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# MD Research News

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## Drug treatment

**Eye (Lond). 2015 Aug 14. [Epub ahead of print]**

**Intravitreal anti-vascular endothelial growth factor monotherapy for large submacular hemorrhage secondary to neovascular age-related macular degeneration.**

Kim HS, Cho HJ, Yoo SG, Kim JH, Han JI, Lee TG, Kim JW; Medscape.

Purpose: To evaluate the efficacy of anti-vascular endothelial growth factor (VEGF) monotherapy for large submacular hemorrhage (SMH) secondary to neovascular age-related macular degeneration (nAMD).

Methods: A total of 49 treatment-naive patients (49 eyes) with large SMH (more than five disc areas (DAs)) secondary to nAMD were retrospectively included. All patients were treated with an initial series of 3 monthly intravitreal anti-VEGF injections, followed by as-needed injections. At the 12-month follow-up, changes in best-corrected visual acuity (BCVA), hemorrhage area, central foveal thickness, and development of vitreous hemorrhage after treatment were evaluated.

Results: The mean SMH area was 13.9±8.8 disk areas (DAs) and mean symptom duration was 7.25±5.9 days at baseline. The mean number of injections was 4.49±1.61. Twelve months after treatment, the mean BCVA significantly improved from 1.14±0.61 logarithm of the minimum angle of resolution (logMAR; 20/276, Snellen equivalent) to 0.82±0.53 logMAR (20/132; P=0.002). Twenty-four eyes (49%) showed improvement of more than three lines of BCVA at 12 months after treatment. Baseline BCVA (odds ratio (OR), 5.119; 95% confidence interval (CI), 1.993-9.545; P=0.004), duration of symptoms (OR, 0.727; 95% CI, 0.332-0.952; P=0.024), hemorrhage area (OR, 0.892; 95% CI, 0.721-0.965; P=0.011), and baseline central foveal thickness (OR, 0.881; 95% CI, 0.722-0.945; P=0.032) were significantly associated with good visual acuity 12 months after treatment.

Conclusions: Intravitreal anti-VEGF monotherapy is a valuable treatment option for large SMH secondary to nAMD.

PMID: 26272443 [PubMed - as supplied by publisher]

**Am J Ophthalmol. 2015 Aug 11. [Epub ahead of print]**

**Assessment of choroidal topographic changes by swept source optical coherence tomography after intravitreal ranibizumab for exudative age-related macular degeneration.**

Razavi S, Souied EH, Darvizeh F, Querques G.

PURPOSE: To investigate choroidal topographic changes by Swept-source optical coherence tomography (Swept-OCT) in patients undergoing intravitreal injections of anti-vascular endothelial growth factor (VEGF)

for exudative age-related macular degeneration (AMD).

DESIGN: Prospective interventional study.

METHODS: Consecutive patients with unilateral treatment-naïve exudative AMD were entered over six-month. Changes in choroidal thickness after intravitreal ranibizumab injections, overall in the macula and in neovascular and non neovascular areas, from baseline to month-3 (loading phase) and month-6 (pro-re-nata phase), were investigated by means of Swept-OCT maps.

RESULTS: Forty-one eyes of 41 patients (mean age: 79.4 ± 7.3 years) were analyzed. Choroidal thickness at study entry was significantly thicker in the study eyes as compared to fellow eyes ($p<0.05$). Analysis of sectorial choroidal thickness over time in study eyes revealed a significant reduction in both neovascular and non neovascular areas from baseline to month-3 and month-6 ($p< 0.0001$ for all). Central choroidal thickness revealed significant variation between treated and fellow eyes from baseline to month-3 ($p= 0.017$) and month-6 ($p= 0.045$). The visual gain was significantly higher ($p= 0.02$) in patients with a larger choroidal thickness reduction (≥ 29 µm, n=11) versus the others (n= 30).

CONCLUSIONS: The thinning of the macular choroid (affected or not by choroidal neovascularization), along with the significantly thicker choroid in exudative AMD eyes before treatment initiation compared to fellow eyes, allows to hypothesize that anti-VEGF treatment may favorably influence the choroidal exudation by reducing choroidal vascular hyperpermeability.

PMID: 26275471 [PubMed - as supplied by publisher]

**PLoS One. 2015 Aug 14;10(8):e0135608.**

**Coaxial Electrospray of Ranibizumab-Loaded Microparticles for Sustained Release of Anti-VEGF Therapies.**

Zhang L, Si T, Fischer AJ, Letson A, Yuan S, Roberts CJ, Xu RX.

Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss and blindness in people over age 65 in industrialized nations. Intravitreous injection of anti-VEGF (vascular endothelial growth factor) therapies, such as ranibizumab (trade name: Lucentis), provides an effective treatment option for neovascular AMD. We have developed an improved coaxial electrospray (CES) process to encapsulate ranibizumab in poly(lactic-co-glycolic) acid (PLGA) microparticles (MPs) for intravitreous injection and sustained drug release. This microencapsulation process is advantageous for maintaining the stability of the coaxial cone-jet configurations and producing drug-loaded MPs with as high as 70% encapsulation rate and minimal loss of bioactivitiy. The utility of this emerging process in intravitreous drug delivery has been demonstrated in both benchtop and in vivo experiments. The benchtop test simulates ocular drug release using PLGA MPs encapsulating a model drug. The in vivo experiment evaluates the inflammation and retinal cell death after intravitreal injection of the MPs in a chick model. The experimental results show that the drug-load MPs are able to facilitate sustained drug release for longer than one month. No significant long term microglia reaction or cell death is observed after intravitreal injection of 200 µg MPs. The present study demonstrates the technical feasibility of using the improved CES process to encapsulate water-soluble drugs at a high concentration for sustained release of anti-VEGF therapy.

