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MD Research News

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Drug treatment

J Control Release. 2016 Oct 31. [Epub ahead of print]

Single ocular injection of a sustained-release anti-VEGF delivers 6months pharmacokinetics and efficacy in a primate laser CNV model.

Adamson P, Wilde T, Dobrzynski E, ey al

Abstract: A potent anti-vascular endothelial growth factor (VEGF) biologic and a compatible delivery system were co-evaluated for protection against wet age-related macular degeneration (AMD) over a 6month period following a single intravitreal (IVT) injection. The anti-VEGF molecule is dimeric, containing two different anti-VEGF domain antibodies (dAb) attached to a human IgG1 Fc region: a dual dAb. The delivery system is based on microparticles of PolyActive™ hydrogel co-polymer. The molecule was evaluated both in vitro for potency against VEGF and in ocular VEGF-driven efficacy models in vivo. The dual dAb is highly potent, showing a lower IC50 than aflibercept in VEGF receptor binding assays (RBAs) and retaining activity upon release from microparticles over 12months in vitro. Microparticles released functional dual dAb in rabbit and primate eyes over 6months at sufficient levels to protect Cynomolgus against laser-induced grade IV choroidal neovascularisation (CNV). This demonstrates proof of concept for delivery of an anti-VEGF molecule within a sustained-release system, showing protection in a pre-clinical primate model of wet AMD over 6 months. Polymer breakdown and movement of microparticles in the eye may limit development of particle-based approaches for sustained release after IVT injection.

PMID: 27810558

Int Ophthalmol. 2016 Nov 8. [Epub ahead of print]

A comparison of responses to intravitreal bevacizumab, ranibizumab, or aflibercept injections for neovascular age-related macular degeneration.

Park DH, Sun HJ, Lee SJ.

PURPOSE: To compare the responses of intravitreal injections of bevacizumab, ranibizumab, or aflibercept for the treatment of neovascular age-related macular degeneration (nAMD).

METHODS: This retrospective study examined 232 eyes of 232 patients who received intravitreal anti-vascular endothelial growth factor (VEGF) injections due to treatment-naïve nAMD. All patients, who were followed-up for at least 1 year, were treated with intravitreal injections monthly until 3 months, and then as needed. We evaluated the effects of intravitreal injections for treatment of nAMD using the central macular thickness (CMT), subretinal fluid (SRF), pigment epithelial detachment (PED) size, and best-corrected visual acuity (BCVA).

RESULTS: CMT, SRF, PED size, and BCVA (LogMAR) were significantly decreased after treatment with all

three anti-VEGF agents. Overall, the bevacizumab, ranibizumab, and aflibercept treatments showed no significant differences in their responses. However, the aflibercept injections decreased PED size more quickly than bevacizumab injections (P = 0.034).

CONCLUSIONS: Bevacizumab, ranibizumab, and aflibercept injections are effective treatments for nAMD and have similar responses, although the number of injections of aflibercept was fewer than other anti-VEGF agents. In addition, aflibercept injections may be a better choice than other anti-VEGF agents for cases of severe increases in PED height.

PMID: 27826933

Arch Soc Esp Oftalmol. 2016 Nov 2. [Epub ahead of print]

Treat-and-extend approach with aflibercept: Effects on different subtypes of age-related choroidal neovascularisation. [Article in English, Spanish]

Castro-Navarro V, Cervera-Taulet E, Montero-Hernández J, Navarro-Palop C.

OBJECTIVE: To describe functional/morphological outcomes of treat-and-extend (TAE) with aflibercept in different subtypes of neovascularizations (CNV) secondary to exudative age-related macular degeneration (AMD).

METHODS: Retrospective study was conducted on 30 eyes of 30 patients treated with 2 mg-aflibercept according to a TAE protocol. Examinations included best corrected visual acuity (BCVA), number of injections, and visits needed. A quantitative/qualitative analysis was also performed with fluorescein angiography and spectral-domain optical coherence tomography (SD-OCT) at baseline, and at 3, 6, and 12 months.

RESULTS: BCVA significantly improved from 0.61±0.26 logMAR to 0.38±0.34 logMAR. Among the total AMD patients, type 1 CNV was diagnosed in 11 eyes (36%), type 2 CNV in 7 eyes (23%), mixed CNV in 5 eyes (16%), and type 3 CNV or retinal angiomatous proliferation (RAP) in 7 eyes (23%). The final mean number of injections was 7.5±1.65, 8.71±0.76, 7.4±0.89, 7.2±0.7, and number of visits 6.6±2.17, 7.89±1.46, 5.8±1.7, and 7.14±1.57, respectively in type 1, type 2, mixed, and type 3 or RAP. There was no difference between the different subtypes of CNV (P>.05).

CONCLUSIONS: Aflibercept in TAE is effective for all exudative-AMD subtypes. No significant differences in patient's visual gain, mean number of injections, or number of visits needed were found among the subtypes of CNV.

PMID: 27816486

BMJ Open. 2016 Oct 24;6(10):e011121.

Cost-effectiveness of community versus hospital eye service follow-up for patients with quiescent treated age-related macular degeneration alongside the ECHoES randomised trial.

Violato M, Dakin H, Chakravarthy U, Reeves BC, Peto T, Hogg RE, Harding SP, Scott LJ, Taylor J, Cappel-Porter H, Mills N, O'Reilly D, Rogers CA, Wordsworth S.

OBJECTIVES: To assess the cost-effectiveness of optometrist-led follow-up monitoring reviews for patients with quiescent neovascular age-related macular degeneration (nAMD) in community settings (including high street opticians) compared with ophthalmologist-led reviews in hospitals.

DESIGN: A model-based cost-effectiveness analysis with a 4-week time horizon, based on a 'virtual' non-inferiority randomised trial designed to emulate a parallel group design.

SETTING: A virtual internet-based clinical assessment, conducted at community optometry practices, and

hospital ophthalmology clinics.

PARTICIPANTS: Ophthalmologists with experience in the age-related macular degeneration service; fully qualified optometrists not participating in nAMD shared care schemes.

INTERVENTIONS: The participating optometrists and ophthalmologists classified lesions from vignettes and were asked to judge whether any retreatment was required. Vignettes comprised clinical information, colour fundus photographs and optical coherence tomography images. Participants' classifications were validated against experts' classifications (reference standard). Resource use and cost information were attributed to these retreatment decisions.

MAIN OUTCOME MEASURES: Correct classification of whether further treatment is needed, compared with a reference standard.

RESULTS: The mean cost per assessment, including the subsequent care pathway, was £411 for optometrists and £397 for ophthalmologists: a cost difference of £13 (95% CI -£18 to £45). Optometrists were non-inferior to ophthalmologists with respect to the overall percentage of lesions correctly assessed (difference -1.0%; 95% CI -4.5% to 2.5%).

CONCLUSIONS: In the base case analysis, the slightly larger number of incorrect retreatment decisions by optometrists led to marginally and non-significantly higher costs. Sensitivity analyses that reflected different practices across eye hospitals indicate that shared care pathways between optometrists and ophthalmologists can be identified which may reduce demands on scant hospital resources, although in light of the uncertainty around differences in outcome and cost it remains unclear whether the differences between the 2 care pathways are significant in economic terms.

PMID: 27797985

Health Technol Assess. 2016 Oct;20(80):1-120.

The Effectiveness, cost-effectiveness and acceptability of Community versus Hospital Eye Service follow-up for patients with neovascular age-related macular degeneration with quiescent disease (ECHoES): a virtual randomised balanced incomplete block trial.

Reeves BC, Scott LJ, Taylor J, Hogg R2, et al

BACKGROUND: Patients with neovascular age-related macular degeneration (nAMD) usually attend regular reviews, even when the disease is quiescent. Reviews are burdensome to health services, patients and carers.

OBJECTIVES: To compare the proportion of correct lesion classifications made by community-based optometrists and ophthalmologists from vignettes of patients; to estimate the cost-effectiveness of community follow-up by optometrists compared with follow-up by ophthalmologists in the Hospital Eye Service (HES); to ascertain views of patients, their representatives, optometrists, ophthalmologists and clinical commissioners on the proposed shared care model.

