among eyes with gradable fluorescein angiography at baseline (N=973) and at one year (N=860) eyes.

RESULTS: Delayed filling was present in 75 (7.7%) of 973 eyes at baseline. Eyes with incident delayed filling at one year (23 (2.9%) of 798) showed a mean decrease of 1.7 letters in visual acuity, whereas eyes without incident delayed filling had a mean improvement of 8.1 letters (Δ=-9.8 [-15.8, -3.9], p<0.01). Eyes with incident delayed filling had a larger increase in mean total lesion area of choroidal neovascularization (3.00 mm2) than eyes without incident delayed filling (0.56 mm2, Δ=2.4 [0.4, 4.4], p=0.02). The proportion with incident delayed filling at one year was similar among eyes treated with ranibizumab (10 (2.4%) of 413) or bevacizumab (13 (3.3%) of 385, p=0.53) and among eyes treated monthly (12 (3.1%) of 388) or as needed (11 (2.7%) of 410, p=0.83).

CONCLUSIONS: Delayed patchy choroidal filling was uncommon at baseline. Although only a small percentage of eyes developed delayed filling during the first year of anti-vascular endothelial growth factor treatment, these eyes had worse visual acuity and a larger increase in total lesion area of choroidal neovascularization.

PMID: 24949820 [PubMed - as supplied by publisher]

Open Ophthalmol J. 2014 May 16;8:3-6. doi: 10.2174/1874364101408010003. eCollection 2014.

Clinical risk factors for poor anatomic response to ranibizumab in neovascular age-related macular degeneration.

Guber J, Josifova T, Henrich PB, Guber I.

PURPOSE: To identify OCT-based anatomical features and clinical characteristics for poor central retinal thickness (CRT) response to ranibizumab in neovascular age-related macular degeneration (AMD).

PATIENTS AND METHODS: Investigating our electronic patient records (Eyeswide), patients with neovascular AMD treated with intravitreal injections of 0.5mg/0.05ml ranibizumab were identified and their notes reviewed. Data collected included gender, age, initial best-corrected visual acuity (BCVA), prior photodynamic therapy, lesion type (classic versus occult), type of macular edema (intraretinal fluid, subretinal fluid, pigment epithelium detachment) and the total number of previous ranibizumab injections.

RESULTS: A total of 210 eyes of 182 patients with neovascular AMD were identified. Mean follow-up time was 1.34 years (SD ± 0.77). Central retinal thickness reduction in women was significantly inferior to that in men ($p=0.05$). Patients with cystoid type macular edema had significantly greater reduction in CRT compared to patients with subretinal fluid ($p<0.001$) or pigment epithelium detachment ($p<0.001$). The percentage drop of CRT was no longer statistically significant after the sixth injection. Age, initial BCVA, prior photodynamic therapy and lesion type had no statistically effect on CRT response.

CONCLUSION: Risk factors for poor central retinal thickness response to ranibizumab include female gender and patients with predominant subretinal fluid or pigment epithelium detachment. Furthermore, the anatomical response decreased after the sixth injection of ranibizumab.

PMID: 24949110 [PubMed]

Ophthalmology. 2014 Jun 14. pii: S0161-6420(14)00427-8. doi: 10.1016/j.ophtha.2014.05.007. [Epub ahead of print]

Intravitreal Therapy in Bilateral Neovascular Age-Related Macular Degeneration.

Barthelmes D, Walton RJ, Arnold JJ, McAllister IL, Simpson JM, Campain A, Hunyor AP, Guymer R, Essex RW, Morlet N, Gillies MC; for the Fight Retinal Blindness! Project Investigators.

PMID: 24939512 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2014 Jun 18. doi: 10.1111/aos.12458. [Epub ahead of print]

Subretinal tissue plasminogen activator injection to treat submacular haemorrhage during age-related macular degeneration.

Dewilde E, Delaere L, Vaninbroukx I, Van Calster J, Stalmans P.

PMID: 24943231 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2014 Jun 18. doi: 10.1111/aos.12489. [Epub ahead of print]

Cat-scratch-disease-associated macular oedema treated with intravitreal ranibizumab.

Manousaridis K, Peter S, Mennel S.

PMID: 24943325 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Optom Vis Sci. 2014 Jun 19. [Epub ahead of print]

Reticular Pseudodrusen in Age-Related Macular Degeneration.

Hogg RE.

