

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

If you have not already subscribed, please email Rob Cummins at research@mdfoundation.com.au with 'Subscribe to MD Research News' in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your 'unsubscribe' request.

Drug treatment

Ophthalmic Surg Lasers Imaging Retina. 2016 Oct 1;47(10):914-923.

Topical Squalamine 0.2% and Intravitreal Ranibizumab 0.5 mg as Combination Therapy for Macular Edema Due to Branch and Central Retinal Vein Occlusion: An Open-Label, Randomized Study.

Wroblewski JJ, Hu AY.

BACKGROUND AND OBJECTIVE: To evaluate the effects of squalamine (OHR-102; Ohr Pharmaceuticals, New York, NY) and ranibizumab (Lucentis; Genentech, South San Francisco, CA) on macular edema (ME) secondary to retinal vein occlusion (RVO).

PATIENTS AND METHODS: Twenty consecutive, treatment-naïve patients with RVO-related ME received topical squalamine and intravitreal ranibizumab 0.5 mg for 10 weeks, followed by randomization to continue or discontinue squalamine. Groups received as-needed ranibizumab from weeks 2 through 34. The primary endpoint was the proportion of eyes gaining 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 38. Safety and tolerability were assessed. Data from 13 treatment-naïve control eyes previously enrolled in three similar trials evaluating monthly ranibizumab 0.5 mg for RVO-related ME were included for comparison.

RESULTS: At baseline, mean best-corrected visual acuity (BCVA) measures were 55.6 ETDRS letters and 55.0 ETDRS letters in the squalamine and control groups, respectively. At week 38, BCVA improved 25.6 letters in the squalamine group; at month 9, BCVA improved 16.3 letters in the control group. This corresponds to a between-treatment-group difference of 9.2 letters. Squalamine and ranibizumab combination therapy was well-tolerated.

CONCLUSIONS: In patients with RVO-related ME, topical squalamine combined with early, as-needed ranibizumab appears to enhance visual recovery versus ranibizumab alone. Combination therapy appears safe and was well-tolerated.

PMID: 27759857

Retina. 2016 Oct 11. [Epub ahead of print]

QUANTITATIVE ANALYSIS OF PIGMENT EPITHELIAL DETACHMENT RESPONSE TO DIFFERENT ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS IN WET AGE-RELATED MACULAR DEGENERATION.

Balaskas K, Karampelas M, Horani M, Hotu O, Keane P, Aslam T.

PURPOSE: To assess whether best-corrected visual acuity and pigment epithelial detachment (PED) height, volume, and reflectivity in patients with wet age-related macular degeneration are influenced by baseline anatomical and functional parameters, including quantifiable metrics of PED morphology and

choice of treatment.

METHODS: One hundred two consecutive, treatment-naïve wet age-related macular degeneration patients with PED ($>50\ \mu\text{m}$) treated with aflibercept (52) or ranibizumab (50) were retrospectively included. Pigment epithelial detachment height, horizontal and vertical dimensions, and volume were recorded at baseline, 3 months, and 1 year, respectively. Bespoke image analysis software provided a quantifiable measure of reflectivity.

RESULTS: Best-corrected visual acuity at 3 months was influenced by baseline best-corrected visual acuity ($P = 0.006$). Pigment epithelial detachment height was influenced by baseline height ($P = 0.009$), subretinal fluid ($P = 0.008$), central macular thickness ($P = 0.006$), and use of aflibercept ($P = 0.003$) at 3 months and by baseline height ($P = 0.018$), volume ($P = 0.017$), vertical dimension ($P = 0.0004$), and aflibercept ($P = 0.015$) at 1 year. Pigment epithelial detachment reflectivity increased from 43.59 to 55.86 (3 months) and 57.35 (1 year) ($P < 0.001$) and was influenced by its baseline values and, interestingly, use of aflibercept at 3 months ($P = 0.013$).

CONCLUSION: Quantifiable metrics of PED morphology improve with treatment, and PED content becomes hyperreflective, more so on aflibercept. Pigment epithelial detachments respond better in the context of more active disease. More hyporeflexive PED content may predispose to better treatment response, especially with aflibercept.

PMID: 27755376

Arch Soc Esp Oftalmol. 2016 Oct 14. [Epub ahead of print]

Functional impact of treatment with ranibizumab under a reactive strategy in patients with neovascular age-related macular degeneration.[Article in English, Spanish]

Gallego-Pinazo R, Dolz-Marco R, Andreu-Fenoll M, Farrés J, Monclús L.

OBJECTIVE: To analyse the functional recovery using a pro re nata (PRN) dosing strategy with intravitreal injections of ranibizumab for patients with neovascular age-related macular degeneration (AMD).

MATERIAL AND METHODS: An observational, retrospective, single-centre study, was conducted on patients with neovascular AMD managed with a PRN strategy with ranibizumab, and were followed-up for a minimum of 18 months. Sociodemographic and clinical data were collected from medical records. The percentage of visual acuity (VA) recovered after losing 5 or more letters was calculated taking into account the previous visit, as well as considering the best VA recorded prior to the retreatment.

RESULTS: The analysis included 128 patients. The mean (SD) follow-up period was 18.9 (2.3) months. The mean (SD) elapsed days between onset of symptoms and diagnosis, and between prescription and administration of treatment was 50.2 (57.4) and 10.9 (16.0), respectively. Only 108 patients were prescribed ranibizumab after losing 5 or more letters of VA. The mean (SD) VA recovery compared to the previous VA was 70.3% (114.4). On the other hand, the mean (SD) VA recovery when considering the best VA registered before the retreatment was 43.5% (112.9), with 59.4% of re-treatments having a VA recovery below 75%, and with 11.7% not presenting any VA recovery.

CONCLUSIONS: A PRN dosing strategy with intravitreal ranibizumab for neovascular AMD may not be efficient in preserving and/or recovering VA in the long-term, due to a cumulative irreversible VA loss.

PMID: 27751585

Am J Ophthalmol. 2016 Oct 13. [Epub ahead of print]

Long-term outcomes of aflibercept treatment for neovascular age-related macular degeneration in a clinical setting.

Eleftheriadou M, Vazquez-Alfageme C, Citu CM, Crosby-Nwaobi R, Sivaprasad S, Hykin P, Hamilton RD, Patel PJ.

PURPOSE: To report 2 year treatment outcomes with intravitreal aflibercept for neovascular age-related macular degeneration (nAMD) in routine clinical practice.

DESIGN: Retrospective, non-randomized, interventional case series.

METHODS: Retrospective analysis of electronic medical record (EMR) notes (OpenEyes), paper case notes and review of spectral-domain optical coherence tomography (SD-OCT) imaging of patients with consecutively treated eyes with previously untreated nAMD. Patients were commenced on aflibercept injections in one or both eyes from 1st October 2013 to 31st December 2013. Data including age, gender, visual acuity (VA) measured on Early Treatment of Diabetic Retinopathy Study charts, injection episodes and complications were recorded. Additionally SD-OCT data including presence or absence of macular fluid and automated central subfield macular thickness (CSMT) at year 1 and 2, were also recorded.