DESIGN: Community-based optometrists and ophthalmologists in the HES classified lesions from vignettes comprising clinical information, colour fundus photographs and optical coherence tomography images. Participants' classifications were validated against experts' classifications (reference standard).

SETTING: Internet-based application.

PARTICIPANTS: Ophthalmologists had to have ≥ 3 years post-registration experience in ophthalmology, have passed part 1 of the Royal College of Ophthalmologists, Diploma in Ophthalmology or equivalent examination, and have experience in the age-related macular degeneration service. Optometrists had to be fully qualified, be registered with the General Optical Council for ≥ 3 years and not be participating in nAMD shared care.

INTERVENTIONS: The trial sought to emulate a conventional trial in comparing optometrists' and ophthalmologists' decision-making, but vignettes, not patients, were assessed; therefore, there were no interventions. Participants received training prior to assessing vignettes.

MAIN OUTCOME MEASURES: Primary outcome - correct classification of the activity status of a lesion based on a vignette, compared with a reference standard. Secondary outcomes - frequencies of potentially sight-threatening errors, participants' judgements about specific lesion components, participant-rated confidence in their decisions and cost-effectiveness of follow-up by community-based optometrists compared with HES ophthalmologists.

RESULTS: In total, 155 participants registered for the trial; 96 (48 in each professional group) completed training and main assessments and formed the analysis population. Optometrists and ophthalmologists achieved 1702 out of 2016 (84.4%) and 1722 out of 2016 (85.4%) correct classifications, respectively [odds ratio (OR) 0.91, 95% confidence interval (CI) 0.66 to 1.25; p = 0.543]. Optometrists' decision-making was non-inferior to ophthalmologists' with respect to the pre-specified limit of 10% absolute difference (0.298 on the odds scale). Frequencies of sight-threatening errors were similar for optometrists and ophthalmologists [57/994 (5.7%) vs. 62/994 (6.2%), OR 0.93, 95% CI 0.55 to 1.57; p = 0.789]. Ophthalmologists assessed lesion components as present less often than optometrists and were more confident about their lesion classifications than optometrists. The mean care-pathway cost for assessment was very similar by group, namely £397.33 for ophthalmologists and £410.78 for optometrists. The optometrist-led monitoring reviews were slightly more costly and less effective than ophthalmologist-led reviews, although the differences were extremely small. There was consensus that optometrist-led monitoring has the potential to reduce clinical workload and be more patient-centred. However, potential barriers are ophthalmologists' perceptions of optometrists' competence, the need for clinical training, the ability of the professions to work collaboratively and the financial feasibility of shared care for Clinical Commissioning Groups.

CONCLUSIONS: The ability of optometrists to make nAMD retreatment decisions from vignettes is non-inferior to that of ophthalmologists. Various barriers to implementing shared cared for nAMD were identified.

FUTURE WORK RECOMMENDATIONS: The Effectiveness, cost-effectiveness and acceptability of Community versus Hospital Eye Service follow-up for patients with neovascular age-related macular degeneration with quiescent disease (ECHoES) study web application was robust and could be used for future training or research. The benefit of reducing HES workload was not considered in the economic evaluation. A framework of programme budgeting and marginal analysis could explicitly explore the resource implications of shifting resources within a given health service area, as the benefit of reducing HES workload was not considered in the economic evaluation. Future qualitative research could investigate professional differences of opinion that were identified in multidisciplinary focus groups.

PMID: 27809956

Ophthalmologe. 2016 Nov 4. [Epub ahead of print]

[What can anti-VEGF therapy achieve in clinical routine? : Effectiveness of anti-VEGF therapy in patients with macular diseases in clinical routine on 1492 eyes in Austria]. [Article in German]

Wiesinger K, Reinelt P, Ennemoser A, Edelmayr M, Schönherr U.

BACKGROUND: The aim of this user observational study was to illustrate the effectiveness of intravitreal operative medication administration (IVOM) in the clinical routine.

DESIGN: A monocentric, single arm, prospective study.

MATERIAL AND METHODS: Included in this study were all patients in whom a macular edema was diagnosed during an ophthalmological examination at the Barmherzigen Brüdern Hospital in Linz from November 2012 to August 2014 and who were treated as outpatients or day clinic patients with IVOM using anti-vascular endothelial growth factor (VEGF). The parameters measured during the clinical routine were as follows: best corrected visual acuity (BCVA) using the early treatment diabetic retinopathy study

(ETDRS) chart, central optical coherence tomography (OCT) thickness, diagnosis and possible prior treatment with IVOM. Following diagnosis, the IVOM was administered in 6-week intervals and a final control with measurement of the named parameters (approximately 19 weeks after diagnosis). If edema was present a further 3-stage series (19 weeks) was initiated. In the case of a "dry" condition the further controls were performed by a private practitioner and the patient only presented again if macular edema reoccurred. A control of the patients with "dry" results at regular intervals was not planned.

RESULTS: A total of 1492 eyes from 1184 patients with an average age of 75.6 ± 11.3 years were included in the study according to the abovenamed criteria. Choroidal neovascularization (CNV) with age-related macular degeneration (AMD) was diagnosed in 879 eyes and 314 eyes were treated for diabetic macular edema (DME). Of the eyes 122 (8.2%) were affected by branch vein thrombosis (AVT) and 63 (4.2%) from central vein thrombosis (CVT). In 47 (3.2%) eyes macular edema with myopic CNV (mCNV) was detected and 67 eyes (4.5%) were not further classified under "others". In all groups a gain in letters could be achieved in the EDTRS chart even after the first IVOM series: AMD + 3.4, DME + 1.3, AVT + 6.1, CVT + 10.1 and mCNV + 7.0. Patients who were treated with IVOM for the first time showed on average a better response than those previously treated with IVOM.

CONCLUSION: As in many other studies our data also underline the necessity for intravitreal injections for treatment of macular edema. Even if a 6-week interval does not nowadays correspond to the current guidelines, we could achieve a stabilization of vision and do not shy away from comparison with large studies, such as the Marina study. In order to provide the increasing numbers of patients the best treatment in the future, an attempt at targeted implementation of resources must be made and if necessary symptoms which can be conservatively treated should be delegated to the private sector.

PMID: 27815675

Retina. 2016 Oct 27. [Epub ahead of print]

CLINICAL AND ELECTROPHYSIOLOGICAL EVALUATION AFTER INTRAVITREAL ZIV-AFLIBERCEPT FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

de Oliveira Dias JR, de Andrade GC, Kniggendorf VF, Novais EA, Maia A, Meyer C, Watanabe SE, Farah ME, Rodrigues EB.

PURPOSE: To evaluate the 6-month safety and efficacy of ziv-aflibercept intravitreal injections for treating exudative age-related macular degeneration.

METHODS: Fifteen patients with unilateral exudative age-related macular degeneration were enrolled. The best-corrected visual acuity was measured and spectral domain optical coherence tomography was performed at baseline and monthly. Full-field electroretinography and multifocal electroretinography were obtained at baseline and 4, 13, and 26 weeks after the first injection. All patients received three monthly intravitreal injections of ziv-aflibercept (1.25 mg) followed by as-needed treatment.

RESULTS: Between baseline and 26 weeks, the mean logMAR best-corrected visual acuity improved ($P = 0.00408$) from 0.93 ± 0.4 (20/200) to 0.82 ± 0.5 (20/160) logarithm of the minimum angle of resolution, respectively; the central retinal thickness decreased significantly ($P = 0.0007$) from 490.3 ± 155.1 microns to 327.9 ± 101.5 microns; the mean total macular volume decreased significantly ($P < 0.0001$) from 9.51 ± 1.36 mm to 8.08 ± 1.34 mm, and the a-wave implicit time increased, with no differences in the other full-field electroretinography parameters. The average multifocal electroretinography macular responses within the first central 15° showed significantly ($P < 0.05$) increased P1 amplitudes at 26 weeks. No systemic or ocular complications developed.

CONCLUSION: Intravitreal ziv-aflibercept significantly improved the best-corrected visual acuity, multifocal electroretinography amplitudes, central retinal thickness, and total macular volume from baseline to 26 weeks. No retinal toxicity on full-field electroretinography or adverse events occurred during the follow-up period.