PMID: 26273831 [PubMed - as supplied by publisher]

**Drug Des Devel Ther. 2015 Aug 6;9:4389-96. eCollection 2015.**

**The role of aflibercept in the management of diabetic macular edema.**

Chang AA, Hong T, Ewe SY, Bahrami B, Broadhead GK.

Abstract: Diabetic macular edema (DME) represents one of the leading causes of visual impairment in

working-age adults. Although there are several proven treatments available for this condition, pharmacotherapy through the use of intravitreal antivascular endothelial growth factor agents has revolutionized the management of DME over the past decade with superior outcomes compared to laser therapy. This review summarizes the pathophysiology and available treatment options for the management of DME, with an emphasis on the efficacy and safety profile of a single particular intravitreal antivascular endothelial growth factor agent, aflibercept.

PMID: 26273198 [PubMed - in process] PMCID: PMC4532215

**Ophthalmology. 2015 Aug 11. [Epub ahead of print]**

**Factors Associated with Recurrence of Age-Related Macular Degeneration after Anti-Vascular Endothelial Growth Factor Treatment: A Retrospective Cohort Study.**

Kuroda Y, Yamashiro K, Miyake M, Yoshikawa M, Nakanishi H, Oishi A, Tamura H, Ooto S, Tsujikawa A, Yoshimura N.

PURPOSE: To investigate the predictive factors associated with recurrence after anti-vascular endothelial growth factor (VEGF) treatment for neovascular age-related macular degeneration (AMD).

DESIGN: Retrospective cohort study.

PARTICIPANTS: A total of 343 eyes of 326 patients with subfoveal neovascular AMD who were treated with an as-needed regimen after 3 monthly loading doses of intravitreal ranibizumab.

METHODS: Patients were followed up by an as-needed regimen for more than 1 year after the first injection. Baseline data and CFH I62V and ARMS2 A69S polymorphisms were analyzed for their association with recurrence after anti-VEGF treatment. Regression analysis was used to identify independent predictors of visual acuity (VA) prognosis.

MAIN OUTCOME MEASURES: The primary end point was the presence or absence of recurrence. The secondary end point was VA improvement.

RESULTS: In total, 236 eyes (68.8%) showed complete resolution of retinal exudative change after the 3 loading injections, and 81 eyes (34.3%) experienced no recurrence during the first year. Of the 236 eyes, 139 (58.9%) were followed for more than 2 years and 35 (25.2%) showed no recurrent retinal exudation during 24 months. Visual acuity improvement was significantly better in eyes without recurrence than in eyes with recurrence during the 2-year period. Baseline characteristics and genotypes had no influence on response to ranibizumab loading treatment. Stepwise analysis revealed that age ($P < 0.001$), subtype of AMD ($P = 0.041$), and VA at baseline ($P < 0.001$) were associated with VA at 24 months. Older patients ($P = 0.006$) and male patients ($P = 0.018$) tended to require re-treatment for recurrence during the first year, yet the statistical significance disappeared when evaluated in 2 years. The subtypes of neovascular AMD were solely associated with the interval to the recurrence, which was shorter in eyes with polypoidal choroidal vasculopathy (PCV) than in eyes with typical AMD ($P = 0.015$).

CONCLUSIONS: Older age and male sex may predict recurrence after 3 monthly ranibizumab injections, and PCV may be associated with shorter interval to recurrence. Predicting the risk of recurrence would help us to choose the most appropriate follow-up treatment strategy for patients with AMD.

PMID: 26271842 [PubMed - as supplied by publisher]

# Other treatment & diagnosis

**Proc Natl Acad Sci U S A. 2015 Aug 12. [Epub ahead of print]**

**Small-molecule-directed, efficient generation of retinal pigment epithelium from human pluripotent stem cells.**

Maruotti J, Sripathi SR, Bharti K, et al

Abstract: Age-related macular degeneration (AMD) is associated with dysfunction and death of retinal pigment epithelial (RPE) cells. Cell-based approaches using RPE-like cells derived from human pluripotent stem cells (hPSCs) are being developed for AMD treatment. However, most efficient RPE differentiation protocols rely on complex, stepwise treatments and addition of growth factors, whereas small-molecule-only approaches developed to date display reduced yields. To identify new compounds that promote RPE differentiation, we developed and performed a high-throughput quantitative PCR screen complemented by a novel orthogonal human induced pluripotent stem cell (hiPSC)-based RPE reporter assay. Chetomin, an inhibitor of hypoxia-inducible factors, was found to strongly increase RPE differentiation; combination with nicotinamide resulted in conversion of over one-half of the differentiating cells into RPE. Single passage of the whole culture yielded a highly pure hPSC-RPE cell population that displayed many of the morphological, molecular, and functional characteristics of native RPE.

PMID: 26269569 [PubMed - as supplied by publisher]

**Curr Eye Res. 2015 Aug 13:1-6. [Epub ahead of print]**

**Imaging Suprachoroidal Layer in Exudative Age-Related Macular Degeneration.**

Kim JH, Chang YS, Kim JW, Lee TG, Lew YJ.

PURPOSE: To evaluate the prevalence of a visible suprachoroidal layer (SCL) on optical coherence tomography (OCT) in exudative age-related macular degeneration (AMD).

MATERIALS AND METHODS: This retrospective study included 252 eyes of 252 patients with treatment-naive typical exudative AMD (n = 80), polypoidal choroidal vasculopathy (PCV) (n = 138) and retinal angiomatous proliferation (RAP) (n = 34). The presence of SCL was identified based on enhanced-depth imaging OCT images, and the prevalence was compared among the three disease groups. In addition, subfoveal choroidal thickness was compared between patients with and without SCL.