RESULTS: Of the 109 eyes of 102 patients treated, data from 94 eyes of 88 patients were available at 2 year follow-up (86% of patients). In the analysis of 2 year outcomes, there were 58 women (60%), the mean ($\pm$ standard deviation) age was 77.5 ± 8 years. Over the 2 years, these eyes received a median of 12 (mean, 11.4 ± 4) injections at a median of 100 (mean, 99.3 ± 5.3) weeks of follow-up. The mean VA changed from 55.9 ± 15 letters at baseline to 61.3 ± 16.9 letters (VA gain 5.4 letters gain) at 1 year and to 61 ± 17.1 letters (VA gain 5.1 ± 14.9 gain) at 2 years. The reduction in CSMT was $79.5 \mu\text{m}$ with absence of macular fluid in 70.4% of the 88 eyes with SD-OCT data available at 2 year follow-up.

CONCLUSIONS and relevance: The VA and SD-OCT results compare favourably with outcomes seen in randomized controlled trials. The results suggest that good long-term outcomes can be achieved using aflibercept for nAMD in clinical settings.

PMID: 27746298

Can J Ophthalmol. 2016 Oct;51(5):342-347. Epub 2016 Sep 3.

Effect of aflibercept on refractory macular edema associated with central retinal vein occlusion.

Cohen MN, Houston SK, Juhn A, Ho AC, Regillo CD, Vander J, Chiang A.

OBJECTIVE: To report short-term visual and anatomic outcomes of patients who were switched to aflibercept for persistent macular edema associated with central retinal vein occlusion (CRVO).

METHODS: Retrospective, consecutive, interventional case series of 17 patients with persistent macular edema secondary to CRVO (defined as intraretinal edema and either $<50 \mu\text{m}$ reduction in central foveal thickness [CFT] or worsening or no improvement in visual acuity [VA] compared to baseline) despite anti-VEGF treatment who were switched to aflibercept treatment. Main outcome measures included VA, anti-VEGF treatment history, and spectral-domain optical coherence tomography evaluation of macular edema and CFT.

RESULTS: The mean age was 77 years, and the mean VA at CRVO diagnosis was 20/135 with a CFT of $523.4 \mu\text{m}$. Mean number of injections before switching to aflibercept was 12.9 (range: 3-40) and mean number of months of anti-VEGF treatment before switching to aflibercept was 18.7. Mean VA at switch to aflibercept was 20/182 ($p = 0.50$) with mean CFT of $547.9 \mu\text{m}$ ($p = 0.66$). Mean aflibercept injections were 4.0, and mean follow-up from switch to last follow-up was 5.2 months. Final mean VA was 20/115 ($p = 0.017$), with a CFT of $315.2 \mu\text{m}$ ($p = 0.0012$). Of the patients, 35.2% gained ≥ 3 lines. 29% of patients had complete resolution of macular edema, and the mean change in CFT was $-233 \mu\text{m}$.

CONCLUSIONS: Aflibercept appears to have a beneficial effect on anatomic and VA outcomes in a subset of patients with macular edema secondary to CRVO that is refractory to treatment with bevacizumab and/or ranibizumab.

PMID: 27769324

Retina. 2016 Oct 20. [Epub ahead of print]

INTRAVITREAL DEXAMETHASONE IMPLANT AS ADJUVANT TREATMENT FOR BEVACIZUMAB- AND RANIBIZUMAB-RESISTANT NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: A Prospective Pilot Study.

Barikian A, Salti H, Safar A, Mahfoud ZR, Bashshur ZF.

PURPOSE: To study the benefit of intravitreal dexamethasone implant in the management of neovascular age-related macular degeneration resistant to bevacizumab and ranibizumab.

METHODS: Patients with persistent macular fluid on optical coherence tomography despite monthly treatment with at least three consecutive bevacizumab injections followed by at least three ranibizumab injections were prospectively enrolled. A single dexamethasone implant was administered followed by intravitreal ranibizumab 1 week later. Ranibizumab was continued afterward on an as-needed basis. Main outcomes were improvement in central retinal thickness and best-corrected visual acuity.

RESULTS: Nineteen patients (19 eyes) were enrolled. There was no significant change in best-corrected visual acuity over 6 months. Greatest reduction in mean central retinal thickness, from 295.2 μ m to 236.2 μ m, occurred 1 month after dexamethasone implant ($P < 0.0001$). By Month 6, mean central retinal thickness was 287.3 μ m ($P = 0.16$). Eyes with only intraretinal fluid (13 eyes) achieved a fluid-free macula. Eyes with predominantly subretinal fluid (6 eyes) did not improve central retinal thickness and continued monthly ranibizumab. Mean baseline intraocular pressure was 13.2 mmHg, which peaked at 15.6 mmHg by Month 2 ($P = 0.004$).

CONCLUSION: Intravitreal dexamethasone implant improved only macular intraretinal fluid in eyes with neovascular age-related macular degeneration resistant to bevacizumab and ranibizumab. However, this treatment had a limited duration.

PMID: 27768640

Retina. 2016 Oct 18. [Epub ahead of print]

OUTCOMES OF AN INTRAVITREAL INJECTION CLINIC.

Atchison EA, Omar AF, Iezzi R, Barkmeier AJ, Bakri SJ.

PURPOSE: To examine the safety outcomes of an intravitreal injection-only clinic where patients needing long-term anti-vascular endothelial growth factor therapy are treated with injections at a predetermined interval for a set number of injections without an accompanying clinic visit.

METHODS: This is a retrospective chart review of all patients with exudative macular degeneration treated in an intravitreal injection clinic over a 4-year period. Data on the outcome measures of interest were gathered from electronic medical records.

RESULTS: There were 556 patients who received 4,386 injections in the injection-only clinic in a total of 1,524 injection cycles. One hundred six cycles were interrupted. The most common causes for interruption were decreased vision in the injected eye (32), decreased vision in the fellow eye (23), flashing lights (6), pain (5), and irritation in the noninjected eye (2). Of patients who had interruption of the cycle, 32 had a new diagnosis (6 corneal abrasions, 6 exudative age-related macular degeneration in fellow eye). There were six instances of conversion to exudative age-related macular degeneration found in the other eye at a routine follow-up visit following the injection clinic.

CONCLUSION: An injection-only clinic may provide a reasonable approach to streamline retina practices to ensure that patients receive timely injections.

PMID: 27759581

Curr Diab Rep. 2016 Dec;16(12):122.

Vascular Endothelial Growth Factor Inhibitors for Diabetic Retinopathy.

Dhoot DS, Avery RL.

