Macular Disease Foundation AUSTRALIA
Our focus is your vision

# MD Research News

Issue 259

Thursday 16 December, 2015

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

**Retina. 2015 Dec 11. [Epub ahead of print]**

**IMPLICATION OF RECURRENT OR RETAINED FLUID ON OPTICAL COHERENCE TOMOGRAPHY FOR VISUAL ACUITY DURING ACTIVE TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION WITH A TREAT AND EXTEND PROTOCOL.**

Wickremasinghe SS, Janakan V, Sandhu SS, Amirul-Islam FM, Abedi F, Guymer RH.

PURPOSE: Assess the correlation between optical coherence tomography findings and change in vision for patients receiving "treat and extend" protocol ranibizumab for neovascular age-related macular degeneration.

METHODS: Optical coherence tomography analysis and best-corrected visual acuity (BCVA) change: mild = 5 to 9 letters, moderate = 10 to 14 letters, and severe ≥15 letters.

RESULTS: A total of 103 eyes (99 patients, 63% female, 65-91 years) followed for 20.8 ± 4.9 months. By 12 months, there were 1.38 ± 0.59 instances of intraretinal fluid (IRF)/subretinal fluid recurrence on optical coherence tomography and 1.25 ± 1.00 instances of BCVA loss (≥5 letters) per patient. When BCVA was lost, IRF/subretinal fluid was present in 37.3% of cases. Occurrences of severe BCVA loss were less likely to recover vision than when BCVA loss was mild (5.9% vs. 75.6%, P = 0.001). New occurrence of IRF (33.9%) or subretinal fluid (29.6%) was more likely to lead to BCVA loss, compared with dry (16.6%) or persistent IRF (11.9%) or persistent subretinal fluid (14%, P < 0.001). With persistent fluid, any new loss of vision had a lower chance of recovery than when fluid was new in onset (64.3% vs. 85.3%, P = 0.04).

CONCLUSION: During ranibizumab treatment, vision can decrease without signs of fluid. When fluid is present, IRF is associated with poorer vision. New occurrence of any fluid on optical coherence tomography is likely to lead to vision loss, but small amounts of persistent fluid can be tolerated without compromising vision.

PMID: 26655608 [PubMed - as supplied by publisher]

**Retina. 2015 Dec 11. [Epub ahead of print]**

**RETINAL PIGMENT EPITHELIAL TEAR AND ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY IN EXUDATIVE AGE-RELATED MACULAR DEGENERATION: Clinical Course and Long-Term Prognosis.**

Heimes B, Farecki ML Jr, Bartels S, Barrelmann A, Gutfleisch M, Spital G, Lommatzsch A, Pauleikhoff D.

BACKGROUND: To document the long-term outcome in cases of retinal pigment epithelial (RPE) tears after treatment of vascularized pigment epithelial detachments with anti-vascular endothelial growth factor therapy.

METHODS: A retrospective analysis of the long-term outcome of a consecutive series of eyes with RPE tear developed during anti-vascular endothelial growth factor therapy for pigment epithelial detachment associated with choroidal neovascularization or retinal angiomatous proliferation (vascularized pigment epithelial detachment) was performed. Best-corrected visual acuity (BCVA), spectral domain optical coherence tomography, and autofluorescence images and also fluorescein angiograms were analyzed to determine the functional and morphologic development over time.

RESULTS: The long-term outcome of 22 eyes (21 patients, 13 women and 8 men; 65-85 years; mean: 76 years) with RPE tear was performed with minimal follow-up of 3 years (range: 3-5 years, mean: 44 months) and re-treatment with different therapeutic strategies. The eyes were differentiated in 2 groups according to the course of BCVA after the first 2 years of follow-up: Group 1 (11 eyes) demonstrated a stabilized or improved BCVA after 2 years and Group 2 (11 eyes) demonstrated a decrease in BCVA after 2 years. The initial BCVA between both groups was comparable. Also the mean initial size of the RPE tear was the same between the 2 groups, the area of the RPE tear decreased continuously during follow-up in Group 1, whereas this was the case in Group 2 only at the beginning of treatment with a further increase of the size of the RPE tear with longer follow-up. This corresponded with a different morphologic development between the two groups. In Group 1, increasing recovery of autofluorescence at the RPE-free area was visible beginning from the outer border, whereas in Group 2, further growth of the neovascular complex in the area of the RPE tear was observed resulting in larger fibrovascular scars. In addition, in both groups, the development of hyperreflective tissue was seen on spectral domain optical coherence tomography in the RPE-free area. The major therapeutic difference between the 2 groups was a significantly larger number of injections especially during the first year in Group 1.

CONCLUSION: The development of RPE tear after anti-vascular endothelial growth factor therapy for vascularized pigment epithelial detachment in exudative age-related macular degeneration does not necessarily result in large disciform scars and functional loss, but multiple injections seem to be beneficial especially in the first year. With this strategy, RPE tears seem to be covered by autofluorescent and hyperreflective tissue and a regrowth of the neovascular complex can be prohibited. As a result, photoreceptor cells regain their metabolic support with functional recovery.

PMID: 26655607 [PubMed - as supplied by publisher]

**Hell J Nucl Med. 2015 Sep-Dec;18 Suppl 1:33-41.**

**Real-world treatment of diabetic macular oedema: a comparison of combined ranibizumab plus macular LASER with macular LASER monotherapy.**

Zygoura V, Papavasileiou E, Vavvas DG, Cortis D, Eleftheriadis H, Jackson TL.

OBJECTIVE: To study real world outcomes of ranibizumab (Lucentis) intravitreal injection in diabetic macular oedema (DMO).

SUBJECTS AND METHODS: We included 100 patients with DMO. Those who had optical coherence tomography central retinal thickness (CRT) of 400μm or more (Group 1) underwent combination treatment with ranibizumab and macular LASER, while those with CRT less than 400μm (Group 2) had LASER monotherapy. The primary outcome measure was change in best corrected visual acuity (BCVA) from baseline. Secondary outcomes were change of CRT from baseline, the number of intravitreal injections in group one during the first and second year of follow-up and the proportion of LASER sessions in both groups at 2 years follow-up. Patients' lipid profile was compared to the presence and extent of macular hard exudates, quantified using masked readers and image analysis software.

RESULTS: Group 1 showed better outcomes in terms of BCVA and CRT compared to Group 2 during the two-year follow-up period. The mean number of ranibizumab intravitreal injections in Group 1 was reduced from 3.86 (standard deviation±1.37) in the first year to 2.02 in the second year. At 2 years, Group 1 had a higher proportion of individuals that had undergone 3 macular LASER treatments (4% Group 1, 28% Group 2). The presence of hard exudates was associated with higher total cholesterol (P=0.004 and P=0.041

group 1 and 2 respectively) and with higher low density lipoprotein (LDL) cholesterol (P=0.01 and P=0.045 respectively). The size of hard exudates was associated with higher total cholesterol (P=0.02 and P=0.03 respectively) and with higher LDL cholesterol (P=0.003 and P=0.01 respectively). Neither high density lipoprotein (HDL) cholesterol, nor triglycerides were related to the presence or size of hard exudates. No serious adverse events were attributed to either LASER or ranibizumab.

CONCLUSIONS: Combination treatment of intravitreal ranibizumab injections and macular LASER appears safe and effective over two years. The need for injection declines over time. There is an association between higher levels of serum total and LDL cholesterol and the presence and the extent of hard exudates.