Abstract: Historically, drusen, which are recognized as the hallmark of age-related macular degeneration (AMD), have been described in terms of size, margins, and texture, and several studies have emphasized the importance of large soft drusen particularly when combined with focal pigmentary irregularities in determining the risk of progression to neovascular AMD. However, recent developments in imaging over the past decade have revealed a further distinct phenotype strongly associated with the development of late AMD, namely, reticular pseudodrusen (RPD) or reticular drusen. Reticular pseudodrusen appear as yellowish interlacing networks in the fundus and, although visible on color photography, are better visualized using infrared imaging or spectral domain optical coherence tomography. Studies correlating spectral domain optical coherence tomography and confocal scanning laser ophthalmoscopy have shown that RPD are subretinal deposits located internal to the retinal pigment epithelium in contrast to traditional drusen, which are located external to the retinal pigment epithelium. As multiple longitudinal studies have revealed RPD are strong predictors for progression to both neovascular AMD and geographic atrophy, the interest in understanding the role that RPD play in the pathogenesis of AMD has grown. This review focuses on the current literature concerning RPD and considers what is currently known regarding their epidemiology, risk factors, appearance in both retinal imaging and histology, impact on visual function, relationship to other AMD lesions, and association with the development of late AMD.

PMID: 24950032 [PubMed - as supplied by publisher]

Eye (Lond). 2014 Jun 20. doi: 10.1038/eye.2014.78. [Epub ahead of print]

Evaluation of focal choroidal excavation in the macula using swept-source optical coherence tomography.

Lim FP, Loh BK, Cheung CM, Lim LS, Chan CM, Wong DW.

Purpose: To evaluate imaging findings of patients with focal choroidal excavation (FCE) in the macula using swept-source optical coherence tomography (SS-OCT) and correlate it clinically.

Methods: Prospective observational case series. Eleven consecutive patients (12 eyes) with FCE were described. Data on demographics and clinical presentation were collected and imaging findings (including color photography, fundus autofluorescence imaging, fluorescein angiography, indocyanine green angiography, spectral-domain optical coherence tomography, and SS-OCT) were analyzed.

Results: The primary diagnosis was epiretinal membrane (two eyes), choroidal neovascularization (one eye), polypoidal choroidal vasculopathy (three eyes), central serous chorioretinopathy (one eye), and dry age-related macular degeneration (two eyes). Eleven out of 12 of the lesions were conforming. One presented with a non-conforming lesion that progressed to a conforming lesion. One eye had multiFCE and two had two overlapping choroidal excavations. Using the SS-OCT, we found the choroid to be thinned out at the area of FCE but sclera remained normal. The choroidal tissue beneath the FCE was abnormal, with high internal reflectivity and poor visualization of choroidal vessels. There was loss of contour of the outer choroidal boundary that appeared to be pulled inward by this abnormal choroidal tissue. A suprachoroidal space was noted beneath this choroidal tissue and the choroidal-scleral interface was smooth. Repeat SS-OCT 6 months after presentation showed the area of excavation to be stable in size.

Conclusion: FCE can be associated with epiretinal membrane, central serous chorioretinopathy, and age-related macular degeneration. The choroid was thinned out in the area of FCE.Eye advance online

publication, 20 June 2014; doi:10.1038/eye.2014.78.

PMID: 24946847 [PubMed - as supplied by publisher]

Mol Vis. 2014 Jun 2;20:760-9. eCollection 2014.

Pinosylvin-mediated protection against oxidative stress in human retinal pigment epithelial cells.

Koskela A, Reinisalo M, Hyttinen JM, Kaarniranta K, Karjalainen RO.

PURPOSE: In this work, we investigated the ability of pinosylvin (PS), 3,5-dihydroxy-trans-stilbene, to modulate oxidative stress in human RPE cells. PS, a stilbenoid polyphenol, occurs in high concentrations in bark byproducts and therefore represents an attractive bioactive compound for health-promoting applications.

METHODS: First, we evaluated the toxicity range of PS by exposing ARPE-19 cells to 0.1-200 µM concentrations of PS for 24 h followed by the cell viability test. In the next stage, the ARPE-19 cells were preincubated in PS for 24 h followed by hydroquinone (HQ) exposure without PS for another 24 h. The cell viability test was conducted after HQ exposure. To elucidate the potential mechanisms behind PS-mediated protection against oxidative stress, the ARPE-19 cells were treated with 5 µM PS for 6 h, and mRNA was extracted at four time points (2 h, 6 h, 12 h, 24 h) to determine changes in the expression of nuclear factor-erythroid 2-related factor-2 (Nrf2), sequestosome 1 (p62/SQSTM1), heme oxygenase-1 (HO-1), and glutathione S-transferase pi 1 (GSTP1) genes. To clarify the molecular mechanism behind PS-mediated protection further, the ARPE-19 cells were transfected with p62 and Nrf2 siRNAs for 24 h, and the roles of p62, Nrf2, and its target gene HO-1 in conferring protection against oxidative stress were studied with quantitative real-time PCR (qRT-PCR) and the cell viability test.