Abstract: The prevalence of diabetes is growing at epidemic rates in the USA. Diabetic retinopathy develops in a large proportion of patients and is a leading cause of blindness worldwide. Systemic management of diabetic retinopathy has included glycemic, hypertension, and lipid control. Local ophthalmic treatment in the form of focal/grid or panretinal laser photocoagulation has been shown to prevent vision loss in diabetic edema and proliferative diabetic retinopathy, respectively. The introduction of anti-vascular endothelial growth factor for diabetic macular edema and retinopathy has provided clinicians with improved clinical outcomes with potentially less damaging effects than laser.

PMID: 27766582

Eur J Ophthalmol. 2016 Oct 18:0. [Epub ahead of print]

Comments to: Ranibizumab for persistent diabetic macular edema after bevacizumab treatment.

Călugăru D, Călugăru M.

PMID: 27768225

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5436-5442.

Assessment of Retinotopic Rod Photoreceptor Function Using a Dark-Adapted Chromatic Perimeter in Intermediate Age-Related Macular Degeneration.

Fraser RG, Tan R, Ayton LN, Caruso E, Guymer RH, Luu CD.

PURPOSE: We determine the feasibility of using a dark-adapted chromatic (DAC) perimeter to obtain dark-adapted static and dynamic rod function at multiple retinal locations, and compare these functional parameters between subjects with intermediate age-related macular degeneration (AMD) and normal controls.

METHODS: Perimetric dark-adapted retinal sensitivities for the 505 and 620 nm stimuli across 7 retinal locations within the central 12° were repeatedly measured after exposing to a single photobleach in 22 intermediate AMD subjects and 8 controls. The sensitivities for each stimulus at 20 minutes after bleach and the sensitivity difference between the stimuli were used to determine static rod function. Sensitivities for the 505 nm stimulus at various times within the initial 20 minutes after bleach were used to estimate the rod criterion time to determine rod function dynamics. The static and dynamic rod functional parameters were compared between AMD and control eyes.

RESULTS: Compared to the control eyes, AMD eyes had a reduction in retinal sensitivities for the 505 nm ($P < 0.001$) and 620 nm ($P < 0.001$) stimuli, a reduction in sensitivity difference ($P < 0.001$), and an increased in rod criterion time ($P < 0.001$). Region within the central 6° appeared to be the most defective and AMD eyes with reticular pseudodrusen (RPD) seemed to have worse function than eyes without RPD.

CONCLUSIONS: It is feasible to use a DAC perimeter to study dark-adapted static and dynamic rod-mediated function at multiple retinal loci. Static and dynamic rod function were abnormal in intermediate AMD and more so in eyes with RPD, particularly within the central 6° retina.

PMID: 27756079

Can J Ophthalmol. 2016 Oct;51(5):378-381. Epub 2016 Sep 7.

Discrepancies in physician-patient agreement in reporting ocular history.

Popovic M, Chaudhary V, McKay BR, Moinul P, Mohaghagh M, Beattie A, Fava M, Eino D, Mann K, Kobetz L, Barbosa J.

OBJECTIVE: The purpose of this study was to investigate the extent of agreement between physicians and patients in reporting ocular history and to determine whether there are any predictive factors for physician-patient consensus.

DESIGN: Retrospective chart review.

PARTICIPANTS: Between June and September 2014, adult patients undergoing cataract surgery were recruited for the study.

METHODS: Before surgery, patient demographics and self-reported ocular history were extracted from a prospectively collected database. Medical charts were retrospectively examined to retrieve physician-reported ocular history.

RESULTS: One hundred and thirty-eight patients participated. Mean cohort logMAR visual acuity was 0.46 ± 0.34 (Snellen equivalent of approximately 20/60) and mean age was 74.1 ± 8.3 years. For glaucoma, Cohen's kappa revealed a moderate-to-good concordance between physicians and patients ($\kappa = 0.604$), whereas a poor-to-fair level of agreement existed in reporting maculopathy, such as age-related macular degeneration and macular holes ($\kappa = 0.254$). The logistic regression model revealed that preoperative visual acuity ($p = 0.223$), sex ($p = 0.736$), age ($p = 0.910$), and education ($p = 0.738$) were not significant predictors of physician-patient agreement.

CONCLUSIONS: The accuracy of patient-reported ocular history varies by pathology. Self-reported glaucoma history is consistent between patients and physicians; however, patients under-report the diagnosis of maculopathy. Age, sex, and level of education do not appear to influence patient-reported accuracy of ocular comorbidities.

PMID: 27769330

Acta Ophthalmol. 2016 Oct 24. [Epub ahead of print]

Imaging retinal inflammatory biomarkers after intravitreal steroid and anti-VEGF treatment in diabetic macular oedema.

Vujosevic S, Torresin T, Bini S, Convento E, Pilotto E, Parrozzani R, Midena E.

PURPOSE: To evaluate changes of specific retinal imaging biomarkers [intraretinal hyper-reflective retinal spots: HRS; subfoveal neuroretinal detachment: SND; and increased foveal autofluorescence: IFAF after intravitreal steroid or anti-vascular endothelial growth factor treatment in diabetic macular oedema (DME)] as possible indicators of retinal inflammatory condition.

METHODS: Retrospective analysis of images and clinical charts of 49 eyes (49 patients) with DME treated with intravitreal dexamethasone (dexamethasone, 23 eyes) or intravitreal ranibizumab (ranibizumab, 26 eyes). All patients had fundus colour photograph, spectral domain optical coherence tomography (SD OCT) and fundus autofluorescence (FAF), best-corrected visual acuity (BCVA) and microperimetry recorded before and 1 month after the end of treatment. Central macular thickness (CMT), number of HRS and presence of SND were evaluated by SD OCT. Fundus autofluorescence images were evaluated for area of (IFAF). Retinal sensitivity within 4° and 12° from fovea was quantified by microperimetry. Changes in morphologic and functional parameters were assessed, and correlation was performed by Pearson's correlation.

RESULTS: Best-corrected visual acuity and CMT improved in all patients, ($p < 0.05$, for both groups). Mean

number of HRS decreased after both treatments ($p < 0.0001$). Subfoveal neuroretinal detachment resolved in 85.7% dexamethasone-treated eyes ($p = 0.014$) and in 50% ranibizumab-treated eyes ($p = 0.025$). Mean IFAF area decreased in both groups, ($p < 0.0001$, for both). A significantly higher decrease in CMT was observed in dexamethasone- versus ranibizumab-treated eyes, ($p = 0.032$). In dexamethasone group, higher number of HRS at baseline and larger IFAF were correlated with higher increase in retinal sensitivity; eyes with SND at baseline had major decrease in CMT versus those without SND, ($p = 0.003$).

CONCLUSION: Higher number of HRS, larger area of IFAF and presence of SND may indicate a prevalent inflammatory condition in DME with specific response to targeted treatment.