RESULTS: The SCL was noted in 56 eyes (22.2%). The prevalence was 22.5% in typical exudative AMD (18 of 80 eyes), 18.8% in PCV (26 of 138 eyes) and 35.3% in RAP (12 of 34 eyes) ($p = 0.118$). Patients with SCL showed significantly thinner choroid ($207.5 \pm 83.9$ µm versus $279.7 \pm 116.5$ µm, $p < 0.001$) and were relatively older ($72.1 \pm 8.1$ versus $70.1 \pm 8.7$ years, $p = 0.124$) than those without SCL.

CONCLUSION: The prevalence of visible SCL was 22.2% in patients with exudative AMD. Age-related changes, including choroidal thinning, may contribute to the development of a visible SCL.

PMID: 26269259 [PubMed - as supplied by publisher]

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

**PERIPAPILLARY RETINAL PIGMENT EPITHELIUM CHANGES IN AGE-RELATED MACULAR DEGENERATION.**

Cohen SY, Dubois L, Grenet T, Nghiem-Buffet S, Jung C, Fajnkuchen F, Delahaye-Mazza C, Quentel G, Tadayoni R.

PURPOSE: To describe peripapillary retinal pigment epithelium changes observed in patients with age-

related macular degeneration (AMD) and evaluate their prevalence.

METHODS: This study is a prospective, monocentric, comparative case series including 104 consecutive patients with AMD, and 34 patients who are more than 60 years old and consulting for other conditions (control group). Color and fundus autofluorescence images centered on the optic disk were taken and graded by 2 independent readers from 0 to 4: 0, absent; 1, uneven background; 2, focal hyperautofluorescent dots and spots; 3, light reticular pattern; 4, dense reticular pattern. Statistical analysis was performed to correlate the presence of peripapillary retinal pigment epithelium changes with age, sex, and AMD subtype.

RESULTS: Peripapillary retinal pigment epithelium changes were observed in 76/104 AMD eyes (73.0%) and were significantly more frequent than in eyes with other conditions (14/34, 41.1%, P = 0.002), whereas groups did not differ for age (P = 0.14). Grade ≥2 peripapillary retinal pigment epithelium changes were more frequently observed in patients with AMD than in controls (41.3 vs. 17.6%, P = 0.013). No differences were found between patients with AMD having peripapillary retinal pigment epithelium changes and other patients for age distribution (P = 0.14), sex ratio (P = 0.34), or AMD type (P = 0.57).

CONCLUSION: Peripapillary retinal pigment epithelium changes were more frequent in patients with AMD than in controls, and when present, they were of higher grade. Peripapillary retinal pigment epithelium changes significance is not yet understood and needs further evaluation.

PMID: 26267678 [PubMed - as supplied by publisher]

**Indian J Ophthalmol. 2015 Jun;63(6):534-6.**

**Microperimetry biofeedback training in a patient with bilateral myopic macular degeneration with central scotoma.**

Raman R, Damkondwar D, Neriyanuri S, Sharma T1.

Abstract: Microperimetry-1 (MP-1) evaluation and MP-1 biofeedback training were done in a case of bilateral myopic macular degeneration with a central scotoma. Fixation behavior, location and stability of preferred retinal locus, eye movement speed, and mean sensitivity were assessed. The mean retinal sensitivities before, after and at 1-year after training in the right eye were 2.9 dB, 2.9 dB and 3.7 dB and in the left eye were 3.5 dB, 3.7 dB and 1.8 dB. The fixation point in the 2° gravitation circle, improved from 40% to 50% in the right eye and from 43% to 67% in the left eye. The average eye speed before, after and at 1-year after training in right eye were 0.19°/s, 0.26°/s and 0.25°/s and in left eye were 0.36°/s, 0.25°/s and 0.27°/s. Thus, biofeedback training using MP-1 can improve the visual function in patients with macular diseases and central scotoma.

PMID: 26265646 [PubMed - in process]

**Br J Ophthalmol. 2015 Aug 10. [Epub ahead of print]**

**Radial versus raster spectral-domain optical coherence tomography scan patterns for detection of macular fluid in neovascular age-related macular degeneration.**

Adam M, Rayess N, Rahimy E, Maguire JI, Hsu J.

BACKGROUND/AIMS: To compare the 12-line radial to the 25-line raster spectral-domain optical coherence tomography (SD-OCT) acquisition patterns at detecting intraretinal or subretinal fluid in eyes with neovascular age-related macular degeneration (AMD).

METHODS: Retrospective cross-sectional analysis of 200 eyes with neovascular AMD. Sequential 12-line radial and 25-line raster scans were evaluated for the presence of intraretinal/subretinal fluid.

RESULTS: A total of 394 SD-OCT scans were interpreted (1.97 scans per eye). The 12-line radial detected intraretinal/subretinal fluid in all but 7 of 394 scans (1.7%; 95% CI 0.7% to 3.6%), resulting in a sensitivity of 98.3%. The 25-line raster detected intraretinal/subretinal fluid in all but 10 of 394 scans (2.5%; 95% CI 1.2% to 4.6%), resulting in a sensitivity of 97.5%. This small difference in fluid detection between the two acquisition patterns for neovascular AMD was not found to be statistically significant (p=0.6276).

CONCLUSIONS: The 12-line radial scan is statistically comparable with the 25-line raster scan in detecting the presence of intraretinal/subretinal fluid in neovascular AMD. The 12-line radial SD-OCT pattern alone may be adequate to guide day-to-day clinical decisions in a more time-efficient manner.

PMID: 26261232 [PubMed - as supplied by publisher]

**Am J Ophthalmol. 2015 Aug 6. [Epub ahead of print]**

**Correlation of type 1 neovascularization associated with acquired vitelliform lesion in the setting of age related macular degeneration.**

Curcio CA, Balaratnasingam C, Messinger JD, Yannuzzi LA, Freund KB.

PURPOSE: To correlate postmortem histology with previously recorded multimodal imaging from a patient with type 1 neovascularization associated with an acquired vitelliform lesion in the setting of age-related macular degeneration (AMD).