RESULTS: PS treatment at concentrations of 5 and 10 µM significantly enhanced cell survival from oxidative stress. The expression levels of an enzyme with antioxidative, anti-inflammatory, and immunomodulatory properties, HO-1, were increased by PS treatment and correlated strongly with cell survival. PS treatment did not elevate the expression levels of Nrf2 or its target genes, p62 or GSTP1, even though it had a clear effect on the expression of HO-1, another gene controlled by Nrf2. RNA interference analysis further confirmed the important role of Nrf2 and HO-1 in PS-mediated protection against oxidative stress whereas the role of p62 seemed to be insignificant at the gene expression and cell viability levels.

CONCLUSIONS: Our results suggest that PS treatment conferred protection against oxidative stress through the induction of HO-1 in human RPE cells. Consequently, PS-stilbene compounds, which can be isolated in significant amounts from bark waste, may possess health-promoting properties against aging-related diseases associated with oxidative stress such as age-related macular degeneration (AMD) and Alzheimer's disease. These natural compounds may offer opportunities for high-value use of bark waste in diverse health-related applications.

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Prog Retin Eye Res. 2014 Jun 13. pii: S1350-9462(14)00037-8. doi: 10.1016/j.preteyeres.2014.06.002. [Epub ahead of print]

Stem cells as source for retinal pigment epithelium transplantation.

Bertolotti E, Neri A, Camparini M, Macaluso C, Marigo V.

Abstract: Inherited maculopathies, age related macular degeneration and some forms of retinitis pigmentosa are associated with impaired function or loss of the retinal pigment epithelium (RPE). Among potential treatments, transplantation approaches are particularly promising. The arrangement of RPE cells

in a well-defined tissue layer makes the RPE amenable to cell or tissue sheet transplantation. Different cell sources have been suggested for RPE transplantation but the development of a clinical protocol faces several obstacles. The source should provide a sufficient number of cells to at least recover the macula area. Secondly, cells should be plastic enough to be able to integrate in the host tissue. Tissue sheets should be considered as well, but the substrate on which RPE cells are cultured needs to be carefully evaluated. Immunogenicity can also be an obstacle for effective transplantation as well as tumorigenicity of not fully differentiated cells. Finally, ethical concerns may represent drawbacks when embryo-derived cells are proposed for RPE transplantation. Here we discuss different cell sources that became available in recent years and their different properties. We also present data on a new source of human RPE. We provide a protocol for RPE differentiation of retinal stem cells derived from adult ciliary bodies of post-mortem donors. We show molecular characterization of the in vitro differentiated RPE tissue and demonstrate its functionality based on a phagocytosis assay. This new source may provide tissue for allogenic transplantation based on best matches through histocompatibility testing.

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PLoS One. 2014 Jun 17;9(6):e100171. doi: 10.1371/journal.pone.0100171. eCollection 2014.

Decreased fixation stability of the preferred retinal location in juvenile macular degeneration.

Bethlehem RA, Dumoulin SO, Dalmaijer ES, Smit M, Berendschot TT, Nijboer TC, Van der Stigchel S.

Abstract: Macular degeneration is the main cause for diminished visual acuity in the elderly. The juvenile form of macular degeneration has equally detrimental consequences on foveal vision. To compensate for loss of foveal vision most patients with macular degeneration adopt an eccentric preferred retinal location that takes over tasks normally performed by the healthy fovea. It is unclear however, whether the preferred retinal locus also develops properties typical for foveal vision. Here, we investigated whether the fixation characteristics of the preferred retinal locus resemble those of the healthy fovea. For this purpose, we used the fixation-offset paradigm and tracked eye-position using a high spatial and temporal resolution infrared eye-tracker. The fixation-offset paradigm measures release from fixation under different fixation conditions and has been shown useful to distinguish between foveal and non-foveal fixation. We measured eye-movements in nine healthy age-matched controls and five patients with juvenile macular degeneration. In addition, we performed a simulation with the same task in a group of five healthy controls. Our results show that the preferred retinal locus does not adopt a foveal type of fixation but instead drifts further away from its original fixation and has overall increased fixation instability. Furthermore, the fixation instability is most pronounced in low frequency eye-movements representing a slow drift from fixation. We argue that the increased fixation instability cannot be attributed to fixation under an unnatural angle. Instead, diminished visual acuity in the periphery causes reduced oculomotor control and results in increased fixation instability.