PMID: 27775223

PLoS One. 2016 Oct 24;11(10):e0164899. eCollection 2016.

Analysis of Macular Drusen and Blood Test Results in 945 *Macaca fascicularis*.

Nishiguchi KM, Yokoyama Y, Fujii Y, Fujita K, Tomiyama Y, Kawasaki R, Furukawa T, Ono F, Shimozawa N, Togo M, Suzuki M, Nakazawa T.

Abstract: Age-dependent formation of macular drusen caused by the focal accumulation of extracellular deposits beneath the retinal pigment epithelium precede the development of age-related macular degeneration (AMD), one of the leading causes of blindness worldwide. It is established that inflammation contributes to the pathogenesis of drusen and AMD. However, development of a preemptive therapeutic strategy targeting macular drusen and AMD has been impeded by the lack of relevant animal models because most laboratory animals lack macula, an anatomic feature present only in humans and a subset of monkeys. Reportedly, macular drusen and macular degeneration develop in monkeys in an age-dependent manner. In this study, we analyzed blood test results from 945 *Macaca fascicularis*, 317 with and 628 without drusen. First, a trend test for drusen frequency (the Cochran-Armitage test) was applied to the quartile data for each parameter. We selected variables with an increasing or decreasing trend with higher quartiles at $P < 0.05$, to which multivariate logistic regression analysis was applied. This revealed a positive association of age (odds ratio [OR]: 1.10 per year, 95% confidence interval [CI]: 1.07-1.12) and white blood cell count (OR: 1.01 per $1 \times 10^3/\mu\text{L}$, 95% CI: 1.00-1.01) with drusen. When the monkeys were divided by age, the association between drusen and white blood cell count was only evident in younger monkeys (OR: 1.01 per $1 \times 10^3/\mu\text{L}$, 95% CI: 1.00-1.02). In conclusion, age and white blood cell count may be associated with drusen development in *M. fascicularis*. Systemic inflammation may contribute to drusen formation in monkeys.

PMID: 27776188

Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5479-5489.

Associations Between Retinal Pigment Epithelium and Drusen Volume Changes During the Lifecycle of Large Drusenoid Pigment Epithelial Detachments.

Balaratnasingam C, Yannuzzi LA, Curcio CA, Morgan WH, Querques G, Capuano V, Souied E, Jung J, Freund KB.

PURPOSE: Drusenoid pigment epithelial detachments (PEDs) are a defined path to atrophy in age-related macular degeneration (AMD). We analyzed the relationships between retinal pigment epithelium (RPE) and drusen volume changes during the PED lifecycle, using spectral-domain optical coherence tomography (SD-OCT).

METHODS: Twenty-one cases of drusenoid PED tracked using SD-OCT through periods of growth and collapse were evaluated. Volumetric calculations and piece-wise linear regression analysis were used to determine the breakpoint between growth and collapse. Spectral-domain OCT scans were independently evaluated for the appearance of intraretinal hyperreflective foci, acquired vitelliform lesions (AVLs), and

disruptions to the RPE+basal lamina band. Timing of these events with respect to the breakpoint was statistically evaluated. Morphometric characteristics of drusenoid PEDs were correlated with rate of PED collapse and final visual acuity.

RESULTS: Mean age of subjects was 75.3 years and mean period of follow up was 4.1 years (median 4.5 years; range, 0.6-6.6 years). The lifecycle of drusenoid PEDs was asymmetric, in that the rate of collapse (0.199 mm³/month) is significantly faster ($P < 0.001$) than the rate of growth (0.022 mm³/month). Appearance of intraretinal hyperreflective foci and AVIs preceded the breakpoint (both $P < 0.001$). The timing of disruptions to the RPE+basal lamina band did not differ from the breakpoint ($P = 0.510$). Maximal height, volume, and diameter of drusenoid PEDs were inversely correlated with final visual acuity (all $P < 0.001$) and positively correlated with the rate of PED collapse (all $P < 0.001$).

CONCLUSIONS: Spectral-domain OCT signatures, plausibly attributable to anteriorly migrated RPE and disintegration of the RPE layer, precede or occur simultaneously with changes in volume of drusenoid PED during the lifecycle of this lesion.

PMID: 27760262

Retina. 2016 Oct 11. [Epub ahead of print]

Fluorescein-Assisted Subretinal Tissue Plasminogen Activator (tPA) Delivery For Submacular Hemorrhage.

Khan MA, Shahlaee A, Bansal AS, Maguire JL.

PURPOSE: To describe a surgical technique for fluorescein-assisted subretinal tissue plasminogen activator delivery during pars plana vitrectomy for submacular hemorrhage.

METHODS: Retrospective, interventional, consecutive case series.

RESULTS: Six eyes of 6 patients were reviewed. Etiology of submacular hemorrhage was age-related macular degeneration in 2 eyes and polypoidal choroidal vasculopathy in 4 eyes. Twenty-three-gauge pars plana vitrectomy was performed and fluorescein-stained tissue plasminogen activator was injected in the subretinal space through a 41-gauge cannula in all eyes. Sulfur hexafluoride (SF₆) gas ($n = 5$ eyes) or air ($n = 1$ eye) tamponade was instilled at the conclusion of surgery. Successful displacement of submacular hemorrhage was achieved in all eyes. Mean visual acuity improved from 20/693 preoperatively to 20/224 postoperatively ($P = 0.14$) at mean follow-up of 560 ± 464 days. No intraoperative or postoperative complications were encountered.

CONCLUSION: Fluorescein-assisted subretinal delivery of tissue plasminogen activator was well tolerated and allowed for improved visualization of subretinal bleb formation during pars plana vitrectomy for submacular hemorrhage.

PMID: 27755377

Retina. 2016 Sep 30. [Epub ahead of print]

HYPERSPECTRAL AUTOFLUORESCENCE IMAGING OF DRUSEN AND RETINAL PIGMENT EPITHELIUM IN DONOR EYES WITH AGE-RELATED MACULAR DEGENERATION.

Tong Y, Ben Ami T, Hong S, Heintzmann R, Gerig G, Ablonczy Z, Curcio CA, Ach T, Smith RT.

PURPOSE: To elucidate the molecular pathogenesis of age-related macular degeneration (AMD) and interpretation of fundus autofluorescence imaging, the authors identified spectral autofluorescence characteristics of drusen and retinal pigment epithelium (RPE) in donor eyes with AMD.

METHODS: Macular RPE/Bruch membrane flat mounts were prepared from 5 donor eyes with AMD. In 12

locations (1-3 per eye), hyperspectral autofluorescence images in 10-nm-wavelength steps were acquired at 2 excitation wavelengths (λ_{ex} 436, 480 nm). A nonnegative tensor factorization algorithm was used to recover 5 abundant emission spectra and their corresponding spatial localizations.