PMID: 27798520

Case Rep Ophthalmol Med. 2016;2016:4164198. Epub 2016 Oct 9.

Successful Resolution of Preretinal Haemorrhage with Intravitreal Ranibizumab.

Noorlaila B, Zunaina E, Raja-Azmi MN.

Abstract: We would like to report two cases of preretinal haemorrhage from two different aetiology courses of bleeding being treated with intravitreal ranibizumab and its outcome. Our first case was a 39-year-old man with a diagnosis of severe aplastic anaemia that presented with bilateral premacular haemorrhages in both eyes. His right eye vision was 6/45 and it was counting finger in the left eye. He was treated with intravitreal ranibizumab once to the right eye and twice to the left eye. Right eye showed complete resolution of premacular haemorrhage and minimal residual premacular haemorrhage in the left eye at 3 months after initial presentation. Our second case was a 32-year-old healthy teacher that presented with preretinal haemorrhage at superotemporal region extending to macular area in left eye secondary to valsalva retinopathy. Her left vision was counting finger. She was treated with single intravitreal ranibizumab to the left eye. There was significant reduction of premacular haemorrhage and her left eye vision improved to 6/6 at 10 weeks after injection. Both cases had favourable outcome with intravitreal ranibizumab and can be considered as nonsurgical treatment option in treating premacular haemorrhage.

PMID: 27800200 PMCID: PMC5075305

Handb Exp Pharmacol. 2016 Nov 5. [Epub ahead of print]

Corticosteroids and Anti-Complement Therapy in Retinal Diseases.

Narayanan R, Kuppermann BD.

Abstract: Corticosteroids are unique in that they are the one class of agents that acts upon most of the multiple processes in the pathophysiology of macular edema. Corticosteroids are capable of inhibiting prostaglandin and leukotriene synthesis as well as interfering with intercellular adhesion molecule-1 (ICAM-1), interleukin-6, VEGF-A, and stromal cell derived factor-1 pathways. Triamcinolone, dexamethasone, and fluocinolone have been extensively used in the treatment of retinal and choroidal vascular diseases. Sustained release implants of steroids have reduced the burden of repeated intravitreal injections necessary in most of the retinal diseases. Complement factors play an important role in the pathogenesis of age-related macular degeneration (AMD). Inhibitors of complement could provide a breakthrough in the treatment of dry AMD. Complement factor inhibitors, such as POT-4, lampalizumab, and eculizumab, have been tested in clinical trials for dry AMD with promising results. However, results of phase 3 trials are awaited.

PMID: 27815789

Eye (Lond). 2016 Nov 4. [Epub ahead of print]

Aflibercept in diabetic macular edema: evaluating efficacy as a primary and secondary therapeutic option.

Călugăru D, Călugăru M.

PMID: 27813522

Eye (Lond). 2016 Nov 4. [Epub ahead of print]

Aflibercept in diabetic macular edema: evaluating efficacy as a primary and secondary therapeutic option.

Ashraf M, Souka A, Adelman R, Forster SH.

PMID: 27813521

Other treatment & diagnosis

Ophthalmol Eye Dis. 2016 Nov 1;8(Suppl 1):5-14. eCollection 2016.

A Historical Analysis of the Quest for the Origins of Aging Macula Disorder, the Tissues Involved, and Its Terminology.

de Jong PT.

Abstract: Although ocular tissues involved in aging macula disorder (AMD) were already known in 300 BC, the last type of photoreceptors was discovered only 10 years ago. The earliest descriptions of AMD appeared around 1850. It took over 150 years, till a clearer concept of AMD was formulated and even longer to grasp its pathophysiology. The uncertainty of researchers about the pathogenesis of AMD over the last century is reflected in its changing terminology. The evolution of this terminology is provided in a table to afford the reader a better insight into explanations proposed by researchers during this quest.

PMID: 27812291 PMCID: PMC5091095

Turk J Ophthalmol. 2016 Jan;46(1):30-37. Epub 2016 Jan 5.

The Choroid and Optical Coherence Tomography.

Sezer T, Altınışık M, Koytak İA, Özdemir MH.

Abstract: The choroid is the most vascular tissue in the eye and it plays an important role in the pathophysiology of various common chorioretinal diseases such as central serous retinopathy, age-related macular degeneration and degenerative myopia. Quantitative assessment of the choroid has been quite challenging with traditional imaging modalities such as indocyanine green angiography and ultrasonography due to limited resolution and repeatability. With the advent of optical coherence tomography (OCT) technology, detailed visualization of the choroid in vivo is now possible. Measurements of choroidal thickness have also enabled new directions in research to study normal and pathological processes within the choroid. The aim of the present study is to review the current literature on choroidal imaging using OCT.

PMID: 27800255 PMCID: PMC5076307

Turk J Ophthalmol. 2015 Dec;45(6):235-238. Epub 2015 Dec 5.

Analysing the Progression Rates of Macular Lesions with Autofluorescence Imaging Modes in Dry Age-Related Macular Degeneration.

Olcay K, Çakır A, Sönmez M, Düzgün E, Yıldırım Y.

OBJECTIVES: In this study we aimed to compare the sensitivity of blue-light fundus autofluorescence (FAF) and near-infrared autofluorescence (NI-AF) imaging for determining the progression rates of macular lesions in dry age-related macular degeneration (AMD).

MATERIALS AND METHODS: The study was designed retrospectively and included patients diagnosed with intermediate and advanced stage dry AMD. Best corrected visual acuities and FAF and NI-AF images were recorded in 46 eyes of 33 patients. Lesion borders were drawn manually on the images using Heidelberg Eye Explorer software and lesion areas were calculated using Microsoft Excel software. BCVA and lesion areas were compared with each other.

RESULTS: Patients' mean follow-up time was 30.98±13.30 months. The lesion area progression rates were 0.85±0.93 mm2/y in FAF and 0.93±1.01 mm2/y in NI-AF, showing statistically significant correlation with each other ($r=0.883$; $p<0.01$). Both imaging methods are moderately correlated with visual acuity impairment ($r=0.362$; $p<0.05$ and $r=0.311$; $p<0.05$, respectively). In addition, larger lesions showed higher progression rates than smaller ones in both imaging methods.

CONCLUSION: NI-AF imaging is as important and effective as FAF imaging for follow-up of dry AMD patients.

PMID: 27800240 PMCID: PMC5082260

Comput Struct Biotechnol J. 2016 Oct 6;14:371-384. eCollection 2016.

A review on automatic analysis techniques for color fundus photographs.

Besenczi R, Tóth J, Hajdu A.

Abstract: In this paper, we give a review on automatic image processing tools to recognize diseases causing specific distortions in the human retina. After a brief summary of the biology of the retina, we give an overview of the types of lesions that may appear as biomarkers of both eye and non-eye diseases. We present several state-of-the-art procedures to extract the anatomic components and lesions in color fundus photographs and decision support methods to help clinical diagnosis. We list publicly available databases and appropriate measurement techniques to compare quantitatively the performance of these approaches. Furthermore, we discuss on how the performance of image processing-based systems can be improved by fusing the output of individual detector algorithms. Retinal image analysis using mobile phones is also addressed as an expected future trend in this field.

PMID: 27800125 PMCID: PMC5072151

Drug Des Devel Ther. 2016 Oct 19;10:3415-3423. eCollection 2016.

Preliminary in vitro and in vivo assessment of a new targeted inhibitor for choroidal neovascularization in age-related macular degeneration.

Li W, Dong L, Ma M, Hu B, Lu Z, Liu X, Liu J, Li X.

Abstract: Choroidal neovascularization (CNV) in age-related macular degeneration usually causes blindness. We established a novel targeted inhibitor for CNV in age-related macular degeneration. The inhibitor CR2-sFlt 1 comprises a CR2-targeting fragment and an anti-vascular endothelial growth factor (VEGF) domain (sFlt 1). The targeting of CR2-sFlt 1 was studied using the transwell assay in vitro and frozen sections in vivo using green fluorescent labeling. Transwell assay results showed that CR2-sFlt 1 migrated to the interface of complement activation products and was present in the retinal tissue of the CR2 -sFlt 1-treated CNV mice. Treatment effects were assessed by investigating the VEGF concentration in retinal pigmented epithelial cell medium and the thickness of the CNV complex in the mice treated with CR2 -sFlt 1. CR2-sFlt 1 significantly reduced the VEGF secretion from retinal pigmented epithelial cells in vitro and retarded CNV progress in a mouse model. Expression analysis of VEGF and VEGFRs after CR2-sFlt 1 intervention indicated the existence of feedback mechanisms in exogenous CR2-sFlt 1, endogenous VEGF, and VEGFR interaction. In summary, we demonstrated for the first time that using CR2-sFlt 1 could inhibit CNV with clear targeting and high selectivity.