PMID: 24937090 [PubMed - in process]

Pathogenesis

Dan Med J. 2014 Jun;61(6):B4872.

Systemic changes in neovascular age-related macular degeneration.

Singh A.

Abstract: Age-related macular degeneration (AMD) is a leading cause of visual impairment in the aged population worldwide. The mechanisms underlying this multifactorial and heterogenic disease are complex and incompletely understood. There is increasing evidence to suggest that regulatory differences in the immune system are involved in the development of the various subtypes of AMD. The purpose of this thesis

was to identify some of these potential differences in patients with early or late (wet, dry, or fibrotic) AMD. Specifically, we sought to determine differences in 1) expression of regulators of the complement pathway (CD46, CD55, and CD59) on circulating leukocytes; 2) expression of microglia-inhibitory proteins (CD200 and CD200R) on circulating leukocytes; and 3) plasma concentrations of 25-hydroxyvitamin D, a factor known to inhibit angiogenesis, fibrosis, inflammation, and oxidation. All participants underwent a semi-structured interview and detailed retinal imaging. Fresh venous blood was obtained and the frequency of cells expressing the proteins in question was determined using flow cytometry. Plasma 25-hydroxyvitamin D was measured using liquid chromatography-tandem mass spectrometry. Also, genotyping as performed in order to determine the frequency of certain single-nucleotide polymorphisms in the vitamin D metabolism. Patients with wet AMD were found to have statistically significant lower frequencies of CD46 and CD59 on CD14+monocytes and higher frequencies of CD200 on CD11b+ monocytes compared to control individuals without AMD ($p = 0.0070$ and $p = 0.047$, respectively). Moreover, we found a lower frequency of CD46 on CD45+lymphocytes in patients with wet AMD and subretinal fibrosis compared to patients with wet AMD without fibrosis ($p = 0.010$). Vitamin D status was not different across AMD subgroups; however, the presence of subretinal fibrosis in patients with wet AMD was associated with a statistically significant lower concentration of 25-hydroxyvitamin D ($p < 0.001$). Our results suggest that inadequate systemic immune modulation is an important pathogenic mechanism in the aetiology of AMD. Moreover, some differences in protein expression and vitamin D status appear to be related to the phenotypical diversity of AMD, proposing that different mechanisms may underlie the different subtypes of AMD.

PMID: 24947635 [PubMed - in process]

J Huazhong Univ Sci Technolog Med Sci. 2014 Jun;34(3):408-14. doi: 10.1007/s11596-014-1292-2. Epub 2014 Jun 18.

Effect of Methyl-CpG binding domain protein 2 (MBD2) on AMD-like lesions in ApoE-deficient mice.

Pan JR, Wang C, Yu QL, Zhang S, Li B, Hu J.

Abstract: The role of methyl-CpG binding domain protein 2 (MBD2) in an ApoE-deficient mouse model of age-related macular degeneration (AMD) was investigated. Eight-week-old Mbd2/ApoE double deficient (Mbd2(-/-) ApoE(-/-)) mice (n=12, 24 eyes, experimental group) and MBD2 (wt) ApoE(-/-) mice (n=12, 24 eyes, control group) were fed on Western-type diet for 4 months. The mice were sacrificed, and total serum cholesterol levels were analyzed and Bruch's membrane (BM) of the eyes was removed for ultrastructural observation by transmission electron microscopy. Moreover, intercellular adhesion molecule 1 (ICAM-1) immunoreactivities were evaluated by fluorescence microscopy in sections of the eyes in both groups for further understanding the function mechanism of MBD2. There was no significant difference in the total serum cholesterol levels between control group and experimental group ($P>0.05$). Transmission electron microscopy revealed that AMD-like lesions, various vacuoles accumulated on BM, notable outer collagenous layer deposits and dilated basal infoldings of retinal pigment epithelium (RPE) were seen in both groups, and the BM in control group was significantly thickened as compared with experimental group ($P<0.05$). Fluorescence micrographs exhibited the expression of ICAM-1 in choroid was higher in control group than in experimental group. We are led to conclude that MBD2 gene knockout may lead to accumulation of more deposits on the BM and influence the pathogenesis of AMD via triggering endothelial activation and inflammatory response in choroid, improving microcirculation, and reducing lipid deposition so as to inhibit the development of AMD-like lesions. Our study helps to provide a new therapeutic approach for the clinical treatment of AMD.