DESIGN: Case study.

METHODS: Multimodal imaging that was obtained ante mortem was matched with ex vivo and high-resolution histological images of the preserved donor macula. Anatomic correlates for multimodal imaging findings were then defined.

RESULTS: Spectral-domain optical coherence tomography (OCT) revealed a split in the retinal pigment epithelial-Bruch's membrane band. Type 1 NV in this case was comprised of 6 layered components: (1) Retinal pigment epithelium, (2) Basal laminar deposits, (3) Fibrovascular membrane, (4) Fibrocellular scar, (5) Hemorrhage, and (6) Bruch's membrane. The anatomic correlates for the hyporeflective band on spectral-domain OCT included a thick basal laminar deposit. Not all structures could be readily separated on the basis of their reflectivity patterns.

CONCLUSIONS: This is an important clinicopathologic correlation of NV secondary to AMD in the spectral-domain OCT era. Our findings of 6 layers include and extend the anatomical framework encapsulated by the double-layer and triple-layer signs. The resolution of current devices does not always permit distinction of the different layers of NV tissue. Thick basal laminar deposits may appear hyporeflective on spectral-domain OCT and may be confused with fluid from a neovascular process. It will be important to perform a larger clinicopathologic series to aid our anatomical interpretation of spectral-domain OCT images.

PMID: 26255578 [PubMed - as supplied by publisher]

## Pathogenesis

**BMC Complement Altern Med. 2015 Aug 12;15:271.**

**Inhibitory effect of Samul-tang on retinal neovascularization in oxygen-induced retinopathy.**

Lee YM, Kim CS, Jo K, Sohn EJ, Kim JS, Kim J.

BACKGROUND: Retinal neovascularization is a common cause of vision loss in proliferative diabetic retinopathy, retinopathy of prematurity and age-related macular degeneration. Samul-tang (SMT) is a widely used traditional herbal medicine in East Asia and is also known as Shimotsu-to in Japanese and Si-

Wu decoction in Chinese. This study was designed to evaluate the inhibitory effect of SMT on retinal pathogenic angiogenesis in a mouse model of oxygen-induced retinopathy (OIR).

METHOD: The mice were exposed to a 75 % concentration of oxygen for five days, starting on postnatal day 7 (P7-P12). The mice were then exposed to room air and were intraperitoneally injected with SMT (10 mg/kg or 50 mg/kg) once per day for five days (P12-P16). On P17, we measured retinal neovascularization and evaluated both the expression of angiogenesis-related proteins and changes in the gene expression level in the mRNA.

RESULTS: SMT reduced the area of the central retina and reduced retinal neovascularization in OIR mice. The protein array revealed that SMT reduced the level of SDF-1 protein expression. Quantitative real-time PCR revealed that the HIF-1α, SDF-1, CXCR4 and VEGF mRNA levels in the retinas of OIR mice were elevated compared with those of normal control mice. However, SMT decreased the levels of HIF-1α, SDF-1, CXCR4 and VEGF mRNA in OIR mice.

CONCLUSION: We are the first to elucidate that SMT inhibits the retinal pathogenic angiogenesis induced by ischemic retinopathy in OIR mice. SMT significantly inhibited retinal neovascularization by downregulating HIF-1α, SDF-1, CXCR4 and VEGF. Based on the results of our study, SMT could be a useful herbal medicine for treating ischemic retinopathy.

PMID: 26264147 [PubMed - in process] PMCID: PMC4534021

**Biochem Biophys Res Commun. 2015 Aug 6. [Epub ahead of print]**

**Lenalidomide, an anti-tumor drug, regulates retinal endothelial cell function: implication for treating ocular neovascular disorder.**

Dong LF, Wang XQ, Yao J, Yan B, Jiang Q.

Abstract: Ocular angiogenesis is an important pathologic character of several ocular diseases, such as retinopathy of prematurity, diabetic retinopathy and age-related macular degeneration (AMD). Inhibition of ocular angiogenesis has great therapeutic value for treating these dieses. Here we show that lenalidomide, an anti-tumor drug, has great anti-angiogenic potential in ocular diseases. Lenalidomide inhibits retinal endothelial cell viability in normal and pathological condition, and inhibits VEGF-induced endothelial cell migration and tube formation in vitro. Moreover, lenalidomide inhibits ocular angiogenesis in vivo through the reduction of angiogenesis- and inflammation-related protein expression. Collectively, lenalidomide is a promising drug for treating ocular angiogenesis through its anti-proliferative and anti-inflammatory property.

PMID: 26255966 [PubMed - as supplied by publisher]

**J Cell Biol. 2015 Aug 10. [Epub ahead of print]**

**Microtubule motors transport phagosomes in the RPE, and lack of KLC1 leads to AMD-like pathogenesis.**

Jiang M, Esteve-Rudd J, Lopes VS, Diemer T, Lillo C, Rump A, Williams DS.

Abstract: The degradation of phagosomes, derived from the ingestion of photoreceptor outer segment (POS) disk membranes, is a major role of the retinal pigment epithelium (RPE). Here, POS phagosomes were observed to associate with myosin-7a, and then kinesin-1, as they moved from the apical region of the RPE. Live-cell imaging showed that the phagosomes moved bidirectionally along microtubules in RPE cells, with kinesin-1 light chain 1 (KLC1) remaining associated in both directions and during pauses. Lack of KLC1 did not inhibit phagosome speed, but run length was decreased, and phagosome localization and degradation were impaired. In old mice, lack of KLC1 resulted in RPE pathogenesis that was strikingly comparable to aspects of age-related macular degeneration (AMD), with an excessive accumulation of

RPE and sub-RPE deposits, as well as oxidative and inflammatory stress responses. These results elucidate mechanisms of POS phagosome transport in relation to degradation, and demonstrate that defective microtubule motor transport in the RPE leads to phenotypes associated with AMD.