PMID: 26665210 [PubMed - as supplied by publisher]

**Hell J Nucl Med. 2015 Sep-Dec;18 Suppl 1:29-32.**

**Intravitreal aflibercept (A-IVI) for the treatment of neovascular age-related macular degeneration (nv-AMD): one year experience.**

Papavasileiou E, Zygoura V, Richardson T, Cortis D, Eleftheriadis H, Jackson TL.

OBJECTIVE: To report the anatomical and functional results of intravitreal injections of aflibercept (Eylea) (A-IVI) for the treatment of naïve eyes with neovascular age-related macular degeneration (nv-AMD).

SUBJECTS AND METHODS: This retrospective, one-center, non-comparative chart review included 26 treatment naïve eyes with nv-AMD of 26 patients (14 male) with a mean age of 80.5 (range 63-91) who had a complete follow-up of 14 months. The morphological analysis included spectral domain optical coherence tomography and fundus fluorescein angiography, while the functional assessment included logarithm of the minimum angle of resolution (LogMAR) best correct visual acuity (BCVA). The timing of the follow-up was: baseline, 3, 6, and 14 months. All patients received 8 A-IVI according to the protocol (first 3 consecutive monthly A-IVI, followed by bi-monthly retreatment for the first year, regardless of disease activity as per local guidelines). Statistical analysis was performed using ANOVA. Improvement of visual acuity more than 15 letters was considered as "improvement", less than 5 letters as "stable" and any letter loss as "worsening".

RESULTS: Mean±standard deviation LogMAR visual acuity improved from 0.26±0.15 at presentation to 0.14±0.20 at the final follow-up of 14 months (P=0.02). BCVA was stable in 23.1%, improved in 61.5% (16 eyes) worsened in 15.4%. A mean pretreatment central macular thickness of 409μm reduced significantly to 229μm at month 14 (P<0.02). The OCT of eyes with worsened BCVA showed resolution of retinal fluid but presence of subretinal fibrosis. No adverse events were attributed to aflibercept.

CONCLUSIONS: Patients who had a worsening in visual acuity were found to have longer duration of symptoms prior to treatment and presence of geographic atrophy, and/or subretinal haemorrhage and/or subretinal fibrosis at baseline. From our experience, with 14 months follow-up, A-IVI is an effective treatment for treatment naïve patients with nv-AMD. Our real world results were similar to pivotal trials.

PMID: 26665209 [PubMed - as supplied by publisher]

**Clin Ophthalmol. 2015 Dec 1;9:2243-2250.**

**Current barriers to treatment for wet age-related macular degeneration (wAMD): findings from the wAMD patient and caregiver survey.**

Varano M, Eter N, Winyard S, Wittrup-Jensen KU, Navarro R, Heraghty J.

PURPOSE: A cross-sectional survey to evaluate the current management of wet age-related macular degeneration (wAMD) and to identify barriers to treatment from a patient and caregiver perspective.

METHODS: An ophthalmologist-devised questionnaire was given to a global cohort of patients who were receiving (or had previously received) antivascular endothelial growth factor injections and to caregivers (paid and unpaid) to evaluate the impact of wAMD on their lives.

RESULTS: Responders included 910 patients and 890 caregivers; wAMD was diagnosed in both eyes in 45% of patients, and 64% had been receiving injections for > 1 year. Many caregivers were a child/grandchild (47%) or partner (23%) of the patient; only 7% were professional caregivers. Most (73%) patients visited a health care professional within 1 month of experiencing vision changes and 54% began treatment immediately. Most patients and caregivers reported a number of obstacles in managing wAMD, including the treatment itself (35% and 39%, respectively). Sixteen percent of patients also missed a clinic visit.

CONCLUSION: Most patients seek medical assistance promptly for a change in vision; however, about a quarter of them do not. This highlights a lack of awareness surrounding eye health and the impact of a delayed diagnosis. Most patients and caregivers identified a number of obstacles in managing wAMD.

PMID: 26664038 [PubMed - as supplied by publisher]

**Retina. 2015 Dec 11. [Epub ahead of print]**

**SHORT-TERM SAFETY PROFILE OF INTRAVITREAL ZIV-AFLIBERCEPT.**

Chhablani J, Narayanan R, Mathai A, Yogi R, Stewart M.

AIM: To evaluate the safety of intravitreal ziv-aflibercept (Zaltrap) in the treatment choroidal neovascularization secondary to age-related macular degeneration.

METHODS: Eligible eyes with choroidal neovascularization secondary to age-related macular degeneration each received a single intravitreal injection of ziv-aflibercept. Comprehensive ophthalmic examinations and detailed systemic evaluations were performed at baseline and Days 1, 7, and 30 after injection, and International Society for Clinical Electrophysiology of Vision standard electroretinography was performed at baseline and Day 30. Primary outcome measures were safety parameters that included signs of clinical and electroretinographic toxicity. Secondary outcome measures included changes in best-corrected visual acuity and central subfield thickness.

RESULTS: Twelve eyes of 12 patients were treated. None of the patients complained of blurred vision, ocular pain, or bulbar injection at any of the follow-up visits, nor was intraocular inflammation noted. There were no significant differences in implicit times, "a" and "b" wave amplitudes, or b/a ratios at 1 month when compared with baseline (P = 0.4). None of the patients experienced serious ocular or systemic adverse events. Mean best-corrected visual acuity improved only slightly at 30 days (LogMAR 0.45 ± 0.31 [Snellen equivalent: 20/60]) compared with baseline (LogMAR 0.37 ± 0.24 [Snellen equivalent: 20/50]; P = 0.51).

CONCLUSION: Single intravitreal injections of ziv-aflibercept into eyes with neovascular age-related macular degeneration appear to be safe through 1 month. Ziv-aflibercept could become a safe, low-cost therapy for macular diseases in developing countries and in those where intravitreal aflibercept (Eylea) is not available.

PMID: 26655620 [PubMed - as supplied by publisher]

**Int Ophthalmol. 2015 Dec 7. [Epub ahead of print]**

**Efficacy of single-dose dexamethasone implantation in patients with persistent diabetic macular edema.**

Arıkan Yorgun M, Toklu Y, Mutlu M, Uysal BS, Çakmak HB.

Abstract: To investigate the efficacy of single-dose intravitreal dexamethasone implantation in the treatment of persistent diabetic macular edema (DME) unresponsive to 3 consecutive ranibizumab injections over a period of 6 months. Forty-one patients with a previous history of treatment for DME including at least three consecutive intravitreal ranibizumab injections were enrolled in this retrospective study. Main outcome measures were change in best-corrected visual acuity (BCVA), central macular thickness (CMT), and intraocular pressure from baseline to 6th month. At the baseline, the mean CMT was 572.4 ± 123.1 μm which improved to 264.2 ± 114.4, 317.7 ± 141.7, 410.6 ± 169.1, and 382.8 ± 181.5 μm at the 1st, 3rd, 5th, and 6th month, respectively ($p < 0.05$). The preoperative mean BCVA was 0.85 ± 0.54 logMAR units which improved to 0.76 ± 0.5 ($p = 0.08$), 0.69 ± 0.4 ($p = 0.02$), 0.74 ± 0.4 ($p = 0.284$), and 0.72 ± 0.3 ($p = 0.489$) logMAR units at the 1st, 3rd, 5th, and 6th months, respectively. Additional injections were required for 13 (31 %) eyes at 3rd month and 14 (34 %) eyes at 5th month due to recurrence of macular edema. Intravitreal dexamethasone implantation caused a significant improvement of BCVA and reduction of CMT in the patients with persistent DME that were unresponsive to 3 consecutive ranibizumab injections. However, retreatment before 6 months in the majority of the patients was needed despite the beneficial effects after the index procedure.