PMID: 27799741 PMCID: PMC5076800

Am J Ophthalmol. 2016 Oct 26. [Epub ahead of print]

Choriocapillaris Non-Perfusion is Associated with Poor Visual Acuity in Eyes with Reticular Pseudodrusen.

Nesper PL, Soetikno BT, Fawzi AA.

PURPOSE: To study choriocapillaris blood flow in age-related macular degeneration (AMD) using optical coherence tomography angiography (OCTA) and study its correlation to vision (VA) in eyes with reticular pseudodrusen (RPD) versus those with drusen without RPD (drusen).

DESIGN: Cross-sectional study METHODS: Patients with either drusen or RPD in early AMD underwent OCTA imaging of the superior, inferior, and/or nasal macula. We quantified "percent choriocapillaris area of non-perfusion" (PCAN) in eyes with RPD versus those with drusen. We assessed the repeatability of PCAN and its correlations with VA.

RESULTS: Twenty-nine eyes of 26 patients with RPD and 21 eyes of 16 age-matched AMD patients with drusen were included. Qualitatively, the choriocapillaris in areas with RPD showed focal dark regions without flow signal on OCTA (non-perfusion). The repeatability coefficient of PCAN was 0.49%. Eyes with RPD had significantly greater PCAN compared to eyes with drusen (7.31% and 3.88%, respectively; $P < 0.001$). We found a significant correlation between PCAN and VA for the entire dataset ($r = 0.394$, $P = 0.005$). When considering eyes with RPD separately, this correlation was stronger ($r = 0.474$, $P = 0.009$) but lost significance when considering eyes with drusen separately ($r = 0.175$, $P = 0.45$).

CONCLUSIONS: Eyes with RPD have significantly larger areas of choriocapillaris non-perfusion compared to eyes with drusen and no RPD. The correlation between PCAN and VA in this RPD population provides a potential mechanistic explanation for vision compromise in RPD compared to other forms of drusen in AMD.

PMID: 27794427

Pathogenesis

Biochem Biophys Res Commun. 2016 Oct 31. [Epub ahead of print]

Lack of the P2X7 receptor protects against AMD-like defects and microparticle accumulation in a chronic oxidative stress-induced mouse model of AMD.

Carver KA, Lin CM, Bowes Rickman C, Yang D.

Abstract: The P2X7 receptor (P2X7R) is an ATP-gated ion channel that is a key player in oxidative stress under pathological conditions. The P2X7R is expressed in the retinal pigmented epithelium (RPE) and neural retina. Chronic oxidative stress contributes to the pathogenesis of age-related macular degeneration (AMD). Mice lacking Cu, Zn superoxide dismutase (Sod1) developed chronic oxidative stress as well as AMD-like features, but whether the P2X7R plays a causative role in oxidative stress-induced AMD is unknown. Thus, the main purpose of this study was to test if concurrent knockout (KO) of P2X7R could block AMD-like defects seen in Sod1 KO mice. Using multiple approaches, we demonstrate that Sod1 KO causes AMD-like defects, including positive staining for oxidative stress markers, 3-nitrotyrosine and carboxymethyl lysine, thinning of the RPE and retina, thickening of Bruch's membrane, presence of basal laminar and linear deposits, RPE barrier disruption and accumulation of microglia/macrophages. Moreover, we find that Sod1 KO mice accumulate more microparticles (MPs) within RPE/choroid tissues. Concurrent KO of the P2X7R protects against AMD-like defects and MP accumulation in Sod1 KO mice. Together, we show for the first time, that deficiency of P2X7R prevents in vivo oxidative stress-induced accumulation of MPs and AMD-like defects. This work could potentially lead to novel therapies for AMD and other oxidative stress-driven diseases.

PMID: 27810364

Graefes Arch Clin Exp Ophthalmol. 2016 Nov 4. [Epub ahead of print]

Oxidative damage induces MCP-1 secretion and macrophage aggregation in age-related macular degeneration (AMD).

Du Z, Wu X, Song M, Li P, Wang L.

PURPOSE: Age-related macular degeneration (AMD) is a major cause of progressive and degenerative visual impairment. Although the exact pathogenic mechanism of AMD is still unknown, clinical observations such as the high accumulation of oxidative products and macrophages in retina suggest the importance of oxidative stress and inflammation in AMD.

METHODS: Mouse photoreceptor-derived 661 W cells and human ARPE-19 cells were treated with oxidized phospholipids (Ox-PC) or H2O2 to mimic oxidative damage. The effect of monocyte chemoattractant protein 1 (MCP-1) secreted by retina cells on the migration of monocyte macrophage RAW 264.7 cells was determined using transwell chambers and antibody neutralization assay. MCP-1, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and vascular endothelial growth factor (VEGF) that secreted into supernatant were measured by ELISA and their intracellular expression was detected by qRT-PCR and western blot. Intracellular Ox-PC level was detected by competitive ELISA. The amount of migrated RAW 264.7 cells was counted by flow cytometry.

RESULTS: Oxidative damage by both H2O2 and Ox-PC induced the secretion of MCP-1 in human ARPE-19 and mouse 661 W cells. MCP-1 induced by oxidative damage enhanced the migration ability of macrophage RAW 264.7 cells and the secretion of TNF-α, IL-1β and VEGF, which could be reduced by anti -MCP-1 neutralizing antibodies.

CONCLUSION: The results indicated that oxidative damage increases intracellular Ox-PC and the secretion of MCP-1 in retina cells. The increased MCP-1 induced by oxidative damage attracts macrophages to retinas, and macrophages release pro-inflammatory factor and promote the process of AMD.

PMID: 27812755

Redox Biol. 2016 Oct 24;10:211-220. [Epub ahead of print]

Oxalomalate reduces expression and secretion of vascular endothelial growth factor in the retinal pigment epithelium and inhibits angiogenesis: Implications for age-related macular degeneration.

Kim SH, Kim H, Ku HJ, Park JH, Cha H, Lee S, Lee JH, Park JW.

Abstract: Clinical and experimental observations indicate a critical role for vascular endothelial growth factor (VEGF), secreted by the retinal pigment epithelium (RPE), in pathological angiogenesis and the development of choroidal neovascularization (CNV) in age-related macular degeneration (AMD). RPE-mediated VEGF expression, leading to angiogenesis, is a major signaling mechanism underlying ocular neovascular disease. Inhibiting this signaling pathway with a therapeutic molecule is a promising anti-angiogenic strategy to treat this disease with potentially fewer side effects. Oxalomalate (OMA) is a competitive inhibitor of NADP+-dependent isocitrate dehydrogenase (IDH), which plays an important role in cellular signaling pathways regulated by reactive oxygen species (ROS). Here, we have investigated the inhibitory effect of OMA on the expression of VEGF, and the associated underlying mechanism of action, using in vitro and in vivo RPE cell models of AMD. We found that OMA reduced the expression and secretion of VEGF in RPE cells, and consequently inhibited CNV formation. This function of OMA was linked to its capacity to activate the pVHL-mediated HIF-1α degradation in these cells, partly via a ROS-dependent ATM signaling axis, through inhibition of IDH enzymes. These findings reveal a novel role for OMA in inhibiting RPE-derived VEGF expression and angiogenesis, and suggest unique therapeutic strategies for treating pathological angiogenesis and AMD development.

PMID: 27810736

Angiogenesis. 2016 Nov 2. [Epub ahead of print]

Tissue factor is an angiogenic-specific receptor for factor VII-targeted immunotherapy and photodynamic therapy.

Hu Z, Cheng J, Xu J, Ruf W, Lockwood CJ.

