

Issue 126

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term "macular degeneration".

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Drug treatment

Expert Opin Pharmacother. 2013 Apr 8. [Epub ahead of print]

An update on the pharmacotherapy of neovascular age-related macular degeneration.

Freund KB, Mrejen S, Gallego-Pinazo R.

Vitreous Retina Macula Consultants of New York , 460 Park Avenue, 5th Floor, New York, NY 10022 , USA
+1 212 861 9797 ; +1 212 628 0698 ; kbfnyf@aol.com.

Introduction: Neovascular age-related macular degeneration (AMD) is currently the most common cause of legal blindness in industrialized countries. The advent of pharmacotherapy with intravitreal VEGF inhibitors has greatly improved outcomes for the treatment of this disease.

Areas covered: The present review is divided into two major sections: the period prior to the use of anti-VEGF agents (triamcinolone acetonide, verteporfin photodynamic therapy) and the period following their introduction (pegaptanib sodium, bevacizumab, ranibizumab, aflibercept). The main pharmacological and clinical characteristics of each therapy are summarized.

Expert opinion: Monotherapy with anti-VEGF agents is currently the 'gold standard' for treating neovascular AMD, but, with several drug choices and various different dosing regimens available, there is still wide variability in how individual clinicians manage their patients. Despite improved visual outcomes, there remains a significant unmet need for better treatments as the frequent office visits and injections associated with anti-VEGF therapy are costly and place a significant burden on patients, their family members and physicians.

PMID: 23560774 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2013;7:621-5. doi: 10.2147/OPTH.S42881. Epub 2013 Mar 26.

A matched-control comparison of serious adverse events after intravitreal injections of bevacizumab for age-related macular degeneration and cataract extraction.

Fischer N, Moisseiev E, Waisbourd M, Goldstein M, Loewenstein A.

Department of Ophthalmology, Tel Aviv Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

PURPOSE: The study reported here investigated the rates of systemic serious adverse events (SAEs)

following treatment with intravitreal bevacizumab for age-related macular degeneration (AMD) in comparison with a matched control group.

METHODS: A retrospective age- and sex-matched case-control design was used. Data were collected using patient charts and telephone surveys. The main outcome measure was difference in number of hospital admissions between the two groups. Hospitalizations were further analyzed according to whether or not they were due to arteriothrombotic SAEs.

RESULTS: Each group comprised 65 participants. There were significantly more hospital admissions among bevacizumab-treated patients than in the control group ($P = 0.039$). Sub-analysis of hospitalizations due to arteriothrombotic causes did not reveal a statistically significant difference between groups ($P = 0.629$).

CONCLUSION: The results suggest that intravitreal bevacizumab is not associated with an increased risk of arteriothrombotic SAEs. Its widespread use for the treatment of AMD appears to be systemically safe.

PMID: 23569355 [PubMed - in process] PMCID: PMC3615876

Indian J Ophthalmol. 2013 Apr 10. [Epub ahead of print]

Different treatment modalities for choroidal neovascularization in two eyes of one patient with bilateral type 2A parafoveal telangiectasia.

Dave V, Chhablani J, Narayanan R.

Smt. Kanuri Santhamma Retina Vitreous Service, LV Prasad Eye Institute, Kallam Anji Reddy Campus, Banjara Hills, Hyderabad, India.

Abstract: A 60-year-old diabetic man presented with a history of decrease in vision in both eyes since 2 weeks. At presentation, best corrected visual acuity (BCVA) in the right eye (RE) was 20/30 and that in the left eye (LE) was 20/80. The right fundus revealed a grayish reflex, yellowish crystalline deposits and retinal pigment epithelial hyperplasia at the macula. The left fundus showed subretinal fluid and temporal subretinal hemorrhage near a grayish reflex at the macula. A diagnosis in both eyes of idiopathic macular telangiectasia (IMT) type 2A with RE stage 4 and LE stage 5, choroidal neovascularization (CNVM) was made. The patient was treated with photodynamic therapy (PDT) in LE. The visual acuity improved to 20/40 over the next 6 months. At a 4-year follow-up, he developed decreased vision in RE diagnosed as IMT with CNV and was treated with intravitreal ranibizumab. At 6-month follow-up post injection, the vision was 20/40p.