PMID: 26644130 [PubMed - as supplied by publisher]

## Other treatment & diagnosis

**PLoS One. 2015 Dec 14;10(12):e0144894.**

**Foveal Damage Due to Subfoveal Hemorrhage Associated with Branch Retinal Vein Occlusion.**

Muraoka Y, Tsujikawa A, Takahashi A, Iida Y, Murakami T, Ooto S, Suzuma K, Uji A, Yoshimura N.

Abstract: To investigate the functional and morphologic prognoses of eyes with subfoveal hemorrhage from acute branch retinal vein occlusion (BRVO), and to examine the effect of intravitreal ranibizumab injection (IVR) on these prognoses, we assessed 81 eyes with acute BRVO, of which 38 did not receive IVR [IVR(-) group], and 43 were treated with IVR [IVR(+) group] for macular edema. The foveal morphologic changes were examined via optical coherence tomography (OCT). At initial examination, 63 eyes exhibited subfoveal hemorrhage. At final examination, the defect lengths in the foveal external limiting membrane (ELM) and ellipsoid lines in these eyes were longer, and final VA was significantly poorer, compared with eyes without subfoveal hemorrhage. In comparisons between the final measurements in eyes with subfoveal hemorrhage in the IVR(-) and IVR(+) groups, while there were no differences in initial ocular conditions, final VA was significantly better in the IVR(+) group. The defects in the ELM and ellipsoid lines in the IVR(+) group were shorter than those of the IVR(-) group ($p = 0.002$ in both). Final VA was correlated with the defect lengths of foveal ELM and ellipsoid lines in both the IVR(-) and IVR(+) groups (both $p < 0.001$). In addition, the defect lengths of foveal ELM and ellipsoid lines were closely correlated with the duration of subfoveal hemorrhage (both $p < 0.001$). BRVO-associated subfoveal hemorrhage caused damage to the foveal photoreceptors, and visual dysfunction. However, IVR improved these prognoses, by accelerating the absorption of the subfoveal hemorrhage.

PMID: 26661582 [PubMed - as supplied by publisher]

**JAMA Ophthalmol. 2015 Dec 10:1-9. [Epub ahead of print]**

**Correlation of 3-Dimensionally Quantified Intraretinal and Subretinal Fluid With Visual Acuity in Neovascular Age-Related Macular Degeneration.**

Waldstein SM, Philip AM, Leitner R, Simader C, Langs G, Gerendas BS, Schmidt-Erfurth U.

IMPORTANCE: Robust and sensitive imaging biomarkers for visual function are an unmet medical need in the management of neovascular age-related macular degeneration.

OBJECTIVE: To determine the correlation of 3-dimensionally quantified intraretinal cystoid fluid (IRC) and subretinal fluid (SRF) with best-corrected visual acuity (BCVA) in treatment-naive neovascular age-related macular degeneration and during antiangiogenic therapy.

DESIGN, SETTING, AND PARTICIPANTS: Retrospective cohort study between November 2009 and November 2011 at an institutional referral center and reading center of patients with treatment-naive subfoveal choroidal neovascularization receiving intravitreal ranibizumab or aflibercept over 12 months. All individual IRC and SRF lesions were manually delineated on each of the 128 B-scan sections of spectral-domain optical coherence tomographic volume scans at baseline and months 1, 6, and 12. Correlations were computed between the IRC and SRF parameters and the baseline BCVA, final BCVA, and BCVA change. A systematic parameter search was conducted to detect annotation-derived variables with best predictive value. An exponential model for BCVA change balancing for the ceiling effect was constructed.

MAIN OUTCOMES AND MEASURES: Goodness of fit of correlations between the IRC and SRF parameters and the baseline BCVA, final BCVA, and BCVA change.

RESULTS: Thirty-eight patients were included (25 female, 13 male; mean [SD] age at enrollment, 78.49 [8.23] years; mean [SD] BCVA score at baseline, 54 [16] Early Treatment Diabetic Retinopathy Study letters [Snellen equivalent approximately 20/160], with a gain to 63 [19] letters [Snellen equivalent approximately 20/100] at month 12). A total of 19 456 scans underwent complete quantification of IRC and SRF. The best correlation with BCVA at baseline was achieved using a coverage-based, foveal area-weighted IRC parameter ($R2 = 0.59$; $P < .001$). The same baseline parameter also predicted BCVA at 12 months ($R2 = 0.21$; $P = .003$). The BCVA gain correlated with IRC decrease in the exponential model ($R2 = 0.40$; $P < .001$) and linear model ($R2 = 0.25$; $P = .002$). No robust associations were found between SRF and baseline BCVA ($R2 = 0.06$; $P = .14$) or BCVA change ($R2 = 0.14$; $P = .02$).

CONCLUSIONS AND RELEVANCE: In this proof-of-principle study, IRC-derived morphometric variables correlated well with treatment-naive BCVA and BCVA outcomes in antiangiogenic therapy. While IRC reduction was associated with BCVA gains, some IRC-mediated neurosensory damage remained permanent.

PMID: 26661463 [PubMed - as supplied by publisher]

**Retina. 2015 Dec 11. [Epub ahead of print]**

**REPRODUCIBILITY OF MACULAR PIGMENT OPTICAL DENSITY MEASUREMENT BY TWO-WAVELENGTH AUTOFLUORESCENCE IN A CLINICAL SETTING.**

You QS, Bartsch DG, Espina M, Alam M, Camacho N, Mendoza N, Freeman WR.

PURPOSE: Macular pigment, composed of lutein, zeaxanthin, and meso-zeaxanthin, is postulated to protect against age-related macular degeneration, likely because of filtering blue light and its antioxidant properties. Macular pigment optical density (MPOD) is reported to be associated with macular function evaluated by visual acuity and multifocal electroretinogram. Given the importance of macular pigment, reliable and accurate measurement methods are important. The main purpose of this study is to determine the reproducibility of MPOD measurement by two-wavelength autofluorescence method using scanning laser ophthalmoscopy.

METHODS: Sixty-eight eyes of 39 persons were enrolled in the study, including 11 normal eyes, 16 eyes with wet age-related macular degeneration, 16 eyes with dry age-related macular degeneration, 11 eyes with macular edema due to diabetic mellitus, branch retinal vein occlusion or macular telangiectasia, and 14 eyes with tractional maculopathy, including vitreomacular traction, epiretinal membrane, or macular hole. MPOD was measured with a two-wavelength (488 and 514 nm) autofluorescence method with the Spectralis HRA + OCT after pupil dilation. The measurement was repeated for each eye 10 minutes later. The analysis of variance and Bland-Altman plot were used to assess the reproducibility between the two measurements.

RESULTS: The mean MPOD at eccentricities of 1° and 2° was 0.36 ± 0.17 (range: 0.04-0.69) and 0.15 ± 0.08 (range: -0.03 to 0.35) for the first measurement and 0.35 ± 0.17 (range: 0.02-0.68) and 0.15 ± 0.08 (range: -0.01 to 0.33) for the second measurement, respectively. The difference between the 2 measurements was not statistically significant, and the Bland-Altman plot showed 7.4% and 5.9% points outside the 95% limits of agreement, indicating an overall excellent reproducibility. Similarly, there is no significant difference between the first and second measurements of MPOD volume within eccentricities of 1°, 2°, and 6° radius, and the Bland-Altman plot showed 8.8%, 2.9%, and 4.4% points outside the 95% limits of agreement, respectively. The data for the reproducibility did not differ significantly among the various disease and normal eyes.