PMID: 24939308 [PubMed - in process]

Med Sci Monit. 2014 Jun 18;20:1003-16. doi: 10.12659/MSM.889887.

Age-related macular degeneration and changes in the extracellular matrix.

Nita M, Strzałka-Mrozik B, Grzybowski A, Mazurek U, Romaniuk W.

Abstract: Age-related macular degeneration (AMD) is the leading cause of permanent, irreversible, central blindness (scotoma in the central visual field that makes reading and writing impossible, stereoscopic vision, recognition of colors and details) in patients over the age of 50 years in European and North America countries, and an important role is attributed to disorders in the regulation of the extracellular matrix (ECM). The main aim of this article is to present the crucial processes that occur on the level of Bruch's membrane, with special consideration of the metalloproteinase substrates, metalloproteinase, and tissue inhibitor of metalloproteinase (TIMP). A comprehensive review of the literature was performed through MEDLINE and PubMed searches, covering the years 2005-2012, using the following keywords: AMD, extracellular matrix, metalloproteinases, tissue inhibitors of metalloproteinases, Bruch's membrane, collagen, elastin. In the pathogenesis of AMD, a significant role is played by collagen type I and type IV; elastin; fibulin-3, -5, and -6; matrix metalloproteinase (MMP)-2, MMP-9, MMP-14, and MMP-1; and TIMP-3. Other important mechanisms include: ARMS2 and HTR1 proteins, the complement system, the urokinase plasminogen activator system, and pro-renin receptor activation. Continuous rebuilding of the extracellular matrix occurs in both early and advanced AMD, simultaneously with the dysfunction of retinal pigment epithelium (RPE) cells and endothelial cells. The pathological degradation or accumulation of ECM structural components are caused by impairment or hyperactivity of specific MMPs/TIMPs complexes, and is also endangered by the influence of other mechanisms connected with both genetic and environmental factors.

PMID: 24938626 [PubMed - in process]

Prog Retin Eye Res. 2014 Jun 14. pii: S1350-9462(14)00036-6. doi: 10.1016/j.preteyeres.2014.06.001. [Epub ahead of print]

The β-adrenergic system as a possible new target for pharmacologic treatment of neovascular retinal diseases.

Casini G, Dal Monte M, Fornaciari I, Filippi L, Bagnoli P.

Abstract: Retinal neovascular pathologies, such as diabetic retinopathy, retinopathy of prematurity (ROP) and age-related macular degeneration, may be treated with intravitreal injections of drugs targeting vascular endothelial growth factor (VEGF), the main inducer of neoangiogenesis; however further improvements and alternative strategies are needed. In the last few years, an intense research activity has focused on the β-adrenergic system. The results indicate that, in different experimental models, a decrease of the β-adrenergic function may result either in reduction or in exacerbation of the vascular changes, thus suggesting possible dual effects of β-adrenoreceptor (β-AR) modulation depending on the experimental setting. In in vivo models of proliferative retinopathies, most of the data point to a strong inhibitory role against vascular changes exerted by the blockade of specific β-ARs. In particular, the β2-AR seems to be the mostly involved in these responses, and the β1-/β2-AR blocker propranolol results highly effective in inhibiting both the increase of VEGF expression caused by a hypoxic insult and the consequent neovascular response. These observations have prompted clinical trials in preterm infants with ROP, where oral administrations of propranolol produced positive results in terms of efficacy, although safety problems were also reported. In addition, the possibility of using topical propranolol administrations in the form of eye drops opens new potential routes of drug administration in humans. A further point that should be considered is that there are data demonstrating significant antiapoptotic effects exerted by β-ARs, therefore if β-AR blockers were used to inhibit aberrant neovascularization, there may be a burden to pay in terms of impaired neuronal viability.

PMID: 24933041 [PubMed - as supplied by publisher]

Neurobiol Aging. 2014 May 15. pii: S0197-4580(14)00361-3. doi: 10.1016/j.neurobiolaging.2014.05.012. [Epub ahead of print]

Death by color: differential cone loss in the aging mouse retina.

Cunea A, Powner MB, Jeffery G.