Abstract: Identification of target molecules specific for angiogenic vascular endothelial cells (VEC), the inner layer of pathological neovasculature, is critical for discovery and development of neovascular-targeting therapy for angiogenesis-dependent human diseases, notably cancer, macular degeneration and endometriosis, in which vascular endothelial growth factor (VEGF) plays a central pathophysiological role. Using VEGF-stimulated vascular endothelial cells (VECs) isolated from microvessels, venous and arterial blood vessels as in vitro angiogenic models and unstimulated VECs as a quiescent VEC model, we examined the expression of tissue factor (TF), a membrane-bound receptor on the angiogenic VEC models compared with quiescent VEC controls. We found that TF is specifically expressed on angiogenic VECs in a time-dependent manner in microvessels, venous and arterial vessels. TF-targeted therapeutic agents, including factor VII (fVII)-IgG1 Fc and fVII-conjugated photosensitizer, can selectively bind angiogenic VECs, but not the quiescent VECs. Moreover, fVII-targeted photodynamic therapy can selectively and completely eradicate angiogenic VECs. We conclude that TF is an angiogenic-specific receptor and the target molecule for fVII-targeted therapeutics. This study supports clinical trials of TF-targeted therapeutics for the treatment of angiogenesis-dependent diseases such as cancer, macular degeneration and endometriosis.

PMID: 27807692

Chem Res Toxicol. 2016 Nov 3. [Epub ahead of print]

4-Hydroxy-7-oxo-5-heptenoic Acid (HOHA) Lactone Induces Angiogenesis through Several Different Molecular Pathways.

Guo J, Linetsky MD, Yu AO, Zhang L, Howell SJ, Folkwein HJ, Wang H, Salomon RG.

Abstract: Oxidative stress and angiogenesis have been implicated not only in normal phenomena such as tissue healing and remodeling but also in many pathological processes. However, the relationships between oxidative stress and angiogenesis still remain unclear, although oxidative stress has been convincingly demonstrated to influence the progression of angiogenesis under physiological and pathological conditions. The retina is particularly susceptible to oxidative stress owing to its intensive oxygenation and high abundance of polyunsaturated fatty acyls. In particular, it has high levels of docosohexanoates whose oxidative fragmentation produces 4-hydroxy-7-oxo-5-heptenoic acid (HOHA)-lactone. Previously, we found that HOHA-lactone is a major precursor of 2-(ω-carboxyethyl)pyrrole (CEP) derivatives that are tightly linked to age-related macular degeneration (AMD). CEPs promote the pathological angiogenesis of late stage AMD. We now report additional mechanisms by which HOHA-lactone promotes angiogenesis. Using cultured ARPE-19 cells; we observed that HOHA-lactone induces secretion of vascular endothelial growth factor (VEGF), which correlated to increases in reactive oxygen species (ROS) and decreases in intracellular glutathione (GSH). Wound healing and tube formation assays provided, for the first time, in vitro evidence that HOHA-lactone induces the release from ARPE-19 cells of VEGF that promotes angiogenesis by human umbilical vein endothelial cells (HUVECs) in culture. Thus, HOHA-lactone can stimulate vascular growth through a VEGF-dependent pathway. In addition, results from MTT and wound healing assays as well as tube formation experiments showed that GSH-conjugated metabolites of HOHA-lactone stimulate HUVEC cell proliferation and promote angiogenesis in vitro. Previous studies demonstrated that HOHA-lactone, through its CEP derivatives, promotes angiogenesis in a novel Toll-like receptor 2-dependent manner that is independent of the VEGF receptor or VEGF expression. The new studies show that HOHA-lactone also participates in other angiogenic signaling pathways that include promoting the secretion of VEGF from RPE cells.

PMID: 27806561

J Vis Exp. 2016 Oct 18;(116).

Assessing Retinal Microglial Phagocytic Function In Vivo Using a Flow Cytometry-based Assay.

Murinello S, Moreno SK, Macauley MS, Sakimoto S, Westenskow PD, Friedlander M.

Abstract: Microglia are the tissue resident macrophages of the central nervous system (CNS) and they perform a variety of functions that support CNS homeostasis, including phagocytosis of damaged synapses or cells, debris, and/or invading pathogens. Impaired phagocytic function has been implicated in the pathogenesis of diseases such as Alzheimer's and age-related macular degeneration, where amyloid-β plaque and drusen accumulate, respectively. Despite its importance, microglial phagocytosis has been challenging to assess in vivo. Here, we describe a simple, yet robust, technique for precisely monitoring and quantifying the in vivo phagocytic potential of retinal microglia. Previous methods have relied on immunohistochemical staining and imaging techniques. Our method uses flow cytometry to measure microglial uptake of fluorescently labeled particles after intravitreal delivery to the eye in live rodents. This method replaces conventional practices that involve laborious tissue sectioning, immunostaining, and imaging, allowing for more precise quantification of microglia phagocytic function in just under six hours. This procedure can also be adapted to test how various compounds alter microglial phagocytosis in physiological settings. While this technique was developed in the eye, its use is not limited to vision research.

PMID: 27805590

Biomed Pharmacother. 2016 Oct 29. [Epub ahead of print]

Expression of adenosine receptors and vegf during angiogenesis and its inhibition by pentoxifylline -A study using zebrafish model.

Nathan JR, Lakshmanan G, Michael FM, Seppan P, Ragunathan M.

Abstract: Angiogenesis, formation of new blood vessels is an important process involved in neovascular diseases and tumor progression. Understanding and defining novel therapeutic targets of neovascular diseases like retinopathy of prematurity, diabetic retinopathy and age-related macular degeneration have been hindered by a lack of appropriate animal models. Zebrafish provides an excellent vertebrate model to study above disorders since its circulatory system and retinal layers are similar to mammals. Adenosine is a known mediator of angiogenesis in hypoxic condition and adenosine receptor antagonists such as theophylline, theobromine are known to exert antiangiogenic properties. We evaluated the anti-angiogenic potential of a methylxanthine pentoxifylline (PTX) with various concentrations (0.1-1mM) at 50% epiboly stage (5.2 hpf) of zebrafish embryos and studied the mRNA expression of major angiogenic factors like vegfaa and its receptors under normal conditions and when treated with an adenosine analog NECA (5'-N-ethylcarboxamidoadenosine). Upregulation of adenosine receptors, hif-1α and vegfaa by NECA could possibly mimic hypoxic condition, but PTX downregulated vegfaa and other growth factors at 1mM concentration. Vegfa protein expression was also downregulated by PTX in the retina and the compound did not damage the retinal cells. Embryos treated with PTX generated abnormal phenotypic variants with poor vasculature, tail bending and developmental delay at 1mM. Survival rates, heart rate and hatching rates were also significantly lower. Targeting the vegf signaling pathway with small molecules inhibiting adenosine receptors in addition to antagonizing vegf might be a promising approach to treat neovascular diseases of the retina and also tumors.

PMID: 27802896

Invest Ophthalmol Vis Sci. 2016 Nov 1;57(14):5910-5918.

Senescence Increases Choroidal Endothelial Stiffness and Susceptibility to Complement Injury: Implications for Choriocapillaris Loss in AMD.

Cabrera AP, Bhaskaran A, Xu J, Yang X, Scott HA, Mohideen U, Ghosh K.

PURPOSE: Age-related macular degeneration (AMD) commonly causes blindness in the elderly. Yet, it is untreatable in the large fraction of all AMD patients that develop the early dry form. Dry AMD is marked by the deposition of membrane attack complex (MAC) on choriocapillaris (CC), which is implicated in CC degeneration and subsequent atrophy of overlying retinal pigment epithelium. Since MAC is also found on the CC of young eyes, here we investigated whether and how aging increases choroidal endothelial susceptibility to MAC injury.

METHODS: Monkey chorioretinal endothelial cells (ECs, RF/6A) were cultured to high passages (>P60) to achieve replicative senescence. We treated ECs with complement-competent human serum to promote MAC deposition and injury, which were assessed by flow cytometry and trypan blue exclusion assay, respectively. Stiffness of EC was measured by atomic force microscopy indentation while Rho GTPase activity was quantified by Rho G-LISA assay.