CONCLUSION: Under routine examination conditions with pupil dilation, MPOD measurement by two-wavelength autofluorescence method showed a high reproducibility.

PMID: 26655614 [PubMed - as supplied by publisher]

**Indian J Ophthalmol. 2015 Oct;63(10):775-778.**

**Predicting postoperative visual outcomes in cataract patients with maculopathy.**

Macky TA, Mohamed AM, Emarah AM, Osman AA, Gado AS.

PURPOSE: To assess the accuracy of the potential acuity meter (PAM) in predicting postcataract surgery visual acuity outcome in patients with healed inactive maculopathies.

STUDY DESIGN: Prospective interventional clinical trial.

PATIENTS AND METHODS: Patients scheduled for phacoemulsification had preoperative and 1 month postoperative best-corrected visual acuity (BCVA), PAM test, fluorescein angiography, and macular optical coherence tomography. Patients were grouped to following preoperative BCVA: PRE1: 0.29 and better, PRE2: 0.25-0.13, and PRE3: 0.1 or worse; age: G1 <60, G2 = 60-70, and G3 >70 years. PAM accuracy was divided into: Grade 1: Postoperative BCVA ≤1 or less line error of the PAM score, Grade 2: Between 1 and 2 lines error, and Grade 3: ≥3 lines or more error.

RESULTS: This study enrolled 57 patients with a mean age of 71.05 ± 6.78 years where 34 were females. There were 21 (36.84%) patients with diabetic maculopathy and 36 (63.16%) with age-related macular degeneration. The mean preoperative BCVA was 0.198 ± 0.12 (0.1-0.5). The mean PAM score was 0.442 ± 0.24 (0.1-1.3). The mean postoperative BCVA was 0.4352 ± 0.19 (0.17-1.00). The PAM score was in Grade 1, 2, and 3 in 46 (80.7%), 54 (94.7%), and 56 (98.2), respectively. There was a highly significant correlation between the PAM score and the postoperative BCVA (P < 0.001, Chi-square test). There was no correlation between the PAM test accuracy and age, gender, diagnosis, and preoperative BCVA (P = 0.661, 0.667, 0. 0.991, 0.833, Chi-square test; respectively).

CONCLUSION: The PAM is an accurate method of predicting postoperative visual acuity for eyes with nuclear cataracts Grade I and II and inactive maculopathies.

PMID: 26655002 [PubMed - as supplied by publisher]

**Arch Soc Esp Oftalmol. 2015 Dec 2. [Epub ahead of print]**

**Focal choroidal excavation: Clinical findings and complications.**

Castro Navarro V, Montero Hernández J, Navarro Palop C2, Palomares Fort P, Cervera Taulet E.

OBJECTIVE: To describe the clinical findings and its complications in 2 patients with focal choroidal excavation (FCE).

METHODS: A retrospective case-series including 4 eyes of 2 patients with FCE that underwent a

comprehensive ophthalmological examination including slit-lamp examination, colour fundus photography, spectral-domain optical coherence tomography (SD-OCT), fluorescein angiography (FA), and indocyanine green angiography.

RESULTS: In the 2 patients, both the anterior and posterior segment evaluations were mostly normal despite the of presence yellowish spots in the macular area of the right eye of patient 1, and of a small yellowish elevated lesion with serous macular detachment in the macular area of the left eye in patient 2. At diagnosis, SD-OCT revealed a conforming FCE in patient 1, and in patient 2, an FCE with perilesional subretinal fluid and a neuroepithelium detachment, suspicious of FCE complicated with central serous retinopathy (CSCR). At one year of follow-up, patient 1 developed choroidal neovascularisation (CNV) over the focal choroidal excavation. FA and indocyanine green angiography examinations revealed areas with hypofluorescence in earlier frames, and a diffuse leakage in late frames. After ranibizumab injections, the SD-OCT of patient 1 revealed no active exudation, while patient 2 showed partial resolution of subretinal fluid.

CONCLUSIONS: FCE is a newly described entity of unclear aetiology. It is characterised by a choroidal excavation in eyes, with absence of posterior staphyloma, scleral ectasia, trauma, or retinal disease. Although most lesions remain stable, there could be an association with CRSC or CNV.

PMID: 26652731 [PubMed - as supplied by publisher]

**Clin Ophthalmol. 2015 Nov 20;9:2159-74.**

**Geographic atrophy in patients with advanced dry age-related macular degeneration: current challenges and future prospects.**

Danis RP, Lavine JA, Domalpally A.

Abstract: Geographic atrophy (GA) of the retinal pigment epithelium (RPE) is a devastating complication of age-related macular degeneration (AMD). GA may be classified as drusen-related (drusen-associated GA) or neovascularization-related (neovascular-associated GA). Drusen-related GA remains a large public health concern due to the burden of blindness it produces, but pathophysiology of the condition is obscure and there are no proven treatment options. Genotyping, cell biology, and clinical imaging point to upregulation of parainflammatory pathways, oxidative stress, and choroidal sclerosis as contributors, among other factors. Onset and monitoring of progression is accomplished through clinical imaging instrumentation such as optical coherence tomography, photography, and autofluorescence, which are the tools most helpful in determining end points for clinical trials at present. A number of treatment approaches with diverse targets are in development at this time, some of which are in human clinical trials. Neovascular -associated GA is a consequence of RPE loss after development of neovascular AMD. The neovascular process leads to a plethora of cellular stresses such as ischemia, inflammation, and dramatic changes in cell environment that further taxes RPE cells already dysfunctional from drusen-associated changes. GA may therefore develop secondary to the neovascular process de novo or preexisting drusen-associated GA may continue to worsen with the development of neovascular AMD. Neovascular-associated GA is a prominent cause of continued vision loss in patients with otherwise successfully treated neovascular AMD. Clearly, treatment with vascular endothelial growth factor (VEGF) inhibitors early in the course of the neovascular disease is of great clinical benefit. However, there is a rationale and some suggestive evidence that anti-VEGF agents themselves could be toxic to RPE and enhance neovascular-associated GA. The increasing prevalence of legal blindness from this condition due to the aging of the general population lends urgency to the search for a therapy to ameliorate GA.

PMID: 26640366 [PubMed] PMCID: PMC4662367

**Klin Oczna. 2015;117(2):119-22.**

**[Geographic atrophy imaging using fundus autofluorescence method]. [Article in Polish]**

Dolar-Szczasny J, Święch-Zubilewicz A, Mackiewicz J.

Abstract: Geographic atrophy is a manifestation of the advanced age-related macular degeneration and form of irreversible atrophy of retinal pigment epithelium and photoreceptor layer. Early detection of changes and the ability to evaluate disease progression accurately constitute a key problem in diagnosis and treatment planning. Fundus autofluorescence is a relatively new imaging method considered nowadays to be the best in diagnosis and observing the natural or treatment-altered course of disease. High resolution images showing the 3D distribution of retinal pigment epithelium autofluorescence as lipofuscin index can be obtained owing to the launch of the confocal scanning laser ophthalmoscope.

PMID: 26638551 [PubMed - in process]

**J Vis Exp. 2015 Nov 15;(105).**

**Enrichment of Bruch's Membrane from Human Donor Eyes.**

McHarg S, Brace N, Bishop PN, Clark SJ.