PMID: 26261180 [PubMed - as supplied by publisher]

**Nat Commun. 2015 Aug 11;6:7847.**

**IL10-driven STAT3 signalling in senescent macrophages promotes pathological eye angiogenesis.**

Nakamura R, Sene A, Santeford A, Gdoura A, Kubota S, Zapata N, Apte RS.

Abstract: Macrophage dysfunction plays a pivotal role during neovascular proliferation in diseases of ageing including cancers, atherosclerosis and blinding eye disease. In the eye, choroidal neovascularization (CNV) causes blindness in patients with age-related macular degeneration (AMD). Here we report that increased IL10, not IL4 or IL13, in senescent eyes activates STAT3 signalling that induces the alternative activation of macrophages and vascular proliferation. Targeted inhibition of both IL10 receptor-mediated signalling and STAT3 activation in macrophages reverses the ageing phenotype. In addition, adoptive transfer of STAT3-deficient macrophages into eyes of old mice significantly reduces the amount of CNV. Systemic and CD163 (+) eye macrophages obtained from AMD patients also demonstrate STAT3 activation. Our studies demonstrate that impaired SOCS3 feedback leads to permissive IL10/STAT3 signalling that promotes alternative macrophage activation and pathological neovascularization. These findings have significant implications for our understanding of the pathobiology of age-associated diseases and may guide targeted immunotherapy.

PMID: 26260587 [PubMed - in process]

## Epidemiology

**Invest Ophthalmol Vis Sci. 2015 Aug 1;56(9):5401-5406.**

**Exposure to Atomic Bomb Radiation and Age-Related Macular Degeneration in Later Life: The Hiroshima-Nagasaki Atomic Bomb Survivor Study.**

Itakura K, Takahashi I, Nakashima E, Yanagi M, Kawasaki R, Neriishi K, Wang JJ, Wong TY, Hida A, Ohishi W, Kiuchi Y.

Purpose: To investigate the association between radiation exposure from the atomic bombings and the prevalence of age-related macular degeneration (AMD) among older residents of Hiroshima and Nagasaki.

Methods: The Adult Health Study is a cohort study of atomic bomb survivors living in Hiroshima and Nagasaki, comprising 2153 participants who underwent examinations with retinal fundus photographs in 2006-2008. The radiation dose to the eye for the analysis was estimated with the revised dosimetry system (DS02). The retinal photographs were graded according to the Wisconsin Age-Related Maculopathy Grading System modified for nonstereoscopic retinal images. Early and late AMD were defined according to the type of lesion detected in the worse eye of the participants. Person-specific data were analyzed by using a logistic regression model to assess the association between radiation dose and AMD.

Results: Among the 1824 subjects with gradable retinal images (84.7% of the overall participants), the estimated eye dose was widely distributed, with a mean of 0.45 Gy and standard deviation of 0.74 Gy. The prevalence of early and late AMD was 10.5% and 0.3%, respectively. There were no significant associations between radiation dose and AMD, with each 1-Gy increase in exposure, adjusted odds ratio was 0.93 (95% confidence interval [CI], 0.75-1.15) for early AMD and 0.79 (95% CI, 0.21-2.94) for late AMD.

Conclusions: No significant associations were found between atomic bomb irradiation early in life and the prevalence of early or late AMD later in life among Japanese atomic bomb survivors.

PMID: 26275137 [PubMed - as supplied by publisher]

**Arch Gerontol Geriatr. 2015 Aug 4. [Epub ahead of print]**

**Association between retinal vasculature and muscle mass in older people.**

Sumukadas D, McMurdo M, Pieretti I, Ballerini L, Price R, Wilson P, Doney A, Leese G, Trucco E.

Abstract: Sarcopenia in older people is a major health issue and its early detection could help target interventions and improve health. Evidence suggests that poor muscle mass is associated with greater arterial stiffness and cardiovascular risk. Arterial stiffness in turn is associated with smaller retinal artery width. This study examined the association of muscle mass in older people with retinal vascular width, a non-invasive measure of vascular function.

METHODS: Participants >65 years were recruited to a cross-sectional study.

EXCLUSIONS: Inability to walk independently; diabetes mellitus; stroke (within 6 months), severe macular degeneration, glaucoma, retinal dystrophy; advanced cataract. Digital Retinal images of both eyes were analysed using the VAMPIRE software suite. Central Retinal Artery and Vein Equivalents (CRVE and CRAE) were measured. Body composition was measured using Dual Energy X ray Absorptimetry (DXA). Appendicular Skeletal Muscle Mass/Height2 was calculated. Physical function was measured: 6-min walk distance, Short Physical performance battery, handgrip strength and quadriceps strength.

RESULTS: 79 participants with mean age 72 (SD 6) years were recruited. 44% were female. Digital Retinal images of sufficient quality for measuring CRAE and CRVE were available for 51/75 (68%) of participants. Regression analysis showed significant association between larger ASMM/H2 and smaller CRAE (β=-0.20, p=0.001) and CRVE (β=-0.12, p=0.05). Handgrip strength, body mass index and sex combined with CRAE explained 88% and with CRVE explained 86% of the variance in ASMM/H2.

CONCLUSION: Larger muscle mass was significantly associated with smaller retinal artery size in older people. This unexpected finding needs further investigation.

PMID: 26276247 [PubMed - as supplied by publisher]

## Genetics

**Int J Clin Exp Pathol. 2015 Jun 1;8(6):7403-8. eCollection 2015.**

**Correlation between the interactions of ABCA4 polymorphisms and smoking with the susceptibility to age-related macular degeneration.**

Wu Y, Tian L, Huang Y.

OBJECTIVE: Our study was aimed to analyze the relationship between retina-specific ATP-binding cassette, sub-family A, member 4 (ABCA4) gene polymorphisms and gene-environment interactions with age-related macular degeneration (AMD) susceptibility.