RESULTS: At λ_{ex} 436 nm, the authors consistently localized a novel spectrum (SDr) with a peak emission near 510 nm in drusen and sub-RPE deposits. Abundant emission spectra seen previously (S0 in Bruch membrane and S1, S2, and S3 in RPE lipofuscin/melanolipofuscin, respectively) also appeared in AMD eyes, with the same shapes and peak wavelengths as in normal tissue. Lipofuscin/melanolipofuscin spectra localizations in AMD eyes varied widely in their overlap with drusen, ranging from none to complete.

CONCLUSION: An emission spectrum peaking at ~510 nm (λ_{ex} 436 nm) appears to be sensitive and specific for drusen and sub-RPE deposits. One or more abundant spectra from RPE organelles exhibit characteristic relationships with drusen.

PMID: 27749696

Orv Hetil. 2016 Oct;157(42):1683-1690.

[Angiography of the ocular fundus without dye: Optical coherence tomography based angiography in exsudative age-related macular degeneration].[Article in Hungarian]

Resch M, Németh C, Barcsay G, Ecsedy M, Borbándy Á, Géhl Z, Balogh A, Szabó A, Nagy ZZ, Papp A.

INTRODUCTION: Vascular endothelial growth factor antibody therapy is an established treatment of exsudative age-related macular degeneration.

AIM: The morphologic characterisation of the macular microvasculature after longstanding treatment.

METHOD: Forty-eight patients (34 women and 14 men; age, 74.4 ± 8.0 years) were enrolled in the study. During follow-up time (53.8 ± 31.0 months), 7.6 ± 4.9 injections were administered in 56 eyes. Optical coherence tomography angiographic examination was performed with AngioVue (Optovue Inc. Fremont, CA, USA).

RESULTS: Distortion of the superficial retinal plexus and foveal avascular zone enlargement were noted in 5/56 eyes, deep retinal plexus defect was detected in 9/56 cases. Destruction of the choriocapillaries and the former neovascularisation could be found in 4 different patterns: 1. pigment epithelium and choriocapillary atrophy, 2. submacular scar, 3. active leaking choroidal neovascularisation, 4. intraretinal cysts.

CONCLUSION: Optical coherence tomography angiography is a novel non-invasive method, which enables the follow up of macular degeneration.

PMID: 27748129

Eye (Lond). 2016 Oct 21. [Epub ahead of print]

Clinical features and long-term progression of reticular pseudodrusen in age-related macular degeneration: findings from a multicenter cohort.

Gil JQ, Marques JP, Hogg R, Rosina C, Cachulo ML, Santos A, Staurenghi G, Chakravarthy U, Silva R.

Purpose: To determine whether reticular pseudodrusen (RPD) confer a long-term increased risk of progression to late age-related macular degeneration (AMD) in the fellow eye of patients with unilateral wet-AMD.

Patients and methods: This was a multicenter, combined prospective and retrospective, longitudinal, observational, study. Patients with wet-AMD in one eye were recruited from two centers and evaluated on

the risk of progression to late-AMD in the second eye (study eye). A minimum follow-up of 5 years was required, unless progression occurred first. Baseline retinal profile of patients was evaluated using multimodal imaging. Baseline images were graded by two separate centers.

Results: We recruited 88 patients (48 female) with a mean age of 75.6 ± 7.1 years and mean follow-up of 65.7 ± 20.9 months. Baseline prevalence of RPD was 58% (n=51). There was no statistically significant association of RPD with increased age ($P=0.29$) or sex distribution ($P=0.39$). The most sensitive image modality for RPD was IR (93%), followed by FAF (92%), OCT (74%), RF (33%) and CFP (29%). After 5 years, 54.50% (n=48) of the study eyes progressed to late-AMD. Of those, 81.25% (n=39) developed CNV and 18.75% (n=9) geographic atrophy. After correcting for age and sex, the presence of RPD was significantly associated with development of late-stage AMD ($OR=2.55$, $P=0.03$).

Conclusion: A multimodal approach is mandatory for RPD detection. RPD are highly prevalent in the fellow eyes of patients with unilateral neovascular AMD. Presence of RPD is associated with increased long-term risk of progression, highlighting the importance of comprehensive multimodal retinal imaging and careful monitoring of at-risk patients.

PMID: 27768118

Clin Hemorheol Microcirc. 2016 Oct 15. [Epub ahead of print]

Rheopheresis in vascular diseases.

Vass M, Diószegi Á, Németh N, Sógor V, Baráth S, Szalai E, Módis L, Pál S.

Abstract: Rheopheresis is an extracorporeal selective double-filtration procedure. In the first part of the treatment the blood is passes through the plasma filter, which separates blood cells from the plasma. Then the plasma flow to a second filter called MONET (Membranefiltration Optimised Novel Extracorporeal Treatment). The MONET filter retains high molecular weight proteins such LDL, Lp(a), fibrinogen, α_2 macroglobulin, vWF and IgM. Hereby the whole blood and plasma viscosity decrease, improves microcirculation, and has a positive effect on lipid profile as well. According to ASFA recommendation rheopheresis is a first line treatment in age-related dry macular degeneration and in sudden sensorineural hearing loss. There are other clinical situations in which rheopheresis has been used effectively. But only few data are available and large clinical trials have not been done in these diseases. In this paper we describe a case history and laboratory findings of a patient who suffers from age related dry macular degeneration and was successfully treated by rheopheresis.

PMID: 27767963

Pathogenesis

Neuroscience. 2016 Oct 14. [Epub ahead of print]

Light-induced retinal damage using different light sources, protocols and rat strains reveals LED phototoxicity.

Krigel A, Berdugo M, Picard E, Levy-Boukris R, Jaadane I, Jonet L, Dernigoghossian M, Andrieu-Soler C, Torriglia A, Behar-Cohen F.

Abstract: To save energy, the European directives from the Eco-design of Energy Using Products (2005/32/CE) have recommended the replacement of incandescent lamps by more economic devices such as Light Emitting Diodes (LEDs). However, the emission spectrum of these devices is enriched in blue radiations, known to be potentially dangerous to the retina. Recent studies showed that light exposure contributes to the onset of early stages of age-related macular degeneration (AMD). Here, we investigate, in albinos and pigmented rats, the effects of different exposure protocols. Twenty-four hours exposure at high luminance was compared to a cyclic (dark/light) exposure at domestic levels for 1week and 1month, using different

LEDs (Cold-white, blue and green), as well as fluorocompact bulbs and fluorescent tubes. The data suggest that the blue component of the white-LED may cause retinal toxicity at occupational domestic illuminance and not only in extreme experimental conditions, as previously reported. It is important to note that the current regulations and standards have been established on the basis of acute light exposure and do not take into account the effects of repeated exposure.

PMID: 27751961

Toxicology. 2016 Oct 14. [Epub ahead of print]

All-trans-retinal dimer formation alleviates the cytotoxicity of all-trans-retinal in human retinal pigment epithelial cells.