RESULTS: Our findings reveal that senescent ECs are significantly stiffer than their normal counterparts, which correlates with higher cytoskeletal Rho activity in these cells and their greater susceptibility to complement (MAC) injury. Importantly, inhibition of Rho activity in senescent ECs significantly reduced cell stiffness and MAC-induced lysis.

CONCLUSIONS: By revealing an important role of senescence-associated choroidal EC stiffening in complement injury, these findings implicate CC stiffening as an important determinant of age-related CC atrophy seen in dry AMD. Future studies are needed to validate these findings in appropriate animal models so new therapeutic targets can be identified for treatment of dry AMD.

PMID: 27802521

Invest Ophthalmol Vis Sci. 2016 Nov 1;57(14):5843-5855.

Distribution and Quantification of Choroidal Macrophages in Human Eyes With Age-Related Macular Degeneration.

McLeod DS, Bhutto I, Edwards MM, Silver RE, Seddon JM, Lutty GA.

PURPOSE: Increasing evidence suggests a role for macrophages in the pathogenesis of age-related macular degeneration (AMD). This study examined choroidal macrophages and their activation in postmortem eyes from subjects with and without AMD.

METHODS: Choroids were incubated with anti-ionized calcium-binding adapter molecule 1 (anti-IBA1) to label macrophages, anti-human leukocyte antigen-antigen D-related (anti-HLA-DR) as a macrophage activation marker, and Ulex europaeus agglutinin lectin to label blood vessels. Whole mounts were imaged using confocal microscopy. IBA1- and HLA-DR-positive (activated) cells were counted in submacula, paramacula, and nonmacula, and cell volume and sphericity were determined using computer-assisted image analysis.

RESULTS: In aged control eyes, the mean number of submacular IBA1+ and HLA-DR+ macrophages was 433/mm2 and 152/mm2, respectively. In early AMD eyes, there was a significant increase in IBA1+ and HLA-DR+ cells in submacula compared to those in controls ($P = 0.0015$ and $P = 0.008$, respectively). In eyes with neovascular AMD, there were significantly more HLA-DR+ cells associated with submacular choroidal neovascularization ($P = 0.001$). Mean cell volume was significantly lower ($P \leq 0.02$), and sphericity was significantly higher ($P \leq 0.005$) in all AMD groups compared to controls.

CONCLUSIONS: The average number of IBA1+ macrophages in submacular and paramacular choroid was significantly higher in early/intermediate AMD compared to that in aged controls. HLA-DR+ submacular macrophages were significantly increased in all stages of AMD, and they were significantly more round and smaller in size in the submacular AMD choroid, suggesting their activation. These findings support the concept that AMD is an inflammatory disease.

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Exp Biol Med (Maywood). 2016 Oct 20. [Epub ahead of print]

Fibronectin in retinal disease.

Miller CG, Budoff G, Prenner JL, Schwarzbauer JE.

Abstract: Retinal fibrosis, characterized by dysregulation of extracellular matrix (ECM) protein deposition by retinal endothelial cells, pigment epithelial cells, and other resident cell-types, is a unifying feature of several common retinal diseases. Fibronectin is an early constituent of newly deposited ECM and serves as a template for assembly of other ECM proteins, including collagens. Under physiologic conditions, fibronectin is found in all layers of Bruch's membrane. Proliferative vitreoretinopathy (PVR), a complication of retinal surgery, is characterized by ECM accumulation. Among the earliest histologic manifestations of diabetic retinopathy (DR) is capillary basement membrane thickening, which occurs due to perturbations in ECM homeostasis. Neovascularization, the hallmark of late stage DR as well as exudative age-related macular degeneration (AMD), involves ECM assembly as a scaffold for the aberrant new vessel architecture. Rodent models of retinal injury demonstrate a key role for fibronectin in complications characteristic of PVR, including retinal detachment. In mouse models of DR, reducing fibronectin gene expression has been shown to arrest the accumulation of ECM in the capillary basement membrane. Alterations in matrix metalloproteinase activity thought to be important in the pathogenesis of AMD impact the turnover of fibronectin matrix as well as collagens. Growth factors involved in PVR, AMD, and DR, such as PDGF and TGFβ, are known to stimulate fibronectin matrix assembly. A deeper understanding of how pathologic ECM deposition contributes to disease progression may help to identify novel targets for therapeutic intervention.

PMID: 27798121

Epidemiology

Front Biosci (Elite Ed). 2017 Jan 1;9:174-191.

Associations of Alzheimer's disease with macular degeneration.

Biscetti L, Luchetti E, Vergaro A, Menduno P, Cagini C, Parnetti L.

Abstract: There is growing evidence of epidemiological, genetic, molecular and clinical links between Alzheimer's disease (AD) and age-related macular degeneration (AMD). Major interest in the relationship between AD and AMD has derived from the evidence that beta-amyloid, the main component of senile plaques, the hallmark of AD, is also an important component of drusen, the hallmark of AMD. This finding has a great potential in the present era of anti-amyloid agents for the treatment of AD. The connection between AD and AMD is also supported by the evidence that the two diseases share other pathophysiological factors, such as oxidative stress and neuroinflammation. Accordingly, a few clinical trials have evaluated the efficacy of antioxidants on visual and cognitive performance in patients presenting both disorders. In this review, we summarize the pathophysiological and clinical evidence of the relationship between these two age-related disorders. Considering the increasing prevalence of both conditions along with the aging of the population, further investigations of this important issue are highly needed.

PMID: 27814598

Genetics

Methods Mol Biol. 2017;1509:93-113.

Exosomal MicroRNA Discovery in Age-Related Macular Degeneration.

Elshelmani H, Rani S.

Abstract: Age-related macular degeneration (AMD) is a common condition causing progressive visual impairment, leading to irreversible blindness. Existing diagnostic tools for AMD are limited to clinical signs in the macula and the visual assessment of the patient. The presence of circulating microRNAs (miRNAs) in the peripheral circulatory system with potential as diagnostic, prognostic and/or predictive biomarkers has been reported in a number of conditions/diseases. miRNAs are key regulators of several biological processes, and miRNA dysregulation has been linked with numerous diseases, most remarkably cancer. miRNAs have been shown to be involved in AMD pathology and several miRNAs target genes and signaling pathways were identified in relation to AMD pathogenesis. Exosomes are 50-90 nm membrane micro-vesicles (MVs), released by several cell types. Although exosomal functions are not completely understood, there is much evidence to suggest that exosomes play an essential role in cell-cell communication. They may stimulate target cells by transferring different bioactive molecules such as miRNA. Here we discuss methods to isolate exosome using serum specimens from AMD patients and miRNA profiling for the better understanding of the disease.

PMID: 27826921

Hum Mol Genet. 2016 Oct 23. [Epub ahead of print]

Structural analysis of X-Linked Retinoschisis mutations reveals distinct classes which differentially effect retinoschisin function.

Ramsay EP, Collins RF, Owens TW, Siebert CA, Jones RP, Wang T, Roseman AM, Baldock C.

Abstract: Retinoschisin, an octameric retinal-specific protein, is essential for retinal architecture with mutations causing X-linked retinoschisis (XLRS), a monogenic form of macular degeneration. Most XLRS-associated mutations cause intracellular retention, however a subset are secreted as octamers and the cause of their pathology is ill-defined. Therefore, here we investigated the solution structure of the retinoschisin monomer and the impact of two XLRS-causing mutants using a combinatorial approach of biophysics and cryo-EM. The retinoschisin monomer has an elongated structure which persists in the octameric assembly. Retinoschisin forms a dimer of octamers with each octameric ring adopting a planar propeller structure. Comparison of the octamer with the hexadecamer structure indicated little conformational change in the retinoschisin octamer upon dimerization, suggesting that the octamer provides a stable interface for construction of the hexadecamer. The H207Q XLRS-associated mutation was found in the interface between octamers and destabilized both monomeric and octameric retinoschisin. Octamer dimerization is consistent with the adhesive function of retinoschisin supporting interactions between retinal cell layers, so disassembly would prevent structural coupling between opposing membranes. In contrast, cryo-EM structural analysis of the R141H mutation at ~4.2Å resolution was found to only cause a subtle conformational change in the propeller tips, potentially perturbing an interaction site. Together, these findings support distinct mechanisms of pathology for two classes of XLRS-associated mutations in the retinoschisin assembly.