Abstract: Differential cell death is a common feature of aging and age-related disease. In the retina, 30% of rod photoreceptors are lost over life in humans and rodents. However, studies have failed to show age-related cell death in mouse cone photoreceptors, which is surprising because cone physiological function declines with age. Moreover in human, differential loss of short wavelength cone function is an aspect of age-related retinal disease. Here, cones are examined in young (3-month-old) and aged (12-month-old) C57 mice and also in complement factor H knock out mice (CFH-/-) that have been proposed as a murine model of age-related macular degeneration. In vivo imaging showed significant age-related reductions in outer retinal thickness in both groups over this period. Immunostaining for opsins revealed a specific significant decline of >20% for the medium/long (M/L)-wavelength cones but only in the periphery. S cones numbers were not significantly affected by age. This differential cell loss was backed up with quantitative real-time polymerase chain reaction for the 2 opsins, again showing S opsin was unaffected, but that M/L opsin was reduced particularly in CFH-/- mice. These results demonstrate aged cone loss, but surprisingly, in both genotypes, it is only significant in the peripheral ventral retina and focused on the M/L population and not S cones. We speculate that there may be fundamental differences in differential cone loss between human and mouse that may question the validity of mouse models of human outer retinal aging and pathology.

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Epidemiology

Aging Ment Health. 2014 Jun 19:1-8. [Epub ahead of print]

Predictors of psychological distress in caregivers of older persons with wet age-related macular degeneration.

Gopinath B, Kifley A, Cummins R, Heraghty J, Mitchell P.

Objectives: Several studies have investigated the biopsychosocial impacts of age-related macular degeneration (AMD) in regards to the older patient; little is known about the impacts associated with caring for individuals with AMD. We aimed to determine the predictors of subjective caregiver distress and other negative outcomes associated with caring for someone with advanced AMD.

Methods: Cross-sectional, self-complete survey involving 500 caregivers of persons with advanced AMD. Respondents were identified from the Macular Disease Foundation of Australia client database. Logistic regression tested the independent effects of care recipient and caregiver characteristics on study outcomes, including: caregiver psychological well-being, participation in recreational/social activities and retirement plans.

Results: Around one third of caregivers self-reported a high level of care recipient dependence. Over one in two caregivers reported a negative state of mind. Comorbid chronic illnesses in the care recipient were associated with the caregiver reporting psychological distress, multivariable-adjusted odds ratio, OR, 1.45 (95% confidence intervals, CI, 1.14-1.86). If the care recipient was highly dependent on the caregiver, there was 99% greater likelihood of caregiver distress, OR 1.99 (95% CI 1.01-3.93). Comorbid chronic conditions in the care recipient was associated with 49% and 31% higher odds of the caregiver reporting disruption to other areas of their life and retirement plans related to the caregiving experience, respectively.

Conclusions: A high prevalence of caregiver distress related to caring for persons with advanced AMD was

observed. Level of dependence on the caregiver and presence of comorbid chronic illnesses were independent predictors of the caregiver experiencing psychological distress.

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Ophthalmic Epidemiol. 2014 Jun 19:1-6. [Epub ahead of print]

Retinal Vascular Caliber and Age-related Macular Degeneration in an Indian Population from Singapore.

Chin YC, Wong TY, Cheung CM, Cheung CY, Zheng Y, Mitchell P, Huang H, Wang JJ, Ikram MK.

Purpose: To examine the association between retinal vascular caliber and early age-related macular degeneration (AMD) in an Indian population.

Methods: A total of 3112 Indian participants aged ≥40 years from the population-based Singapore Indian Eye Study who had data available on retinal vascular caliber measurements and AMD status were included. Retinal arteriolar and venular calibers were measured from digital photographs using computer-assisted software according to a standardized protocol. Images of the macular region were graded according to the modified Wisconsin age-related maculopathy grading system. Right eyes were selected for analyses. Binary logistic regression models were used to assess the association, adjusting for age, sex, systolic blood pressure, total cholesterol, random blood glucose, body mass index, and the companion retinal vascular caliber.

Results: A total of 107 participants (3.4%) were diagnosed with early AMD. Neither arteriolar nor venular caliber was related to AMD. For early AMD, the age-, sex-, and companion retinal vascular caliber-adjusted odds ratio (OR) per standard deviation (SD) decrease in arteriolar caliber was 0.95 (95% CI 0.84-1.31; p = 0.671), and per SD increase in venular caliber was OR: 0.96 (95% CI: 0.77-1.20); p = 0.714. No trend was found after categorizing retinal vascular calibers into quartiles. Multivariate adjustment and stratified analyses did not alter these results.

Conclusion: Retinal vascular calibers were not related to early AMD among Indian participants. These findings differ from those of several previous studies performed in Caucasian and Asian populations.