Li J, Zhang Y, Cai X, Xia Q, Chen J, Liao Y, Liu Z, Wu Y.

Abstract: Effective clearance of all-trans-retinal (atRAL) from retinal pigment epithelial (RPE) cells is important for avoiding its cytotoxicity. However, the metabolism of atRAL in RPE cells is poorly clarified. The present study was designed to analyze metabolic products of atRAL and to compare the cytotoxicity of atRAL versus its derivative all-trans-retinal dimer (atRAL-dimer) in human RPE cells. We found that all-trans-retinol (atROL) and a mixture of atRAL condensation metabolites including atRAL-dimer and A2E were generated after incubating RPE cells with atRAL for 6h, and the amount of atRAL-dimer was significantly higher than that of A2E. In the eyes of *Rdh8*^{-/-} *Abca4*^{-/-} mice, a mouse model with defects in retinoid cycle that displays some symbolic characteristics of age-related macular degeneration (AMD), the level of atRAL-dimer was increased compared to wild-type mice, and was even much greater than that of A2E & isomers. The cytotoxicity of atRAL-dimer was reduced compared with its precursor atRAL. The latter could provoke intracellular reactive oxygen species (ROS) overproduction, increase the mRNA expression of several oxidative stress related genes (*Nrf2*, *HO-1*, and γ -GCSH), and induce Δ Ym loss in RPE cells. By contrast, the abilities of atRAL-dimer to induce intracellular ROS and oxidative stress were much weaker versus that of concentration-matched atRAL, and atRAL-dimer exhibited no toxic effect on mitochondrial function at higher concentrations. In conclusion, the formation of atRAL-dimer during atRAL metabolic process ameliorates the cytotoxicity of atRAL by reducing oxidative stress.

PMID: 27751755

Exp Eye Res. 2016 Oct 14. [Epub ahead of print]

The Alzheimer's-related amyloid beta peptide is internalised by R28 neuroretinal cells and disrupts the microtubule associated protein 2 (MAP-2).

Taylor-Walker G, Lynn SA, Keeling E, Munday R, Johnston DA, Page A, Scott JA, Goverdhan S, Lotery AJ, Ratnayaka JA.

Abstract: Age-related Macular Degeneration (AMD) is a common, irreversible blinding condition that leads to the loss of central vision. AMD has a complex aetiology with both genetic as well as environmental risks factors, and share many similarities with Alzheimer's disease. Recent findings have contributed significantly to unravelling its genetic architecture that is yet to be matched by molecular insights. Studies are made more challenging by observations that aged and AMD retinas accumulate the highly pathogenic Alzheimer's-related Amyloid beta ($A\beta$) group of peptides, for which there appears to be no clear genetic basis. Analyses of human donor and animal eyes have identified retinal $A\beta$ aggregates in retinal ganglion cells (RGC), the inner nuclear layer, photoreceptors as well as the retinal pigment epithelium. $A\beta$ is also a major drusen constituent; found correlated with elevated drusen-load and age, with a propensity to aggregate in retinas of advanced AMD. Despite this evidence, how such a potent driver of neurodegeneration might impair the neuroretina remains incompletely understood, and studies into this important aspect of retinopathy remains limited. In order to address this we exploited R28 rat retinal cells which due to its heterogeneous nature, offers diverse neuroretinal cell-types in which to study the molecular pathology of

A β . R28 cells are also unaffected by problems associated with the commonly used RGC-5 immortalised cell-line, thus providing a well-established model in which to study dynamic A β effects at single-cell resolution. Our findings show that R28 cells express key neuronal markers calbindin, protein kinase C and the microtubule associated protein-2 (MAP-2) by confocal immunofluorescence which has not been shown before, but also calretinin which has not been reported previously. For the first time, we reveal that retinal neurons rapidly internalised A β 1-42, the most cytotoxic and aggregate-prone amongst the A β family. Furthermore, exposure to physiological amounts of A β 1-42 for 24 h correlated with impairment to neuronal MAP-2, a cytoskeletal protein which regulates microtubule dynamics in axons and dendrites. Disruption to MAP-2 was transient, and had recovered by 48 h, although internalised A β persisted as discrete puncta for as long as 72 h. To assess whether A β could realistically localise to living retinas to mediate such effects, we subretinally injected nanomolar levels of oligomeric A β 1-42 into wildtype mice. Confocal microscopy revealed the presence of focal A β deposits in RGC, the inner nuclear and the outer plexiform layers 8 days later, recapitulating naturally-occurring patterns of A β aggregation in aged retinas. Our novel findings describe how retinal neurons internalise A β to transiently impair MAP-2 in a hitherto unreported manner. MAP-2 dysfunction is reported in AMD retinas, and is thought to be involved in remodelling and plasticity of post-mitotic neurons. Our insights suggest a molecular pathway by which this could occur in the senescent eye leading to complex diseases such as AMD.

PMID: 27751744

Discov Med. 2016 Sep;22(120):129-145.

Association of lipids with age-related macular degeneration.

Shen J, He J, Wang F.

Abstract: In the past decades, much investigation has been done on the role of lipids in the development and progression of age-related macular degeneration (AMD). The lipids involved in those research studies had included PUFAs, phospholipids, sphingolipids, cholesterol, lipid protein, etc. There are a large number of clinical research studies on the association of PUFAs with the development and progression of AMD. The relationship between cholesterol level and AMD has been explored for decades and much data and analysis results have been obtained. As for phospholipids, sphingolipids, and lipid proteins, progress towards understanding their role in AMD has been achieved mainly at the laboratory level. The goal of this paper is to review the most recent published findings according to different lipid types and discuss the roles various lipids might play in AMD pathogenesis and their implications in future preventive measures and treatments.

PMID: 27755968

Nat Chem Biol. 2016 Oct 24. [Epub ahead of print]

Small-molecule factor D inhibitors targeting the alternative complement pathway.

Maibaum J, Liao SM, Vulpetti A, et al.

Abstract: Complement is a key component of the innate immune system, recognizing pathogens and promoting their elimination. Complement component 3 (C3) is the central component of the system. Activation of C3 can be initiated by three distinct routes-the classical, the lectin and the alternative pathways-with the alternative pathway also acting as an amplification loop for the other two pathways. The protease factor D (FD) is essential for this amplification process, which, when dysregulated, predisposes individuals to diverse disorders including age-related macular degeneration and paroxysmal nocturnal hemoglobinuria (PNH). Here we describe the identification of potent and selective small-molecule inhibitors of FD. These inhibitors efficiently block alternative pathway (AP) activation and prevent both C3 deposition onto, and lysis of, PNH erythrocytes. Their oral administration inhibited lipopolysaccharide-induced AP activation in FD-humanized mice. These data demonstrate the feasibility of inhibiting the AP with small-

molecule antagonists and support the development of FD inhibitors for the treatment of complement-mediated diseases.