PMID: 23571237 [PubMed - as supplied by publisher]

Pharmacogenomics. 2013 Apr;14(6):623-30. doi: 10.2217/pgs.13.43.

VEGF-A polymorphisms predict short-term functional response to intravitreal ranibizumab in exudative age-related macular degeneration.

Lazzeri S, Figus M, Orlandi P, Fioravanti A, Di Desidero T, Agosta E, Sartini MS, Posarelli C, Nardi M, Danesi R, Bocci G.

Ophthalmology Unit, University of Pisa, Pisa, Italy.

Aim: To investigate the association between VEGF gene SNPs and early response to intravitreal ranibizumab for exudative age-related macular degeneration.

Materials & methods: Sixty-four patients (64 eyes) were prospectively enrolled and treated for neovascular

age-related macular degeneration with ranibizumab monotherapy. Visual acuity was measured using the ETDRS chart. A loading phase of 3 monthly intravitreal injections of ranibizumab 0.5 mg/0.05 ml was performed. The analyzed VEGF-A gene SNPs were rs699947 (-2578A/C) and rs1570360 (-1154G/A); the allelic discrimination was performed in real-time PCR platform. The difference of best corrected visual acuity (ETDRS letters) read before and after treatment was considered as functional outcome.

Results: Ranibizumab was significantly more effective as measured by best corrected visual acuity in patients harboring the VEGF-A -2578C allele (from +6.26 to +7.44 ETDRS letters), whereas patients carrying the VEGF-A -2578AA genotype revealed an absence of early functional response to ranibizumab (-1.78 ETDRS letters; $p = 0.0192$).

Conclusion: This study suggests that the VEGF-A -2578A/C SNP may represent an important molecular determinant of the early functional outcome of ranibizumab.

PMID: 23570466 [PubMed - in process]

Pharmacotherapy. 2013 Apr 11. doi: 10.1002/phar.1264. [Epub ahead of print]

Age-Related Macular Degeneration.

Cheung LK, Eaton A.

Department of Pharmacy Practice, Texas Southern University, College of Pharmacy and Health Sciences, Houston, Texas.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly, and the prevalence of the disease increases exponentially with every decade after age 50 years. It is a multifactorial disease involving a complex interplay of genetic, environmental, metabolic, and functional factors. Besides smoking, hypertension, obesity, and certain dietary habits, a growing body of evidence indicates that inflammation and the immune system may play a key role in the development of the disease. AMD may progress from the early form to the intermediate form and then to the advanced form, where two subtypes exist: the nonneovascular (dry) type and the neovascular (wet) type. The results from the Age-Related Eye Disease Study have shown that for the nonneovascular type of AMD, supplementation with high-dose antioxidants (vitamin C, vitamin E, and β -carotene) and zinc is recommended for those with the intermediate form of AMD in one or both eyes or with advanced AMD or vision loss due to AMD in one eye. As for the neovascular type of the advanced AMD, the current standard of therapy is intravitreal injections of vascular endothelial growth factor inhibitors. In addition, lifestyle and dietary modifications including improved physical activity, reduced daily sodium intake, and reduced intake of solid fats, added sugars, cholesterol, and refined grain foods are recommended. To date, no study has demonstrated that AMD can be cured or effectively prevented. Clearly, more research is needed to fully understand the pathophysiology as well as to develop prevention and treatment strategies for this devastating disease.

PMID: 23580402 [PubMed - as supplied by publisher]

Ophthalmologica. 2013 Apr 3. [Epub ahead of print]

Reduced-Fluence Photodynamic Therapy Combined with Ranibizumab for Nonproliferative Macular Telangiectasia Type 2.