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Retina. 2014 Jun 14. [Epub ahead of print]

FIBROVASCULAR PIGMENT EPITHELIAL DETACHMENT IS A RISK FACTOR FOR LONG-TERM VISUAL DECAY IN NEOVASCULAR AGE-RELATED MACULAR DEGENERETION.

Hoerster R, Muether PS, Sitnilska V, Kirchhof B, Fauser S.

BACKGROUND: The individual outcome of anti-vascular endothelial growth factor treatment in neovascular age-related macular degeneration is variable. To investigate the prognostic value of spectral domain optical coherence tomography structures for best-corrected visual acuity (BCVA) outcome, volumetric analysis of spectral domain optical coherence tomography structures was performed in neovascular age-related macular degeneration correlated with BCVA after 24 months.

METHODS: At the Department of Ophthalmology, University of Cologne, Germany, 75 patients with neovascular age-related macular degeneration were analyzed prospectively over 24 months. Patients received three initial consecutive monthly intravitreal ranibizumab injections followed by monthly spectral domain optical coherence tomography controls. Therapy was continued as a pro re nata regimen. Volumetric analysis of spectral domain optical coherence tomography images was performed using commercially available software (3D-Doctor).

RESULTS: Subretinal tissue, subretinal fluid, serous pigment epithelial detachment, and fibrovascular pigment epithelial detachment (FPED) were identified. By contrast to all other structures, FPED did not respond to ranibizumab therapy. Volume of FPED at baseline and after the loading phase correlated most with impaired BCVA after 24 months (r = -0.0215, P = 0.9263 [subretinal tissue]; r = -0.3120, P = 0.0216 [subretinal fluid]; r = -0.0757, P = 0.6470 [serous pigment epithelial detachment]; r = -0.4182, P = 0.0111 (FPED baseline); r = -0.4768; P = 0.0002 [FPED after loading phase]).

CONCLUSION: Of all identified structures, FPED was most deleterious for BCVA after 24 months. The knowledge about possible BCVA course can influence the decision for more intense treatment regimens.

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Genetics

PLoS One. 2014 Jun 20;9(6):e100322. doi: 10.1371/journal.pone.0100322. eCollection 2014.

Integrating EMR-Linked and In Vivo Functional Genetic Data to Identify New Genotype-Phenotype Associations.

Mosley JD, Van Driest SL, Weeke PE, Delaney JT, Wells QS, Bastarache L, Roden DM, Denny JC.

Abstract: The coupling of electronic medical records (EMR) with genetic data has created the potential for implementing reverse genetic approaches in humans, whereby the function of a gene is inferred from the shared pattern of morbidity among homozygotes of a genetic variant. We explored the feasibility of this approach to identify phenotypes associated with low frequency variants using Vanderbilt's EMR-based BioVU resource. We analyzed 1,658 low frequency non-synonymous SNPs (nsSNPs) with a minor allele frequency (MAF)<10% collected on 8,546 subjects. For each nsSNP, we identified diagnoses shared by at least 2 minor allele homozygotes and with an association p<0.05. The diagnoses were reviewed by a clinician to ascertain whether they may share a common mechanistic basis. While a number of biologically compelling clinical patterns of association were observed, the frequency of these associations was identical to that observed using genotype-permuted data sets, indicating that the associations were likely due to chance. To refine our analysis associations, we then restricted the analysis to 711 nsSNPs in genes with phenotypes in the On-line Mendelian Inheritance in Man (OMIM) or knock-out mouse phenotype databases. An initial comparison of the EMR diagnoses to the known in vivo functions of the gene identified 25 candidate nsSNPs, 19 of which had significant genotype-phenotype associations when tested using matched controls. Twleve of the 19 nsSNPs associations were confirmed by a detailed record review. Four of 12 nsSNP-phenotype associations were successfully replicated in an independent data set: thrombosis (F5,rs6031), seizures/convulsions (GPR98,rs13157270), macular degeneration (CNGB3,rs3735972), and GI bleeding (HGFAC,rs16844401). These analyses demonstrate the feasibility and challenges of using reverse genetics approaches to identify novel gene-phenotype associations in human subjects using low frequency variants. As increasing amounts of rare variant data are generated from modern genotyping and sequence platforms, model organism data may be an important tool to enable discovery.

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Diet & lifestyle

Optom Vis Sci. 2014 Jun 19. [Epub ahead of print]

Nutrition and Age-Related Macular Degeneration: Research Evidence in Practice.