PMID: 27798099

Diet, lifestyle and low vision

Ophthalmology. 2016 Nov 5. [Epub ahead of print]

Mediterranean Diet Score and Its Association with Age-Related Macular Degeneration: The European Eye Study.

Hogg RE, Woodside JV, McGrath A, Young IS, Vioque JL, Chakravarthy U, de Jong PT, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F, Fletcher AE.

PURPOSE: To examine associations between adherence to a Mediterranean diet and prevalence of age-related macular degeneration (AMD) in countries ranging from Southern to Northern Europe.

DESIGN: Cross-sectional, population-based epidemiologic study.

PARTICIPANTS: Of 5060 randomly sampled people aged 65 years or older from 7 study centers across Europe (Norway, Estonia, United Kingdom, France, Italy, Greece, and Spain), full dietary data were available in 4753. The mean age of participants was 73.2 years (standard deviation, 5.6), and 55% were women.

METHODS: Participants underwent an eye examination and digital retinal color photography. The images were graded at a single center. Dietary intake during the previous 12 months was assessed by using a semiquantitative food-frequency questionnaire (FFQ). A previously published Mediterranean Diet Score (MDS) was used to classify participants according to their responses on the FFQ. Multivariable logistic regression was used to investigate the association of the MDS score and AMD, taking account of potential confounders and the multicenter study design.

MAIN OUTCOME MEASURES: Images were graded according to the International Classification System for age-related maculopathy and stratified using the Rotterdam staging system into 5 exclusive stages (AMD 0-4) and a separate category of large drusen (≥125 μm). Age-related macular degeneration 4 included neovascular AMD (nvAMD) and geographic atrophy (GA).

RESULTS: Increasing MDS was associated with reduced odds of nvAMD in unadjusted and confounder-adjusted analysis. Compared with the lowest MDS adherence (≤4 score), those in the highest category MDS adherence (>6 score) showed lower odds of nvAMD (odds ratio, 0.53; 0.27-1.04; P trend = 0.01). The association with MDS did not differ by Y204H risk allele (P = 0.89). For all early AMD (grade 1-3), there was no relationship with MDS (P trend = 0.9). There was a weak trend (P = 0.1) between MDS and large drusen; those in the highest category of MDS had 20% reduced odds compared with those in the lowest (P = 0.05).

CONCLUSIONS: This study adds to the limited evidence of the protective effect of adherence to a Mediterranean dietary pattern in those with late AMD, although it does not support previous reports of a relationship with genetic susceptibility. Interventions to encourage the adoption of the Mediterranean diet should be developed, and methods by which such behavior change can be achieved and maintained investigated.

PMID: 27825655

Crit Rev Food Sci Nutr. 2017 Feb 11;57(3):559-565.

Modulatory effects of 1,25-dihydroxyvitamin D3 on eye disorders: A critical review.

Nebbioso M, Buomprisco G, Pascarella A, Pescosolido N.

Abstract: Many studies have shown that the presence of 1,25-dihydroxyvitamin D3 in the eye is able to modulate inflammatory responses. In fact, it has been demonstrated that topical administration of vitamin D3 inhibits Langerhans cells migration from the central cornea, corneal neovascularization, and production of cytokines (i.e., interleukin-1-6-8) in experimental animals. Moreover, both in vitro and in vivo studies have demonstrated that vitamin D is a potent inhibitor of retinal neovascularization. It has been shown that calcitriol, the biologically active form of vitamin D, inhibits angiogenesis both in cultured endothelial cells and in retinas from guinea pigs with retinoblastoma or oxygen-induced ischemic retinopathy. In addition, it seems that this compound is able to prevent the progression from early to neovascular age-related macular degeneration (AMD) and, at the same time, to down-regulate the characteristic inflammatory cascade at the retinal pigment epithelium-choroid interface due to its anti-inflammatory and immunomodulatory capabilities. Furthermore, 1,25-dihydroxyvitamin D3 and its analogue, 2-methylene-19-nor-1,25-dihydroxyvitamin D3, are able to modulate intraocular pressure (IOP) through gene expression. Several studies have suggested a role in glaucoma and diabetic retinopathy therapies for vitamin D3. In conclusion, this review summarizes our current knowledge on the potential use of vitamin D3 in the protection and treatment of ocular diseases in ophthalmology.

PMID: 26054653

Clin Ophthalmol. 2016 Oct 31;10:2149-2155. eCollection 2016.

Preliminary analysis of the relationship between serum lutein and zeaxanthin levels and macular pigment optical density.

Fujimura S, Ueda K, Nomura Y, Yanagi Y.

PURPOSE: To assess the relationship between combined serum lutein and zeaxanthin (L+Z) concentration and macular pigment optical density (MPOD), and to investigate the effect of L+Z+docosahexaenoic acid (DHA) dietary supplementation on the spatial distribution of MPOD.

METHODS: Twenty healthy fellow eyes with unilateral wet age-related macular degeneration or chronic central serous chorioretinopathy were included. All participants received a dietary supplement for 6 months that contained 20 mg L, 1 mg Z, and 200 mg DHA. The best-corrected visual acuity and contrast sensitivity (CS) were measured at baseline and at 1, 3, and 6 months. Serum L+Z concentrations were measured at baseline and at 3 months. MPOD was calculated at each time point using fundus autofluorescent images.

RESULTS: Serum L+Z concentration was correlated with MPOD at 1°-2° eccentricity at baseline ($r=0.63$, $P=0.003$) and 3 months ($r=0.53$, $P=0.015$). Serum L+Z concentration increased by a factor of 2.3±1.0 ($P<0.0001$). At 6 months, MPOD was significantly higher compared to the baseline level at 0°-0.25° ($P=0.034$) and 0.25°-0.5° ($P=0.032$) eccentricity. CS improved after 3 or 6 months of L+Z+DHA supplementation ($P<0.05$).

CONCLUSION: Juxtafoveal MPOD was associated with serum L+Z concentration. Foveal MPOD was increased by L+Z+DHA dietary supplementation.

PMID: 27826180

Optom Vis Sci. 2016 Nov 1. [Epub ahead of print]

Fixation Stability and Viewing Distance in Patients with AMD.

Tarita-Nistor L, González EG, Brin T, Mandelcorn MS, Scherlen AC, Mandelcorn ED, Steinbach MJ.

PURPOSE: People with normal vision perform activities of daily living binocularly, while changing viewing distance frequently and effortlessly. Typically, in patients with age-related macular degeneration (AMD), fixation stability is recorded with monocular instruments at a fixed viewing distance (i.e. optical infinity) to determine the location and precision of the preferred retinal loci (PRLs)-the part of the functional retina that fulfills the role of a pseudo-fovea. Fixation stability recorded with these instruments has been related to performance on visual tasks at shorter viewing distances, although it is not known how viewing distance affects the precision of ocular motor control in these patients. This study examined whether viewing distance affects fixation stability during binocular and monocular viewing.

METHODS: Thirty patients with bilateral AMD, 10 older controls, and 10 younger controls participated. Each patient's better eye (BE) and worse eye (WE) were identified based on their visual acuity. Fixation stability was recorded with a binocular eye-tracker at three viewing distances (40 cm, 1 m, 6 m) in binocular and monocular (with BE and with WE) viewing conditions. Fixation stability was evaluated with a bivariate contour ellipse area.

RESULTS: For the AMD group, there was no effect of viewing distance on fixation stability, regardless of viewing condition (i.e. binocular, monocular with the BE or with the WE). The same pattern of results was found for the two control groups.

CONCLUSIONS: Viewing distance does not affect fixation stability in patients with AMD. Fixation stability data recorded with an instrument at a fixed viewing distance can be related to performance on visual tasks at other viewing distances.

PMID: 27811525

Eye (Lond). 2016 Nov 4. [Epub ahead of print]

Comparison of vision-related quality of life in primary open-angle glaucoma and dry-type age-related macular degeneration.

Karadeniz Ugurlu S, Kocakaya Altundal AE, Altin Ekin M.