METHODS: 98 AMD patients and 110 healthy controls, matched in age and sex, were enrolled in this study. ABCA4 polymorphisms (2633C>A, 5646G>A and 6389T>A) were determined by direct sequencing. Differences of genotype and allele distributions were analyzed by χ(2) test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were adopted to represent the relative risk of AMD. Gene-environment interactions were analyzed using crossover analysis.

RESULTS: 2633C>A polymorphism had no obvious correlation with AMD risk. Genotype AA and allele A in

5646G>A polymorphism significantly increased the risk of AMD (OR=4.753, 95% CI=1.249-18.085; OR=1.944, 95% CI=1.209-3.126). 6389T>A polymorphism AA genotype had no significant correlation with AMD risk, but the A allele distinctly enhanced the AMD risk (OR=1.681, 95% CI=1.071-2.639). Afterwards, we analyzed the interactions between ABCA4 polymorphisms and smoking on AMD. Smoking had interactions with all of 2633C>A (CC+CA), 5646G>A and 6389T>A polymorphisms, and the interactions were significantly correlated with AMD.

CONCLUSIONS: 2633C>A (CC+CA) genotype, 5646G>A and 6389T>A polymorphisms of ABCA4 gene and smoking are susceptible factors for AMD, and the interactions of ABCA4 polymorphisms with smoking increased the risk of AMD.

PMID: 26261643 [PubMed - in process] PMCID: PMC4525977

**Mol Vis. 2015 Jul 17;21:767-82. eCollection 2015.**

**Reduced macular function in ABCA4 carriers.**

Kjellström U.

PURPOSE: To study retinal function and morphology in ABCA4 carriers to investigate if ABCA4 carriership is associated with any functional or morphological changes and, if so, to explore whether certain mutations may be associated with particularly severe alterations.

METHODS: Eighteen subjects were recruited by means of being the parents of 10 teenagers/young adults with genetically confirmed ABCA4-associated retinal degenerations. The teenagers/young adults are well-known patients and have been followed in our clinic for many years. The eighteen subjects underwent careful ophthalmological examinations, including fundus photography and autofluorescence imaging, Goldmann perimetry, optical coherence tomography (OCT), full-field electroretinography (ffERG), multifocal electroretinography (mERG), and ABCA4 gene sequencing. The ffERG and mERG results were compared with those of healthy controls.

RESULTS: All subjects carried at least one ABCA4 mutation. Two subjects were compound heterozygous and therefore were excluded from the group-wise statistical analysis. Thirteen different ABCA4 mutations were found. C.2894 A>G (5/18) and c.768 G>T (4/18) were most common. Fourteen of 16 ABCA4 carriers demonstrated significantly altered mERG parameters (reduced amplitudes and/or delayed implicit times (ITs)) compared to normal values. In addition, the two subjects with compound heterozygous ABCA4 mutations had altered mERG parameters. A statistical comparison to the control group showed significantly reduced amplitudes and delayed ITs; p≤0.003 for all mERG parameters. FfERG parameters were altered in two ABCA4 carriers and one of the subjects with compound heterozygous ABCA4 mutations (reduced amplitude and delayed IT for the 30 Hz flicker ERG). No significant alterations were found for the whole group of ABCA4 carriers compared to the ffERG control group. Fundus photographs showed subtle to extensive pigmentary changes in several ABCA4 carriers.

CONCLUSIONS: In this study, ABCA4 carriers demonstrated reduced macular function measured by mERG along with none to subtle and even extensive morphological retinal changes. The c.768 G>T, c.5461 -10T>C, and c.319 C>T mutations were associated with the most deviant ERGs, including both significant reduction of mERG amplitudes and prolongation of mERG ITs, as well as with reduced amplitude or delayed IT for the 30 Hz flicker ffERG in a few cases. They may therefore be considered serious mutations. The c.5917delG and c.4469 G>A mutations were associated with milder or no macular alteration. Long-term follow-up of these and other ABCA4 carriers may be of importance to elucidate the role of ABCA4 mutations in age-related macular degeneration. Moreover, improved knowledge of separate ABCA4 mutations may help us to better understand their role in ABCA4-associated retinal degenerations.

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**Sci Rep. 2015 Aug 10;5:12875.**

**A Validated Phenotyping Algorithm for Genetic Association Studies in Age-related Macular Degeneration.**

Simonett JM, Sohrab MA, Pacheco J, Armstrong LL, Rzhetskaya M, Smith M, Geoffrey Hayes M, Fawzi AA.

Abstract: Age-related macular degeneration (AMD), a multifactorial, neurodegenerative disease, is a leading cause of vision loss. With the rapid advancement of DNA sequencing technologies, many AMD-associated genetic polymorphisms have been identified. Currently, the most time consuming steps of these studies are patient recruitment and phenotyping. In this study, we describe the development of an automated algorithm to identify neovascular (wet) AMD, non-neovascular (dry) AMD and control subjects using electronic medical record (EMR)-based criteria. Positive predictive value (91.7%) and negative predictive value (97.5%) were calculated using expert chart review as the gold standard to assess algorithm performance. We applied the algorithm to an EMR-linked DNA bio-repository to study previously identified AMD-associated single nucleotide polymorphisms (SNPs), using case/control status determined by the algorithm. Risk alleles of three SNPs, rs1061170 (CFH), rs1410996 (CFH), and rs10490924 (ARMS2) were found to be significantly associated with the AMD case/control status as defined by the algorithm. With the rapid growth of EMR-linked DNA biorepositories, patient selection algorithms can greatly increase the efficiency of genetic association study. We have found that stepwise validation of such an algorithm can result in reliable cohort selection and, when coupled within an EMR-linked DNA biorepository, replicates previously published AMD-associated SNPs.