Downie LE, Keller PR.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment in

developed countries. In the absence of effective treatments to slow AMD progression, it is predicted that the prevalence of AMD will double over the next 20 years. One area of significant interest is the potential role that nutrition may play in preventing and/or delaying the progression of AMD. Specifically, is there any benefit in oral antioxidant and/or mineral supplementation? This review critically evaluates the currently available evidence relating to nutrition and AMD, with particular reference to the key findings of two large National Eye Institute-sponsored clinical studies, namely, the Age-Related Eye Disease Study (AREDS) and AREDS2. Topical controversies relating to nutrition and AMD are considered and analyzed in the context of the published literature to guide practitioners through assessing the merit, or otherwise, of common claims. This article provides a foundation for clinicians to provide informed advice to AMD patients based on available research evidence.

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VITAMIN D DEFICIENCY IN NEOVASCULAR VERSUS NONNEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Itty S, Day S, Lyles KW, Stinnett SS, Vajzovic LM, Mruthyunjaya P.

PURPOSE: To compare 25-hydroxyvitamin D (25OHD) levels in patients with neovascular age-related macular degeneration (NVAMD) with patients with nonneovascular age-related macular degeneration and control patients.

METHODS: Medical records of all patients diagnosed with age-related macular degeneration and tested for serum 25OHD level at a single medical center were reviewed. Control patients were selected from patients diagnosed with pseudophakia but without age-related macular degeneration. The lowest 25OHD level available for each patient was recorded.

RESULTS: Two hundred sixteen patients with nonneovascular age-related macular degeneration, 146 with NVAMD, and 100 non-age-related macular degeneration control patients were included. The levels of 25OHD (mean ± SD) were significantly lower in NVAMD patients (26.1 ± 14.4 ng/mL) versus nonneovascular age-related macular degeneration (31.5 ± 18.2 ng/mL, P = 0.003) and control (29.4 ± 10.1 ng/mL, P = 0.049) patients. The prevalence of vitamin D insufficiency (<30 ng/mL 25OHD), deficiency (<20 ng/mL), and severe deficiency (<10 ng/mL) were highest in the NVAMD group. The highest quintile of 25OHD was associated with a 0.35 (95% confidence interval, 0.18-0.68) odds ratio for NVAMD.

CONCLUSION: This is the largest study to compare 25OHD levels in patients with the different clinical forms of age-related macular degeneration. Mean 25OHD levels were lower and vitamin D deficiency was more prevalent in NVAMD patients. These associations suggest that further research is necessary regarding vitamin D deficiency as a potentially modifiable risk factor for the development of NVAMD.

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Efficacy of multivitamin/mineral supplementation to reduce chronic disease risk: a critical review of the evidence from observational studies and randomized controlled trials.

Angelo G, Drake VJ, Frei B.

Abstract: We reviewed recent scientific evidence regarding the effects of MVM supplements on risk of chronic diseases, including cancer, cardiovascular disease, and age-related eye diseases. Data from randomized controlled trials (RCTs) and observational, prospective cohort studies were examined. The

majority of scientific studies investigating the use of MVM supplements in chronic disease risk reduction reported no significant effect. However, the largest and longest RCT of MVM supplements conducted to date, the Physicians' Health Study II (PHS II), found a modest and significant reduction in total and epithelial cancer incidence in male physicians, consistent with the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) trial. In addition, PHS II found a modest and significant reduction in the incidence of nuclear cataract, in agreement with several other RCTs and observational, prospective cohort studies. The effects of MVM use on other subtypes of cataract and age-related macular degeneration remain unclear. Neither RCTs nor prospective cohort studies are without their limitations. The placebo-controlled trial design of RCTs may be inadequate for nutrient interventions, and residual confounding, measurement error, and the possibility of reverse causality are inherent to any observational study. National surveys show that micronutrient inadequacies are widespread in the US and that dietary supplements, of which MVMs are the most common type, help fulfill micronutrient requirements in adults and children.

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Vision for improvement: Expressive writing as an intervention for people with Stargardt's disease, a rare eye disease.

Bryan JL, Lu Q.

Abstract: This study implemented and evaluated the effectiveness of an expressive writing intervention among patients with Stargardt's disease, a rare disease due to macular degeneration. Participants were randomly assigned to either an expressive writing intervention or a neutral writing condition. Participants completed measures at three time points: baseline, 3 weeks, and 6 weeks post-intervention. Psychological health outcomes improved at the 3-week follow-up for the intervention condition compared to control. Self-reported physical health improved at the 6-week follow-up in the intervention condition compared to control. These results suggest that expressive writing may be an effective, practical, and low-cost intervention for those with Stargardt's disease.

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