Zehetner C, Haas G, Treiblmayr B, Kieselbach GF, Kralinger MT.

Department of Ophthalmology, Innsbruck Medical University, Innsbruck, Austria.

Purpose: To report the efficacy of reduced-fluence photodynamic therapy (PDT) combined with intravitreal ranibizumab for the treatment of nonproliferative macular telangiectasia (MacTel) type 2.

Methods: Noncomparative, interventional, retrospective case series; 5 eyes of 4 patients were studied. Patients were treated with reduced-fluence PDT and intravitreal ranibizumab within 24 h. After initial treatment, follow-up was at least 12 months in all patients.

Results: At baseline median logMAR (logarithm of the minimal angle of resolution) best-corrected visual acuity (BCVA) was 1.0 (range, 1.0-0.3). At 3 months of follow-up vision increased in 3 out of 5 eyes and median BCVA was 0.4 (range, 1.0-0.2). The gain of BCVA ranged from 6 lines to 1 line. Visual acuity remained stable in the other 2 study eyes. No eyes lost vision at 3 months of follow-up. At 12 months of follow-up median logMAR BCVA was 0.7 (range, 1.3-0.3). Two eyes had maintained their gain in BCVA compared to baseline. Two eyes lost vision compared to baseline and 1 eye showed unchanged visual acuity at 12 months of follow-up.

Conclusion: A combination therapy with reduced-fluence PDT and intravitreal ranibizumab might be a valuable treatment option for eyes with progressive vision loss due to nonproliferative MacTel type 2.

PMID: 23572022 [PubMed - as supplied by publisher]

Clin Exp Optom. 2013 Apr 8. doi: 10.1111/cxo.12042. [Epub ahead of print]

Single intravitreal ranibizumab injection for optic disc neovascularisation due to possibly traumatic, direct carotid cavernous fistula.

Saatci AO, Selver OB, Men S, Bajin MS.

Department of Ophthalmology, Dokuz Eylul University, Izmir, Turkey. osman.saatci@yahoo.com.

Abstract: We report a patient with optic disc neovascularisation due to possibly traumatic direct carotid cavernous fistula treated by a single dose of intravitreal ranibizumab prior to neurointervention. A 25-year-old man had a 10-month history of bilateral proptosis and left sixth nerve paralysis was evaluated. Conjunctival vessels were markedly dilated, especially in the left eye. Clinical examination and fundus fluorescein angiography revealed disc neovascularisation in the left eye with subtle peripheral retinal ischaemia. Magnetic resonance imaging suggested a high-flow carotid cavernous fistula on the left side and this was confirmed by catheter angiography. A single dose of intravitreal ranibizumab was injected prior to neuro-intervention. The disc neovascularisation regressed completely three days later. The left direct carotid cavernous fistula was later treated successfully with coil embolisation. Optic disc neovascularisation is a very rare feature of carotid cavernous fistula and intravitreal ranibizumab may be a useful therapeutic adjunct prior to neuro-interventional techniques to reduce neovascularisation-induced haemorrhage following the intervention.

PMID: 23560946 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2013 Apr 9. pii: iovs.12-11449v1. doi: 10.1167/iov.12-11449. [Epub ahead of print]

Automatic Drusen Quantification and Risk Assessment of Age-related Macular Degeneration on Color Fundus Images.

van Grinsven MJ, Lechanteur YT, van de Ven JP, van Ginneken B, Hoyng CB, Theelen T, Sanchez CI.

Diagnostic Image Analysis Group, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

PURPOSE: To evaluate a machine learning algorithm that allows for computer aided diagnosis (CAD) of non-advanced age-related macular degeneration (AMD) by providing an accurate detection and

Macular Disease Foundation Australia Suite 902, 447 Kent Street, Sydney, NSW, 2000, Australia.

4

Tel: +61 2 9261 8900 | Fax: +61 2 9261 8912 | E: research@mdfoundation.com.au | W: www.mdfoundation.com.au

quantification of drusen location, area and size.