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**Invest Ophthalmol Vis Sci. 2015 Aug 1;56(9):5353-5361.**

**The Contribution of Genetic Architecture to the 10-Year Incidence of Age-Related Macular Degeneration in the Fellow Eye.**

Miyake M, Yamashiro K, Tamura H, Kumagai K, et al.

Purpose: To correlate a genetic risk score based on age-related macular degeneration (AMD) susceptibility genes with the risk of AMD in the second eye.

Methods: This is a retrospective, open cohort study consisting of 891 unilateral AMD patients, who were followed for at least 12 months and recruited from three institutes. DNAs were genotyped using Illumina OmniExpress, HumanOmni2.5-8, and/or HumanExome. Survival analyses and Cox proportional hazard models were used to examine the association between 11 AMD susceptibility genes and the duration until second-eye involvement in 499 samples from Kyoto University, which were replicated in two other cohorts. Genetic risk score (GRS) was also evaluated.

Results: The ARMS2 rs10490924 recessive model (hazard ratio [HR]meta = 2.04; Pmeta = 3.4 × 10-3) and CFH rs800292 additive model (HRmeta = 1.77; Pmeta = 0.013) revealed significant associations with second-eye involvement. The dominant model of TNFRSF10A rs13278062, VEGFA rs943080, and CFI rs4698775 showed consistent effects across three datasets (I2 = 0%; HRmeta = 1.46, 1.30, 1.51, respectively). The GRS using these five single nucleotide polymorphisms (SNPs) was also significantly associated (HRmeta [per score] = 2.42; P = 2.2 × 10-5; I2 = 0%). After 10 years from the first visit, the patients within the top 10% by GRS showed a 51% hazard rate, in contrast to 2.3% among patients within the lowest 10% by GRS.

Conclusions: We demonstrated that the GRS using ARMS2, CFH, TNFRSF10A, VEGFA, and CFI was significantly associated with second-eye involvement. Genetic risk has high predictive ability for second-eye involvement of AMD.

PMID: 26275133 [PubMed - as supplied by publisher]

**Ophthalmology. 2015 Jul 25. [Epub ahead of print]**

**Choroidal Nevus in the United States Adult Population: Racial Disparities and Associated Factors in the National Health and Nutrition Examination Survey.**

Qiu M, Shields CL.

PURPOSE: To describe the prevalence of choroidal nevus in the US population and identify possible associated factors.

DESIGN: Cross-sectional study.

PARTICIPANTS: A total of 5575 participants aged ≥40 years from the 2005-2008 National Health and Nutrition Examination Survey (NHANES) who underwent retinal imaging examination.

METHODS: Predictor variables included a spectrum of demographic, ophthalmic, dermatologic, systemic, socioeconomic, or occupational factor variables available in NHANES.

MAIN OUTCOME MEASURES: Choroidal nevus on retinal imaging.

RESULTS: The prevalence of choroidal nevus was 4.7% overall and increased with age (4.7%, 3.1%, 5.4%, 6.6%, and 7.5% in subjects aged 40-49, 50-59, 60-69, 70-79, and ≥80 years, respectively). The prevalence was 5.0% in men, 4.4% in women, 5.6% in whites, 2.7% in Hispanics, 0.6% in blacks, and 2.1% in others. After adjusting for age and race, the odds of choroidal nevus were 10-fold higher in whites than in blacks, 5-fold higher in Hispanics than in blacks, 4-fold higher in others than in blacks, and 2-fold higher in whites than in Hispanics. Choroidal nevus was associated with hypertension (odds ratio [OR], 1.40; 95% confidence interval [CI], 0.99-1.98); psoriasis (OR, 3.90; 95% CI, 1.57-9.66); lower high-density lipoprotein (OR, 0.99; 95% CI, 0.98-0.99); higher uric acid (OR, 1.13; 95% CI, 1.04-1.22); working in installation, maintenance, or repairs (OR, 1.42; 95% CI, 1.03-1.96); and having never worked (OR, 1.56; 95% CI, 1.03-2.37; P = 0.04). There was no association with visual symptoms, visual functioning, visual acuity, refractive error, visual field, diabetic retinopathy, age-related macular degeneration, or elevated cup-to-disc ratio on retinal imaging. There was no association with skin melanoma, other cancers, lung/liver/kidney/thyroid disease, alcohol/drug use, income/education, hemoglobin A1C, C-reactive protein, lactate dehydrogenase, electrolytes, or urine albumin.

CONCLUSIONS: Among US adults, the prevalence of choroidal nevus located within two 45° areas centered on the macula and optic disc is 4.7%. The prevalence increases with age, is highest among whites (5.6%), is lowest among blacks (0.6%), and has been previously under-recognized among Hispanics (2.7%). Extrapolating to the entire fundus, the true prevalence of choroidal nevus is even higher but difficult to accurately estimate. Possible associations with cardiovascular, renal, autoimmune, and occupational risk factors warrant further investigation.

PMID: 26255109 [PubMed - as supplied by publisher]

**Acta Ophthalmol. 2015 Aug 13. [Epub ahead of print]**

**Rare CFH mutations and early-onset age-related macular degeneration.**

Hughes AE, Meng W, Bridgett S, Bradley DT.

PMID: 26268811 [PubMed - as supplied by publisher]

# Diet, lifestyle and low vision

**Nutr Hosp. 2015 Apr 28;32(1):50-4.**

**[NUTRITIONAL COMPONENTS AND MACULAR DEGENERATION AGE-RELATED].[Article in Spanish]**

García-Montalvo IA, Matías-Pérez D.

OBJECTIVE: Nutritional components such as antioxidants may modify the risk of Macular Degeneration Age-related (AMD). This article is a systematic review of published studies relating to the modification of lifestyle, nutrition and vitamin intake to prevent or delay the onset or progression of Macular Degeneration Age-related (AMD).