Abstract: Age-related macular degeneration (AMD) is a leading cause of visual impairment in the developed world. The disease manifests itself by the destruction of the center of the retina, called the macula, resulting in the loss of central vision. Early AMD is characterised by the presence of small, yellowish lesions called soft drusen that can progress onto late AMD such as geographic atrophy (dry AMD) or neovascularisation (wet AMD). Although the clinical changes are well described, and the understanding of genetic influences on conferring AMD risk are getting ever more detailed, one area lacking major progress is an understanding of the biochemical consequences of genetic risk. This is partly due to difficulties in understanding the biochemistry of Bruch's membrane, a very thin extracellular matrix that acts as a biological filter of material from the blood supply and a scaffold on which the retinal pigment epithelial (RPE) cell monolayer resides. Drusen form within Bruch's membrane and their presence disrupts nutrient flow to the RPE cells. Only by investigating the protein composition of Bruch's membrane, and indeed how other proteins interact with it, can researchers hope to unravel the biochemical mechanisms underpinning drusen formation, development of AMD and subsequent vision loss. This paper details methodologies for enriching either whole Bruch's membrane, or just from the macula region, so that it can be used for downstream biochemical analysis, and provide examples of how this is already changing the understanding of Bruch's membrane biochemistry.

PMID: 26650722 [PubMed - as supplied by publisher]

## Pathogenesis

**Protein J. 2015 Dec 14. [Epub ahead of print]**

**Prohibitin as the Molecular Binding Switch in the Retinal Pigment Epithelium.**

Sripathi SR, Sylvester O, He W, Moser T, Um JY, Lamoke F, Ramakrishna W, Bernstein PS, Bartoli M, Jahng WJ.

Abstract: Previously, our molecular binding study showed that prohibitin interacts with phospholipids, including phosphatidylinositide and cardiolipin. Under stress conditions, prohibitin interacts with cardiolipin as a retrograde response to activate mitochondrial proliferation. The lipid-binding switch mechanism of prohibitin with phosphatidylinositol-3,4,5-triphosphate and cardiolipin may suggest the role of prohibitin effects on energy metabolism and age-related diseases. The current study examined the region-specific expressions of prohibitin with respect to the retina and retinal pigment epithelium (RPE) in age-related macular degeneration (AMD). A detailed understanding of prohibitin binding with lipids, nucleotides, and proteins shown in the current study may suggest how molecular interactions control apoptosis and how we can intervene against the apoptotic pathway in AMD. Our data imply that decreased prohibitin in the peripheral RPE is a significant step leading to mitochondrial dysfunction that may promote AMD

progression.

PMID: 26661103 [PubMed - as supplied by publisher]

**Circulation. 2015 Dec 9. [Epub ahead of print]**

**Targeting NCK-Mediated Endothelial Cell Front-Rear Polarity Inhibits Neo-Vascularization.**

Dubrac A, Genet G, Ola R, Zhang F, Pibouin-Fragner L, Han J, Zhang J, Thomas JL, Chedotal A, Schwartz MA, Eichmann A.

BACKGROUND: Sprouting angiogenesis is a key process driving blood vessel growth in ischemic tissues and an important drug target in a number of diseases, including wet macular degeneration and wound healing. Endothelial cells forming the sprout must develop front-rear polarity to allow sprout extension. The adaptor proteins Nck1 and 2 are known regulators of cytoskeletal dynamics and polarity, but their function in angiogenesis is poorly understood. Here we show that the Nck adaptors are required for endothelial cell front-rear polarity and migration downstream of the angiogenic growth factors VEGF-A and Slit2.

METHODS AND RESULTS: Mice carrying inducible, endothelial-specific Nck1/2 deletions fail to develop front-rear polarized vessel sprouts and exhibit severe angiogenesis defects in the postnatal retina and during embryonic development. Inactivation of NCK1 and 2 inhibits polarity by preventing Cdc42 and Pak2 activation by VEGF-A and Slit2. Mechanistically, NCK binding to ROBO1 is required for both Slit2 and VEGF induced front-rear polarity. Selective inhibition of polarized endothelial cell migration by targeting Nck1/2 prevents hypersprouting induced by Notch or Bmp signaling inhibition, as well as pathological ocular neovascularization and wound healing.

CONCLUSIONS: These data reveal a novel signal integration mechanism involving NCK1/2, ROBO1/2 and VEGFR2 that controls endothelial cell front-rear polarity during sprouting angiogenesis.

PMID: 26659946 [PubMed - as supplied by publisher]

**Light Sci Appl. 2015 Sep;4(9). Epub 2015 Sep 25.**

**Visible light optical coherence tomography measures retinal oxygen metabolic response to systemic oxygenation.**

Yi J, Liu W, Chen S, Backman V, Sheibani N, Sorenson CM, Fawzi AA, Linsenmeier RA, Zhang HF.

Abstract: The lack of capability to quantify oxygen metabolism noninvasively impedes both fundamental investigation and clinical diagnosis of a wide spectrum of diseases including all the major blinding diseases such as age-related macular degeneration, diabetic retinopathy, and glaucoma. Using visible light optical coherence tomography (vis-OCT), we demonstrated accurate and robust measurement of retinal oxygen metabolic rate (rMRO2) noninvasively in rat eyes. We continuously monitored the regulatory response of oxygen consumption to a progressive hypoxic challenge. We found that both oxygen delivery, and rMRO2 increased from the highly regulated retinal circulation (RC) under hypoxia, by 0.28 ± 0.08 μL min-1 ($p < 0.001$), and 0.20 ± 0.04 μL min-1 ($p < 0.001$) per 100 mmHg systemic pO2 reduction, respectively. The increased oxygen extraction compensated for the deficient oxygen supply from the poorly regulated choroidal circulation. Results from an oxygen diffusion model based on previous oxygen electrode measurements corroborated our in vivo observations. We believe that vis-OCT has the potential to reveal the fundamental role of oxygen metabolism in various retinal diseases.

PMID: 26658555 [PubMed]

**Sci Rep. 2015 Dec 14;5:17857.**

**Broadband activation by white-opsin lowers intensity threshold for cellular stimulation.**

Batabyal S, Cervenka G, Birch D, Kim YT, Mohanty S.

Abstract: Photoreceptors, which initiate the conversion of ambient light to action potentials via retinal circuitry, degenerate in retinal diseases such as retinitis pigmentosa and age related macular degeneration leading to loss of vision. Current prosthetic devices using arrays consisting of electrodes or LEDs (for optogenetic activation of conventional narrow-band opsins) have limited spatial resolution and can cause damage to retinal circuits by mechanical or photochemical (by absorption of intense narrow band light) means. Here, we describe a broad-band light activatable white-opsin for generating significant photocurrent at white light intensity levels close to ambient daylight conditions. White-opsin produced an order of magnitude higher photocurrent in response to white light as compared to narrow-band opsin channelrhodopsin-2, while maintaining the ms-channel kinetics. High fidelity of peak-photocurrent (both amplitude and latency) of white-opsin in response to repetitive white light stimulation of varying pulse width was observed. The significantly lower intensity stimulation required for activating white-opsin sensitized cells may facilitate ambient white light-based restoration of vision for patients with widespread photoreceptor degeneration.

PMID: 26658483 [PubMed - as supplied by publisher]

**Mol Pharm. 2015 Dec 10. [Epub ahead of print]**

**Characterization of the pH and Temperature in the Rabbit, Pig and Monkey Eye: Key Parameters for the Development of Long Acting Delivery Ocular Strategies.**

Lorget F, Parenteau A, Carrier M, Lambert D, Gueorguieva A, Schuetz C, Bantseev V, Thackaberry E.