PMID: 27775713

Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5558-5567.

Fundus Camera-Delivered Light-Induced Retinal Degeneration in Mice With the RPE65 Leu450Met Variant is Associated With Oxidative Stress and Apoptosis.

Zhong X, Aredo B, Ding Y, Zhang K, Zhao CX, Ufret-Vincenty RL.

PURPOSE: Oxidative stress, partly due to light, has an important role in many retinal diseases, including macular degeneration and retinal dystrophies. The Leu450Met variant of RPE65 is expressed in C57BL/6 and in many genetically modified mice. It confers significant resistance to light induced retinal degeneration (LIRD). Our goal was to develop an effective and efficient method to induce LIRD in resistant mice that would recapitulate mechanisms seen in known models of LIRD.

METHODS: The retinas of C57BL/6J mice were exposed to light using a murine fundus camera. Two protocols (with and without intraperitoneal fluorescein) were used. Optical coherence tomography (OCT) helped determine the location and extent of retinal damage. Histology, TUNEL assay, quantitative (q) PCR, and immunohistochemistry were performed.

RESULTS: Both protocols consistently generated LIRD in C57BL/6J mice. Optical coherence tomography and histology demonstrated that retinal damage starts at the level of the photoreceptor/outer retina and is more prominent in the superior retina. Fundus camera-delivered light-induced retinal degeneration (FCD-LIRD) is associated with apoptosis, subretinal microglia/macrophages, increased expression of oxidative stress response genes, and C3d deposition.

CONCLUSIONS: We characterize two new models of light-induced retinal degeneration that are effective in C57BL/6J mice, and can be modulated in terms of severity. We expect FCD-LIRD to be useful in exploring mechanisms of LIRD in resistant mice, which will be important in increasing our understanding of the retinal response to light damage and oxidative stress.

PMID: 27768794

Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5525-5534.

Thy-1 Regulates VEGF-Mediated Choroidal Endothelial Cell Activation and Migration: Implications in Neovascular Age-Related Macular Degeneration.

Wang H, Han X, Kunz E, Hartnett ME.

PURPOSE: This study addresses the hypothesis that age-related stresses upregulate Thy-1 in choroidal endothelial cells (CECs) and contribute to CEC activation and migration, processes important in choroidal neovascularization (CNV).

METHODS: Measurements were made of Thy-1 protein (Western blot) in CECs and Thy-1 mRNA (real time quantitative PCR) in CECs treated with VEGF, CCL11, or PBS or in RPE/choroids from young or old donors or lasered or nonlasered mice. Immunolabeled Thy-1 in ocular sections was compared from young versus old human donor eyes or those with or without neovascular AMD or from lasered versus nonlasered mice. Choroidal endothelial cells transfected with Thy-1 or control siRNA or pretreated with Thy-1 blocking peptide or control were stimulated with VEGF or 7-ketocholesterol (7-KC). Choroidal endothelial cell migration, proliferation, cytoskeletal stress fibers, Rac1 activation, and phosphorylated VEGF receptor 2 (VEGFR2), integrin β 3, and Src were measured. Statistics were performed using ANOVA.

RESULTS: Thy-1 was expressed in retinal ganglion cells and in vascular endothelial-cadherin-labeled choroid and localized to human or mouse laser-induced CNV lesions. Thy-1 protein and mRNA were significantly increased in CECs treated with VEGF or CCL11 and in RPE/choroids from aged versus young donor eyes or from lasered mice versus nonlasered controls. Knockdown or inhibition of Thy-1 in CECs significantly reduced VEGF-induced CEC migration and proliferation, stress fiber formation and VEGFR2, Src, integrin $\beta 3$ and Rac1 activation, and 7-KC-induced Rac1 and Src activation.

CONCLUSIONS: Thy-1 in CECs regulates VEGF-induced CEC activation and migration and links extracellular 7-KC to intracellular signaling. Future studies elucidating Thy-1 mechanisms in neovascular AMD are warranted.

PMID: 27768790

Epidemiology

Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5593-5601.

Epidemiology of Reticular Pseudodrusen in Age-Related Macular Degeneration: The Rotterdam Study.

Buitendijk GH, Hooghart AJ, Brussee C, de Jong PT, Hofman A, Vingerling JR, Klaver CC.

PURPOSE: Reticular pseudodrusen (RPD) are considered to be a distinct feature in AMD. Population studies have studied the epidemiology of RPD using standard color fundus photographs (CFP). However, recent studies have shown that RPD are better imaged using near-infrared (NIR) imaging. We studied the epidemiology of RPD in a large population-based study using NIR and CFP.

METHODS: Participants aged 65+ years from the Rotterdam Study underwent ophthalmologic examination including NIR and CFP. Both images were graded for the presence of RPD and soft indistinct drusen (SID). Associations with demographic and environmental factors, 26 genetic variants, and total genetic risk score were analyzed using logistic regression analysis.

RESULTS: Reticular pseudodrusen were detected in 137 (4.9%) of 2774 study participants; of these, 92.7% were detected with NIR imaging and 38% on CFP. Most eyes with RPD showed presence of SID, whereas other drusen types coincided less frequently. Reticular pseudodrusen were significantly associated with age (odds ratio [OR] 1.21, 95% Confidence Interval [CI] 1.17-1.24) and female sex (OR 2.10, 95% CI 1.41-3.13). Environmental factors did not show a significant association with RPD. Major AMD risk variants were significantly associated with RPD and SID; however, ARMS2, C3, and VEGFA were more associated with RPD (RPD vs. SID $P < 0.05$). Total genetic risk score did not differ significantly ($P = 0.88$).

CONCLUSION: Detection of RPD was better with NIR imaging than on CFP in a population-based setting. Presence of RPD often coincided with presence of SID; however, they showed quantitative differences in genetic risk profile.

PMID: 27768796

Genetics

Ophthalmology. 2016 Oct 19. [Epub ahead of print]

Heritability of Choroidal Thickness in the Amish.

Sardell RJ, Nittala MG, Adams LD, et al

PURPOSE: To evaluate the heritability of choroidal thickness and its relationship to age-related macular

degeneration (AMD).

DESIGN: Cohort study.

PARTICIPANTS: Six hundred eighty-nine individuals from Amish families with early or intermediate AMD.

METHODS: Ocular coherence tomography was used to quantify choroidal thickness, and fundus photography was used to classify eyes into categories using a modified Clinical Age-Related Maculopathy Staging (CARMS) system. Repeatability and heritability of choroidal thickness and its phenotypic and genetic correlations with the AMD phenotype (CARMS category) were estimated using a generalized linear mixed model (GLMM) approach that accounted for relatedness, repeated measures (left and right eyes), and the effects of age, gender, and refraction.