RESULTS: The analysis of the results of research consulted shows that AMD is one of the most common causes of blindness in individuals over 55 years. AMD is characterized by decreased vision, metamorphopsias, macropsias, micropsias and central scotoma. Disease that must be diagnosed early because it can lead to irreversible blindness. Between components of the diet in many epidemiological studies have shown an inverse association with AMD and are reviewed in this paper are: vitamins (vitamin E and C), minerals (eg. zinc, selenium, manganese and copper) and carotenoids.

CONCLUSIONS: There is substantial evidence that can be applied nutritional support for patients with AMD. This requires determining the nutritional benefits of these nutrients (vitamins, minerals and carotenoids) or nutraceutical foods for health in this group of patients.

PMID: 26262695 [PubMed - in process]

**Indian J Ophthalmol. 2015 Jun;63(6):516-23.**

**Cost-effectiveness of anti-oxidant vitamins plus zinc treatment to prevent the progression of intermediate age-related macular degeneration. A Singapore perspective.**

Saxena N, George PP, Heng BH, Lim TH, Yong SO.

PURPOSE: To determine if providing high dose anti-oxidant vitamins and zinc treatment age-related eye disease study (AREDS formulation) to patients with intermediate age-related macular degeneration (AMD) aged 40-79 years from Singapore is cost-effective in preventing progression to wet AMD.

METHODS: A hypothetical cohort of category 3 and 4 AMD patients from Singapore was followed for 5 calendar years to determine the number of patients who would progress to wet AMD given the following treatment scenarios: (a) AREDS formulation or placebo followed by ranibizumab (as needed) for wet AMD. (b) AREDS formulation or placebo followed by bevacizumab (monthly) for wet AMD. (c) AREDS formulation or placebo followed by aflibercept (VIEW I and II trial treatment regimen). Costs were estimated for the above scenarios from the providers' perspective, and cost-effectiveness was measured by cost per disability-adjusted life year (DALY) averted with a disability weight of 0.22 for wet AMD. The costs were discounted at an annual rate of 3%.

RESULTS: Over 5400 patients could be prevented from progressing to wet AMD cumulatively if AREDS formulation were prescribed. AREDS formulation followed by ranibizumab was cost-effective compared to placebo-ranibizumab or placebo-aflibercept combinations (cost per DALY averted: SGD$23,662.3 and SGD$21,138.8, respectively). However, bevacizumab (monthly injections) alone was more cost-effective compared to AREDS formulation followed by bevacizumab.

CONCLUSION: Prophylactic treatment with AREDS formulation for intermediate AMD patients followed by ranibizumab or for patients who progressed to wet AMD was found to be cost-effective. These findings

have implications for intermediate AMD screening, treatment and healthcare planning in Singapore.

PMID: 26265643 [PubMed - in process]

**Invest Ophthalmol Vis Sci. 2015 Aug 1;56(9):5344-5352.**

**CD1 Mouse Retina Is Shielded From Iron Overload Caused by a High Iron Diet.**

Bhoiwala DL, Song Y, Cwanger A, Clark E, Zhao LL, Wang C, Li Y, Song D, Dunaief JL.

Purpose: High RPE iron levels have been associated with age-related macular degeneration. Mutation of the ferroxidase ceruloplasmin leads to RPE iron accumulation and degeneration in patients with aceruloplasminemia; mice lacking ceruloplasmin and its homolog hephaestin have a similar RPE degeneration. To determine whether a high iron diet (HID) could cause RPE iron accumulation, possibly contributing to RPE oxidative stress in AMD, we tested the effect of dietary iron on mouse RPE iron.

Methods: Male CD1 strain mice were fed either a standard iron diet (SID) or the same diet with extra iron added (HID) for either 3 months or 10 months. Mice were analyzed with immunofluorescence and Perls' histochemical iron stain to assess iron levels. Levels of ferritin, transferrin receptor, and oxidative stress gene mRNAs were measured by quantitative PCR (qPCR) in neural retina (NR) and isolated RPE. Morphology was assessed in plastic sections.

Results: Ferritin immunoreactivity demonstrated a modest increase in the RPE in 10-month HID mice. Analysis by qPCR showed changes in mRNA levels of iron-responsive genes, indicating moderately increased iron in the RPE of 10-month HID mice. However, even by age 18 months, there was no Perls' signal in the retina or RPE and no retinal degeneration.

Conclusions: These findings indicate that iron absorbed from the diet can modestly increase the level of iron deposition in the wild-type mouse RPE without causing RPE or retinal degeneration. This suggests regulation of retinal iron uptake at the blood-retinal barriers.

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**J Agric Food Chem. 2015 Aug 11. [Epub ahead of print]**

**The Leaves of Persimmon (Diospyros kaki Thunb.) Ameliorate N-methyl-N-nitrosourea (MNU)-Induced Retinal Degeneration in Mice.**

Kim KA, Kang SW, Ahn HR, Song Y, Yang SJ, Jung SH.

Abstract: The purpose of the study was to investigate the protective effects of the ethanol extract of Diospyros kaki (EEDK) Persimmon leaves to study N-methyl-N-nitrosourea (MNU)-induced retinal degeneration in mice. EEDK was orally administered after MNU-injection. Retinal layer thicknesses were significantly increased in the EEDK-treated group, compared with the MNU-treated group. The outer nuclear layer was preserved in the retinas of EEDK-treated mice. Moreover, EEDK treatment reduced the MNU-dependent up-regulation of glial fibrillary acidic protein (GFAP) and nestin expression in Müller and astrocyte cells. EEDK treatment also inhibited MNU-dependent down-regulation of rhodopsin expression. Quercetin exposure significantly attenuated the negative effects of H2O2 in R28 cells, suggesting that quercetin can act in an anti-oxidative capacity. Thus, EEDK may be considered as an agent for treating or preventing degenerative retinal diseases, such as retinitis pigmentosa and age-related macular degeneration.

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