Purpose: To compare quality of life (QoL) in patients with primary open-angle glaucoma (POAG) and dry-type age-related macular degeneration (AMD) with similar best-corrected visual acuity.

Methods: Age-, sex-, and visual acuity-matched POAG and dry AMD patients were included in the study. Each patient performed 24-2 and 10-2 SITA standard visual field tests. Contrast sensitivity was evaluated with CSV-1000 HGT instrument. The 25 item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) was used to analyze QoL. Overall and subscale scores were converted to scores between 0 and 100, the higher scores indicating better vision-related QoL.

Results: Overall NEI-VFQ-25 scores were 86.44 and 84.66 in glaucoma and AMD groups, respectively (P=0.244). The highest scores were obtained in 'vision-related dependency' subgroup in glaucoma and 'color and peripheral vision' in AMD group, whereas the lowest scores were noted 'in peripheral vision' in both glaucoma and AMD patients. Glaucoma patients had significantly lower scores in ocular pain, color vision, and peripheral vision subgroups compared with the AMD group, whereas AMD patients had lower scores in near and distance vision activities, vision-related social activity, and dependency subgroups. Contrast sensitivity results and mean defect values showed correlation with NEI-VFQ-25 scores in both groups.

Conclusions: Glaucoma and AMD patients with similar visual acuity experienced similar overall impairment in QoL. However, glaucoma patients described more difficulty with peripheral vision and ocular pain, whereas AMD patients complained more about near and distance vision and dependency items.Eye advance online publication, 4 November 2016; doi:10.1038/eye.2016.219.

PMID: 27813519

Exp Biol Med (Maywood). 2016 Oct 20. [Epub ahead of print]

Carrot solution culture bioproduction of uniformly labeled 13C-lutein and in vivo dosing in non-human primates.

Smith JW, Rogers RB, Jeon S, Rubakhin SS, Wang L, Sweedler JV, Neuringer M, Kuchan MJ, Erdman JW Jr.

Abstract: Lutein is a xanthophyll abundant in nature and most commonly present in the human diet through consumption of leafy green vegetables. With zeaxanthin and meso-zeaxanthin, lutein is a component of the macular pigment of the retina, where it protects against photooxidation and age-related macular degeneration. Recent studies have suggested that lutein may positively impact cognition throughout the lifespan, but outside of the retina, the deposition, metabolism, and function(s) of lutein are poorly understood. Using a novel botanical cell culture system (Daucus carota), the present study aimed to produce a stable isotope lutein tracer for use in future investigations of dietary lutein distribution and metabolism. Carrot cultivars were initiated into liquid solution culture, lutein production conditions optimized, and uniformly labeled 13C-glucose was provided as the sole media carbon source for four serial growth cycles. Lutein yield was 2.58 ± 0.24 µg/g, and mass spectrometry confirmed high enrichment of 13C: 64.9% of lutein was uniformly labeled and 100% of lutein was labeled on at least 37 of 40 possible carbons. Purification of carrot extracts yielded a lutein dose of 1.92 mg with 96.0 ± 0.60% purity. 13C-lutein signals were detectable in hepatic extracts of an adult rhesus macaque monkey (Macaca mulatta) dosed with 13C-lutein, but not in hepatic samples collected from control animals. This novel botanical biofactory approach can be used to produce sufficient quantities of highly enriched and pure 13C-lutein doses for use in tracer studies investigating lutein distribution, metabolism, and function.

PMID: 27798119

Dan Med J. 2016 Nov;63(11).

Physical activity patterns in patients with early and late age-related macular degeneration.

Subhi Y, Sørensen TL.

INTRODUCTION: Age-related macular degeneration (AMD) leads to visual impairment that affects visual functioning and thereby the ability to be physically active. We investigated physical activity patterns in patients with AMD.

METHODS: Patients with early and late AMD and elderly controls were recruited for this hospital-based cross-sectional study. All participants had their best-corrected visual acuity measured and were interviewed about their physical activity based on questions that covered regular physical activity, physical activity that would work up sweat, climbing the stairs and time spent on walking outdoors.

RESULTS: We recruited 198 participants of whom 196 were eligible for inclusion in the analyses (68 controls, 25 with early AMD and 103 with late AMD). The frequency of regular physical activity did not differ between patients with early and late AMD and elderly controls. Lower best-corrected visual acuity in the best-seeing and the worse-seeing eye was associated with less engagement in physical activities that would work up sweat and a lower number of steps taken daily. Patients with bilateral vision loss from late AMD engaged in physical activities that were more controlled and less demanding of sharp central vision.

CONCLUSION: Patients with late AMD may still be physically active even when the disease progresses and vision is lost, but activities may change into more controlled and less central vision-demanding ones.

PMID: 27808038

Turk J Ophthalmol. 2016 Jun;46(3):118-122. Epub 2016 Jun 6.

Low Vision Rehabilitation in Older Adults.

Özen Tunay Z, İdil A, Seza Petriçli İ, Özdemir Ö.

OBJECTIVES: To evaluate the diagnosis distribution, low vision rehabilitation methods and utilization of low vision rehabilitation in partially sighted persons over 65 years old.

MATERIALS AND METHODS: One hundred thirty-nine partially sighted geriatric patients aged 65 years or older were enrolled to the study between May 2012 and September 2013. Patients' age, gender and the distribution of diagnosis were recorded. The visual acuity of the patients both for near and distance were examined with and without low vision devices and the methods of low vision rehabilitation were evaluated.

RESULTS: The mean age of the patients was 79.7 years and the median age was 80 years. Ninety-six (69.1%) of the patients were male and 43 (30.9%) were female. According to the distribution of diagnosis, the most frequent diagnosis was senile macular degeneration for both presenile and senile age groups. The mean best corrected visual acuity for distance was 0.92±0.37 logMAR and 4.75±3.47 M for near. The most frequently used low vision rehabilitation methods were telescopic glasses (59.0%) for distance and hyperocular glasses (66.9%) for near vision. A significant improvement in visual acuity both for distance and near vision were determined with low vision aids.

CONCLUSION: The causes of low vision in presenile and senile patients in our study were similar to those of patients from developed countries. A significant improvement in visual acuity can be achieved both for distance and near vision with low vision rehabilitation in partially sighted geriatric patients. It is important to guide them to low vision rehabilitation.

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Turk J Ophthalmol. 2016 Apr;46(2):73-76. Epub 2016 Apr 5.

Necessity of Periodic Ophthalmological Examinations in Binocular B Class Driving Licence Holders Over 50 Years of Age.

Kurt A, Öktem Ç, Karabıçak Acer A, Kocamış Ö, Taşdemir S.

OBJECTIVE: To determine whether binocular B class driving licence (BBCDL) holders over 50 years old are in compliance with the BBCDL criteria for visual acuity, to determine the age-based prevalence of ophthalmological disorders reducing visual acuity in this group, and to investigate whether periodic ophthalmological examinations are needed in licence holders over 50 years of age.

MATERIALS AND METHODS: This prospective study enrolled 451 adults over 50 years old having a BBCDL. The study subjects were categorized into 3 age groups as group 1 (51-60 years), group 2 (61-70 years), and group 3 (over 71 years).

RESULTS: The mean age of the subjects was 60.02±7.27 years; 338 (74.9%) were male and 113 (25.1%) were female. The BBCDL criteria were met by 353 (78.3%) subjects whereas 98 (21.7%) subjects did not meet them. Eighty-four (85.7%) of 98 patients not meeting BBCDL criteria still drove. The mean age of the subjects meeting BBCDL criteria (58.82±6.77 years) was significantly lower than the subjects not meeting them (64.34±7.40 years) ($p<0.001$). The most common pathologies in the individuals still driving despite not meeting BBCDL criteria were senile cataract (38.5%) and diabetic retinopathy (23.1%) in group 1, senile cataract (55.3%) and diabetic retinopathy (14.9%) in group 2, and senile cataract (63.6%) and senile macular degeneration+senile cataract (18.2%) in group 3.

CONCLUSION: More than a fifth of individuals over 50 years old did not meet the BBCDL criteria, due predominantly to senile cataract, and the majority of these individuals continue to drive. Therefore, we believe that individuals over 50 years old who have a BBCDL should undergo periodic ophthalmological examinations.

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