MAIN OUTCOME MEASURES:

Heritability of choroidal thickness and its phenotypic and genetic correlation with the AMD phenotype (CARMS category).

RESULTS: Phenotypic correlation between choroidal thickness and CARMS category was moderate (Spearman's rank correlation, $r_s = -0.24$; $n = 1313$ eyes) and significant (GLMM posterior mean, -4.27 ; 95% credible interval [CI], -7.88 to -0.79 ; $P = 0.02$) after controlling for relatedness, age, gender, and refraction. Eyes with advanced AMD had thinner choroids than eyes without AMD (posterior mean, -73.8 ; 95% CI, -94.7 to -54.6 ; $P < 0.001$; $n = 1178$ eyes). Choroidal thickness was highly repeatable within individuals (repeatability, 0.78 ; 95% CI, 0.68 to 0.89) and moderately heritable (heritability, 0.40 ; 95% CI, 0.14 to 0.51), but did not show significant genetic correlation with CARMS category, although the effect size was moderate (genetic correlation, -0.18 ; 95% CI, -0.49 to 0.16). Choroidal thickness also varied with age, gender, and refraction. The CARMS category showed moderate heritability (heritability, 0.49 ; 95% CI, 0.26 to 0.72).

CONCLUSIONS: We quantify the heritability of choroidal thickness for the first time, highlighting a heritable, quantitative trait that is measurable in all individuals regardless of AMD affection status, and moderately phenotypically correlated with AMD severity. Choroidal thickness therefore may capture variation not captured by the CARMS system. However, because the genetic correlation between choroidal thickness and AMD severity was not significant in our data set, genes associated with the 2 traits may not overlap substantially. Future studies should therefore test for genetic variation associated with choroidal thickness to determine the overlap in genetic basis with AMD.

PMID: 27771146

Int J Environ Res Public Health. 2016 Oct 18;13(10).

The Association between LIPC rs493258 Polymorphism and the Susceptibility to Age-Related Macular Degeneration.

Wang Y, Wang M, Zhang X, Nie J, Zhang M, Liu X, Ma L.

Abstract: The purpose of this study was to evaluate the association of the hepatic lipase (LIPC) rs493258 polymorphism and susceptibility to age-related macular degeneration (AMD). A systematic search in PubMed, EMBASE, and ISI web of science databases was performed to identify eligible published studies without language restrictions up to April 2016. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) in different stages of AMD were estimated under different genetic models using meta-analytic methods. Seven studies comprising 20,559 cases and 17,200 controls met the inclusion criteria and were included in the meta-analysis. The LIPC rs493258 polymorphism showed a significant association with a lower risk of AMD under the allelic model (OR = 0.87 , 95% CI = 0.84 - 0.90). Significant relationships between the variant and AMD were also observed in other genetic models (OR ranging from 0.71 to 0.86 , all $p < 0.05$). Stratified analysis based on ethnicity found that LIPC rs493258 polymorphism had a significant association with the decreased risk of the disease in the Caucasian population, but not in the

Asian population. For late AMD, significant associations of the rs493258 polymorphism with a lower risk of this disease were also observed in the allelic genetic model (OR = 0.87, 95% CI = 0.83-0.90). This meta-analysis demonstrates that the T allele in the LIPC rs493258 polymorphism was significantly associated with the risk of any and late AMD. The associations of the locus with early and late AMD risk in various populations need further exploration.

PMID: 27763569

Diet, lifestyle and low vision

Int J Mol Sci. 2016 Oct 14;17(10).

Development of an Advanced HPLC-MS/MS Method for the Determination of Carotenoids and Fat-Soluble Vitamins in Human Plasma.

Hrvolová B, Martínez-Huélamo M, Colmán-Martínez M, Hurtado-Barroso S, Lamuela-Raventós RM, Kalina J.

Abstract: The concentration of carotenoids and fat-soluble vitamins in human plasma may play a significant role in numerous chronic diseases such as age-related macular degeneration and some types of cancer. Although these compounds are of utmost interest for human health, methods for their simultaneous determination are scarce. A new high pressure liquid chromatography (HPLC)-tandem mass spectrometry (MS/MS) method for the quantification of selected carotenoids and fat-soluble vitamins in human plasma was developed, validated, and then applied in a pilot dietary intervention study with healthy volunteers. In 50 min, 16 analytes were separated with an excellent resolution and suitable MS signal intensity. The proposed HPLC-MS/MS method led to improvements in the limits of detection (LOD) and quantification (LOQ) for all analyzed compounds compared to the most often used HPLC-DAD methods, in some cases being more than 100-fold lower. LOD values were between 0.001 and 0.422 µg/mL and LOQ values ranged from 0.003 to 1.406 µg/mL, according to the analyte. The accuracy, precision, and stability met with the acceptance criteria of the AOAC (Association of Official Analytical Chemists) International. According to these results, the described HPLC-MS/MS method is adequately sensitive, repeatable and suitable for the large-scale analysis of compounds in biological fluids.

PMID: 27754400

Indian J Med Res. 2016 Jun;143(6):756-762.

Homocysteine & its metabolite homocysteine-thiolactone & deficiency of copper in patients with age related macular degeneration - A pilot study.

Bharathselvi M, Biswas S, Raman R, Selvi R, Coral K, Narayanansamy A, Ramakrishnan S, Sulochana KN.

BACKGROUND & OBJECTIVES: Age related macular degeneration (ARMD) is a leading cause of blindness, particularly in persons above 60 yr of age. Homocysteine is implicated in many ocular diseases including ARMD. This study was undertaken to assess the status and relationship between plasma homocysteine, homocysteine - thiolactone, homocysteinylated protein and copper levels in patients with ARMD.

METHODS: A total of 16 patients with ARMD and 16 age-matched controls were recruited for the study. Plasma glutathione, homocysteine, homocysteine - thiolactone and extent of homocysteine conjugation with proteins, copper and thiobarbituric acid reactive substances were measured.

RESULTS: Homocysteine levels were elevated with increase in homocysteine-thiolactone, thiobarbituric acid reactive substances and a decrease of glutathione. The levels of homocysteinylated protein were elevated in ARMD. The elevated homocysteine, homocysteine-thiolactone correlated with the decrease in

copper level.

INTERPRETATION & CONCLUSIONS: Elevated homocysteine and its metabolite homocysteine-thiolactone and decreased levels of copper may play an important role in the pathogenesis of ARMD.

PMID: 27748300

Patient Prefer Adherence. 2016 Oct 3;10:1853-1854. eCollection 2016.

Depression and anxiety in age-related macular degeneration.

Kim ES, Kim Y, Yu SY, Kim M.

PMID: 27757018

Disclaimer: This newsletter is provided as a free service to eye care professionals by the Macular Disease Foundation Australia. The Macular Disease Foundation cannot be liable for any error or omission in this publication and makes no warranty of any kind, either expressed or implied in relation to this publication.