Abstract: The treatment of disorders affecting the posterior segment of the eye, such as macular degeneration, warrants monthly or every other month intravitreal (ITV) injections. Reducing dosing frequency (e.g. every 4 to 6 months) by using sustained delivery of the therapeutic agent would present undeniable clinical benefits. Many long acting delivery strategies rely on pH- and/or temperature-driven release of the therapeutic agent and degradation of the drug carrier. Yet, these physiological parameters are poorly characterized in ocular animal models. We used anesthetized white New Zealand rabbits, Yucatan mini pigs and cynomolgus monkeys to characterize pH and temperature in several vitreous locations and the central aqueous location. We also established post mortem pH changes in the vitreous. Our data showed several temperature gradients across the vitreous of all species. Temperatures were generally higher in the medial (close to the nose) vitreous and near the retina while lower in the lateral (close to the temporal bone) vitreous. Overall, temperature (central vitreous) was higher in the rabbit (36.9° C, SD 0.6) versus monkey (35.3°C, SD 0.6) and pig (35.6°C, 0.64). The pH in the central vitreous was 7.29 (SD 0.03) in the rabbit and monkey, and 7.16 (SD 0.04) in the mini pig. Rapid pH decreases were observed in-situ postmortem while pH increases were noted when the vitreous was air-exposed. In the aqueous, pH values were generally higher and temperature values lower in comparison to the vitreous. These regional and species differences need to be factored into strategies for developing biodegradable long acting delivery systems.

PMID: 26655747 [PubMed - as supplied by publisher]

**Redox Biol. 2015 Nov 29;7:78-87. {Epub ahead of print]**

**Oxidative stress-induced premature senescence dysregulates VEGF and CFH expression in retinal pigment epithelial cells: Implications for Age-related Macular Degeneration.**

Marazita MC, Dugour A, Marquioni-Ramella MD, Figueroa JM, Suburo AM.

Abstract: Oxidative stress has a critical role in the pathogenesis of Age-related Macular Degeneration (AMD), a multifactorial disease that includes age, gene variants of complement regulatory proteins and smoking as the main risk factors. Stress-induced premature cellular senescence (SIPS) is postulated to contribute to this condition. In this study, we hypothesized that oxidative damage, promoted by endogenous or exogenous sources, could elicit a senescence response in RPE cells, which would in turn dysregulate the expression of major players in AMD pathogenic mechanisms. We showed that exposure of a human RPE cell line (ARPE-19) to a cigarette smoke concentrate (CSC), not only enhanced Reactive Oxygen Species (ROS) levels, but also induced 8-Hydroxydeoxyguanosine-immunoreactive (8-OHdG) DNA lesions and phosphorylated-Histone 2AX-immunoreactive (p-H2AX) nuclear foci. CSC-nuclear damage was followed by premature senescence as shown by positive senescence associated-β-galactosidase (SA-β-Gal) staining, and p16INK4a and p21Waf-Cip1 protein upregulation. N-acetylcysteine (NAC) treatment, a ROS scavenger, decreased senescence markers, thus supporting the role of oxidative damage in CSC-induced senescence activation. ARPE-19 senescent cultures were also established by exposure to hydrogen peroxide (H2O2), which is an endogenous stress source produced in the retina under photo-oxidation conditions. Senescent cells upregulated the proinflammatory cytokines IL-6 and IL-8, the main markers of the senescence-associated secretory phenotype (SASP). Most important, we show for the first time that senescent ARPE-19 cells upregulated vascular endothelial growth factor (VEGF) and simultaneously downregulated complement factor H (CFH) expression. Since both phenomena are involved in AMD pathogenesis, our results support the hypothesis that SIPS could be a principal player in the induction and progression of AMD. Moreover, they would also explain the striking association of this disease with cigarette smoking.



PMID: 26654980 [PubMed - as supplied by publisher]

**Angiogenesis. 2015 Dec 9. [Epub ahead of print]**

**Functional characterization of a VEGF-A-targeting Anticalin, prototype of a novel therapeutic human protein class.**

Gille H, Hülsmeyer M, Trentmann S, Matschiner G, Christian HJ, Meyer T, Amirkhosravi A, Audoly LP, Hohlbaum AM, Skerra A.

Abstract: Human tear lipocalin (Tlc) was utilized as a protein scaffold to engineer an Anticalin that specifically binds and functionally blocks vascular endothelial growth factor A (VEGF-A), a pivotal inducer of physiological angiogenesis that also plays a crucial role in several neovascular diseases. Starting from a naive combinatorial library where residues that form the natural ligand-binding site of Tlc were randomized, followed by affinity maturation, the final Anticalin PRS-050 was selected to bind all major splice forms of VEGF-A with picomolar affinity. Moreover, this Anticalin cross-reacts with the murine ortholog. PRS-050 efficiently antagonizes the interaction between VEGF-A and its cellular receptors, and it inhibits VEGF-induced mitogenic signaling as well as proliferation of primary human endothelial cells with subnanomolar IC50 values. Intravitreal administration of the Anticalin suppressed VEGF-induced blood-retinal barrier breakdown in a rabbit model. To allow lasting systemic neutralization of VEGF-A in vivo, the plasma half-life of the Anticalin was extended by site-directed PEGylation. The modified Anticalin efficiently blocked VEGF-mediated vascular permeability as well as growth of tumor xenografts in nude mice, concomitantly with reduction in microvessel density. In contrast to bevacizumab, the Anticalin did not trigger platelet aggregation and thrombosis in human FcγRIIa transgenic mice, thus suggesting an improved safety profile. Since neutralization of VEGF-A activity is well known to exert beneficial effects in cancer and other neovascular diseases, including wet age-related macular degeneration, this Anticalin offers a novel potent small protein antagonist for differentiated therapeutic intervention in oncology and ophthalmology.

PMID: 26650228 [PubMed - as supplied by publisher]

**J Immunol. 2015 Dec 7. [Epub ahead of print]**

**Cutting Edge: IL-1 Receptor Signaling is Critical for the Development of Autoimmune Uveitis.**

Wan CK, He C, Sun L, Egwuagu CE, Leonard WJ.

Abstract: IL-1β is a proinflammatory cytokine important for local and systemic immunity. However, aberrant production of this cytokine is implicated in pathogenic mechanisms of a number of inflammatory diseases, including Behçet's disease and age-related macular degeneration. In this study, we report the increased secretion of IL-1β in the retina by neutrophils, macrophages, and dendritic cells during ocular inflammation and show that loss of IL-1R signaling confers protection from experimental autoimmune uveitis. Moreover, the amelioration of experimental autoimmune uveitis in Il1r-deficient mice was associated with reduced infiltration of inflammatory cells into the retina and decreased numbers of uveitogenic Th17 cells that mediate uveitis. These findings indicate the possible utility of IL-1R-blocking agents for the treatment of ocular inflammatory diseases.

PMID: 26643477 [PubMed - as supplied by publisher]

**Eur J Pharmacol. 2015 Nov 28;770:1-8. doi: 10.1016/j.ejphar.2015.11.050. [Epub ahead of print]**

**Quercetin phospholipid complex significantly protects against oxidative injury in ARPE-19 cells associated with activation of Nrf2 pathway.**

Xu XR, Yu HT, Yang Y, Hang L, Yang XW, Ding SH.

Abstract: Age-related macular degeneration (AMD) is a major cause of blindness worldwide. Oxidative stress plays a crucial role in the pathogenesis of dry AMD. Quercetin has potent anti-oxidative activities, but poor bioavailability limits its therapeutic application. Herein, we prepared the phospholipid complex of quercetin (quercetin-PC), characterized its structure by differential scanning calorimetry, infrared spectrum and x-ray diffraction. Quercetin-PC had equilibrium solubility of 38.36 and 1351.27μg/ml in water and chloroform, respectively, which was remarkably higher than those of quercetin alone. Then we established hydrogen peroxide (H2O2)-induced oxidative injury model in human ARPE-19 cells to examine the effects of quercetin-PC. Quercetin-PC, stronger than quercetin, promoted cell proliferation, and the proliferation rate was increased to be 78.89% when treated with Quercetin-PC at 400μM. Moreover, quercetin-PC effectively prevented ARPE-19 cells from apoptosis, and the apoptotic rate was reduced to be 3.1% when treated with Quercetin-PC at 200μM. In addition, quercetin-PC at 200μM significantly increased the activities of SOD, CAT and GSH-PX, and reduced the levels of reactive oxygen species and MDA in H2O2-treated ARPE-19 cells, but quercetin at 200μM failed to do so. Molecular examinations revealed that quercetin-PC at 200μM significantly activated Nrf2 nuclear translocation and significantly enhanced the expression of target genes HO-1, NQO-1 and GCL by different folds at both mRNA and protein levels. Our current data collectively indicated that quercetin-PC had stronger protective effects against oxidative-induced damages in ARPE-19 cells, which was associated with activation of Nrf2 pathway and its target genes implicated in antioxidant defense.

PMID: 26643168 [PubMed - as supplied by publisher]

## Epidemiology

**Sci Rep. 2015 Dec 14;5:18280.**

**The association between statin use and risk of age-related macular degeneration.**

Ma L, Wang Y, Du J, Wang M, Zhang R, Fu Y.

Abstract: The aim of the present study was to evaluate the association between statin use and the risk of

age-related macular degeneration (AMD). A systematic search of the PubMed, EMBASE and ISI web of science databases was used to identify eligible published literatures without language restrictions up to April 2015. Summary relative ratios (RRs) and 95% CIs were estimated using a fixed-effect or random-effects model. A total of 14 studies met the inclusion criteria and were included in this meta-analysis. No significant association was observed between statin use and the risk of any AMD (RR, 0.95; 95% CI, 0.74-1.15); and stratified analysis showed that statins had a significantly different effects on early and late stages of AMD. For early AMD, statin use significantly reduced the risk approximately 17% (RR, 0.83; 95% CI, 0.66-0.99). At the late stage, we observed a significant protective association of statin use with exudative AMD (RR, 0.90; 95% CI, 0.80-0.99), in contrast with the absent association between statins and geographic atrophy (RR, 1.16; 95% CI, 0.77-1.56). These results demonstrated that statin use was protective for early and exudative AMD. Additional large prospective cohort studies and RCTs are required to determine the potential effect of statins on AMD prevention.

PMID: 26658620 [PubMed - as supplied by publisher]

**Glob J Health Sci. 2015 Oct 20;8(5):47874.**

**A Retrospective Study of Causes of Low Vision in Saudi Arabia, A Case of Eye World Medical Complex in Riyadh.**

Z Alotaibi A.

Abstract: Vision is the ability of seeing with a definite understanding of features, color and contrast, and to distinguish between objects visually. In the year 1999, the World Health Organization (WHO) and the International Agency for the Prevention of Blindness formulated a worldwide project for the eradication of preventable loss of sight with the subject of "Vision 2020: the Right to Sight". This global program aims to eradicate preventable loss of sight by the year 2020. This study was conducted to determine the main causes of low vision in Saudi Arabia and also to assess their visual improvement after using low vision aids (LVD).The study is a retrospective study and was conducted in low vision clinic at Eye World Medical Complex in Riyadh, Saudi Arabia. The file medical record of 280 patients attending low vision clinics from February 2008 to June 2010 was included. A data sheet was filled which include: age, gender, cause of low vision, unassisted visual acuity for long distances and short distances, low vision devices needed for long distances and short distances that provides best visual acuity. The result shows that the main cause of low vision was Optic atrophy (28.9%). Retinitis pigmentosa was the second cause of low vision, accounting for 73 patients (26%) followed by Diabetic retinopathy and Macular degeneration with 44 patients (15.7%) and 16 patients (5.7%) respectively. Inter family marriage could be one of the main causes of low vision. Public awareness should be embarked on for enlightenment on ocular diseases result in consanguineous marriage. Also, it is an important issue to start establishing low vision clinics in order to improve the situation.

PMID: 26652071 [PubMed - as supplied by publisher]

**Can J Ophthalmol. 2015 Dec;50(6):451-460.**

**Association of CX3CR1 (V249I and T280M) polymorphisms with age-related macular degeneration: a meta-analysis.**

Li D, Peng X, Sun H.

OBJECTIVE: Studies investigating the associations between CX3CR1 genetic polymorphisms and age-related macular degeneration (AMD) have reported controversial results. Therefore, this meta-analysis aims to clarify the effects of CX3CR1 T280M and V249I polymorphisms on AMD risk.

DESIGN: Meta-analysis.

PARTICIPANTS: Results from six studies were pooled in the meta-analysis.

METHODS: Relevant studies were selected through an extensive search of PubMed, EMBASE, and the Web of Science databases. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using random-effects model.

RESULTS: Six studies with were included in this systematic review and meta-analysis. There was no significant association between CX3CR1 T280M polymorphism and risk of AMD under all genetic models (TT vs CC/CT: OR = 1.57, 95% CI = 0.87-2.84; CC vs TT/CT: OR = 0.75, 95% CI = 0.54-1.06; TT vs CC: OR = 0.58, 95% CI = 0.30-1.144; CT vs CC: OR = 1.25, 95% CI = 0.91-1.70). The CX3CR1 V249I polymorphism also did not significantly affect the AMD risk (AA vs GG/AG: OR = 1.23, 95% CI = 0.98-1.55; AG/AA vs GG: OR = 0.56, 95% CI = 0.29-1.07; AA vs GG: OR = 1.43, 95% CI = 0.97-2.09; AG vs GG: OR = 1.07, 95% CI = 0.85-1.36).

CONCLUSIONS: This meta-analysis suggested that CX3CR1 T280M and V249I polymorphisms may not be associated with an increased risk of AMD based on current published data. Given the limited sample size, the finding on CX3CR1 polymorphisms needs further investigation.

PMID: 26651305 [PubMed - as supplied by publisher]

**Caspian J Intern Med. 2015 Summer;6(3):141-7.**

**Prevalence of age-related macular degeneration among the elderly.**

Rasoulinejad SA, Zarghami A, Hosseini SR, Rajaee N, Rasoulinejad SE, Mikaniki E.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in elderly population in the developing countries. Previous epidemiological studies revealed various potential modifiable risk factors for this disease. The purpose of this study was to evaluate the prevalence of AMD among elderly living in Babol, North of Iran.

METHODS: The study population of this cross-sectional study came from the Amirkola Health and Ageing Project (AHAP), the first comprehensive cohort study of the health of people aged 60 years and over in Amirkola, North of Iran. The prevalence of AMD was estimated and its risk was determined using logistic regression analysis (LRA) with regard to variables such as smoking, hyperlipidemia, hypertension and diabetes.

RESULTS: Five hundred and five participants with mean age of 71.55±5.9 (ranged 60-89) years entered the study. The prevalence of AMD was 17.6%. There was a significant association between AMD and smoking (P<0.001) but no association was seen with AMD and age, level of education, history of hyperlipidemia, hypertension and diabetes. Multiple LRAs revealed that smoking increased AMD by odds ratio of 5.03 (95% confidence interval 2.47-10.23 p<0.001) as compared to nonsmokers.

CONCLUSION: According to our findings, the prevalence of AMD was relatively high and smoking increased the risk of AMD in the elderly population.

PMID: 26644880 [PubMed] PMCID: PMC4650788

**Invest Ophthalmol Vis Sci. 2015 Dec 1;56(13):7766-73.**

**Genetic Variants and Systemic Complement Activation Levels Are Associated With Serum Lipoprotein Levels in Age-Related Macular Degeneration.**

Paun CC, Ersoy L, Schick T, Groenewoud JM, Lechanteur YT, Fauser S, Hoyng CB, de Jong EK, den Hollander AI.

PURPOSE: Genetic variants in genes encoding components of lipid metabolism have been associated with

AMD. The aims of this study were to evaluate the relation of these genetic variants with serum lipid levels in AMD in a large case-control cohort (n = 3070) and to test for correlations between lipids and complement activation.

METHODS: Single nucleotide polymorphisms (SNPs) in eight lipid metabolism genes, previously described to be associated with AMD, were genotyped and tested for their association in our case-control cohort. Serum apolipoprotein B (ApoB), apolipoprotein AI (Apo-AI), cholesterol, triglycerides (TG), high-density lipoprotein-cholesterol (HDLC), and complement activation levels (C3d/C3) were measured and tested for association with AMD. Non-HDL cholesterol and LDL were inferred based on the measurements of the other lipids and lipoproteins. General linear models and $\chi 2$ tests were used to evaluate the relation of SNPs and lipids/lipoproteins to the disease as well as their interrelations.

RESULTS: Significant genotypic associations with AMD were observed for SNPs in CETP, APOE, and FADS1. The serum levels of Apo-AI and HDLC were significantly higher in patients compared with controls. Triglycerides (TG) levels were lower in AMD compared with controls. A cumulative effect was observed for APOE and CETP genotypes on HDLC and Apo-AI levels. Complement activation levels correlated positively with HDLC and Apo-AI, and negatively with TG. Both the lipids/lipoproteins and the complement activation levels associate independently to AMD.

CONCLUSIONS: This study bridges the gap between genetic associations and physiological lipid levels in AMD. Additionally, the observed correlations between complement activation and lipid levels link two major systems that previously were always assessed independently.

PMID: 26641553 [PubMed - in process]

**Klin Oczna. 2015;117(2):130-5.**

**[The genetic variability of complement system in pathogenesis of age-related macular degeneration]. [Article in Polish]**

Kubicka-Trząska A, Karska-Basta I, Dziedzina S, Sanak M.

Abstract: Age-related macular degeneration is the leading cause of irreversible central vision impairment in people aged over 50 in developed countries. Age-related macular degeneration is a complex disease derived from environmental, immune and genetic factors. The complement pathway has been implicated in the pathogenesis of many diseases. Recently, variants in several genes, such as complement H (CFH), complement factor B (CFB), complement 2 (C2), and complement 3 (C3), encoding complement pathway proteins, have been identified as associated with age-related macular degeneration. However, the associations between these genes and age-related macular degeneration varied due to genetic variation within populations and various ethnics groups. The strongest association was found between the age-related macular degeneration and SNP Y402H rs 1061170 variant of CFH gene, which is present in 30% to 50% of age-related macular degeneration patients in Caucasian population and which is a risk factor for the development of age-related macular degeneration. Cohort studies showed that polymorphism Arg102Gly (SNP rs 2230199) of C3 protein could serve as a high-risk genetic marker for the development of age-related macular degeneration. Other rare variants of C3 (Lys155Gln, Lys65Gln, Arg735Trp, Ser1619Arg), may also be associated with a high incidence of age-related macular degeneration in some ethnic groups. A protective haplotype of variants E318D and IVS10 in the C2 gene as well as L9H and R320 in the BF were associated with age-related macular degeneration but only in Caucasians. The genetic findings in age -related macular degeneration patients stress the importance of detailed phenotyping to identify age-related macular degeneration subtypes, which may be associated with the presence of different polymorphisms and various environmental risk factors in any population. Further studies may be helpful to improve the effectiveness of prophylaxis and therapeutic options in age-related macular degeneration oatients.

PMID: 26638553 [PubMed - in process]

## Genetics

**Pharmacogenomics. 2015 Dec 14. [Epub ahead of print]**

**IL-8 and VEGFR-2 polymorphisms modulate long-term functional response to intravitreal ranibizumab in exudative age-related macular degeneration.**

Lazzeri S, Orlandi P, Piaggi P, Sartini MS, Casini G, Guidi G, Figus M, Fioravanti A, Di Desidero T, Ripandelli G, Parravano M, Varano M, Nardi M, Bocci G.

AIM: To investigate possible associations between VEGFR-2 and IL-8 gene SNPs and 1-year response to intravitreal ranibizumab for exudative age-related macular degeneration.

MATERIALS & METHODS: Sixty-four eyes underwent a loading phase of three monthly intravitreal injections of ranibizumab 0.5 mg/0.05 ml followed by Pro Re Nata retreatment. VEGFR-2 rs2071559 (-604 A/G) and IL-8 rs4073 (-251 A/T) were analyzed.

RESULTS: Ranibizumab was significantly more effective as measured by visual acuity in patients harboring the IL-8 rs4073 TT genotype (p = 0.045), whereas patients carrying the VEGFR-2 rs2071559 CC genotype revealed better functional response as measured by mean retinal sensitivity (p = 0.034).

CONCLUSION: IL-8 rs4073 and VEGFR-2 rs2071559 genotypes may represent important molecular determinants to modulate final outcomes in neovascular age-related macular degeneration patients.

PMID: 26653034 [PubMed - as supplied by publisher]

**Medicine (Baltimore). 2015 Dec;94(49):e2238.**

**Single Nucleotide Polymorphisms of the Sirtuin 1 (SIRT1) Gene are Associated With age-Related Macular Degeneration in Chinese Han Individuals: A Case-Control Pilot Study.**

Chen Z, Zhai Y, Zhang W, Teng Y, Yao K.

Abstract: To investigate whether 3 variants in sirtuin 1 (SIRT1) gene contributed differently in patients with age-related macular degeneration (AMD) in a Chinese Han population.We conducted a case-control study in a group of Chinese patients with AMD (n=253) and contrasted the results against a control group (n= 292). Three single nucleotide polymorphisms (SNPs) of SIRT1 gene including rs12778366, rs3740051, and rs4746720 were genotyped using improved multiplex ligase detection reaction. The association between targeted SNPs and AMD was then analyzed by codominant, dominant, recessive, and allelic models.The genotyping data of rs12778366, rs3740051, and rs4746720 revealed significant deviations from Hardy-Weinberg equilibrium tests in the AMD group but not in the control group.We detected significantly differences of rs12778366 allele distribution between 2 groups in recessive and codominant model (P< 0.05). Homozygous carriers of the risk allele C displayed a higher chance of developing AMD (P=0.036, odds ratio=3.227; 95% confidence interval: 1.015-10.265).Our study, for the first time, raises the possibility that genetic variations of SIRT1 could be implicated in the pathophysiology of AMD in the Chinese Han population.

PMID: 26656366 [PubMed - as supplied by publisher]