METHODS: Color fundus photographs of 407 eyes without AMD or with early to moderate AMD were randomly selected from a large European multicenter database. A machine learning system was developed to automatically detect and quantify drusen on each image. Based on detected drusen, the CAD software provided a risk assessment to develop advanced AMD. Evaluation of the CAD system was performed using annotations made by two blinded human graders.

RESULTS: Free-response Receiver Operating Characteristics (FROC) analysis showed that the proposed system approaches the performance of human observers in detecting drusen. The estimated drusen area showed excellent agreement with both observers, with mean intra-class correlation coefficients (ICC) larger than 0.85. Maximum druse diameter agreement was lower with a maximum ICC of 0.69 but comparable to the interobserver agreement (ICC=0.79). For automatic AMD risk assessment, the system achieved areas under the Receiver Operating Characteristic (ROC) curve of 0.948 and 0.954, reaching similar performance as human observers.

CONCLUSIONS: A machine learning system, capable of separating high risk from low risk patients with non-advanced AMD by providing accurate detection and quantification of drusen, was developed. The proposed method allows for quick and reliable diagnosis of AMD, opening the way for large dataset analysis within population studies and genotype-phenotype correlation analysis.

PMID: 23572106 [PubMed - as supplied by publisher]

Cell Res. 2013 Apr 9. doi: 10.1038/cr.2013.48. [Epub ahead of print]

Multipotent stem cells isolated from the adult mouse retina are capable of producing functional photoreceptor cells.

Li T, Lewallen M, Chen S, Yu W, Zhang N, Xie T.

Stowers Institute for Medical Research, 1000 East 50th Street, Kansas City, MO 64110, USA.

Abstract: Various stem cell types have been tested for their potential application in treating photoreceptor degenerative diseases, such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD). Only embryonic stem cells (ESCs) have so far been shown to generate functional photoreceptor cells restoring light response of photoreceptor-deficient mice, but there is still some concern of tumor formation. In this study, we have successfully cultured Nestin+Sox2+Pax6+ multipotent retinal stem cells (RSCs) from the adult mouse retina, which are capable of producing functional photoreceptor cells that restore the light response of photoreceptor-deficient rd1 mutant mice following transplantation. After they have been expanded for over 35 passages in the presence of FGF and EGF, the cultured RSCs still maintain stable proliferation and differentiation potential. Under proper differentiation conditions, they can differentiate into all the major retinal cell types found in the adult retina. More importantly, they can efficiently differentiate into photoreceptor cells under optimized differentiation conditions. Following transplantation into the subretinal space of slowly degenerating rd7 mutant eyes, RSC-derived photoreceptor cells integrate into the retina, morphologically resembling endogenous photoreceptors and forming synapses with resident retinal neurons. When transplanted into eyes of photoreceptor-deficient rd1 mutant mice, a RP model, RSC-derived photoreceptors can partially restore light response, indicating that those RSC-derived photoreceptors are functional. Finally, there is no evidence for tumor formation in the photoreceptor-transplanted eyes. Therefore, this study has demonstrated that RSCs isolated from the adult retina have the potential of producing functional photoreceptor cells that can potentially restore lost vision caused by loss of photoreceptor cells in RP and AMD. Cell Research advance online publication 9 April 2013; doi:10.1038/cr.2013.48.

PMID: 23567557 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2013;7:615-20. doi: 10.2147/OPTH.S43566. Epub 2013 Mar 27.

Five-year results of photodynamic therapy with verteporfin for Japanese patients with neovascular age-related macular degeneration.

Tsuchihashi T, Mori K, Ueyama K, Yoneya S.

Department of Ophthalmology, Saitama Medical University, Iruma, Saitama, Japan.

PURPOSE: To describe the treatment outcome of photodynamic therapy (PDT) in Japanese patients with age-related macular degeneration (AMD) followed for 5 years.

PATIENTS AND METHODS: We retrospectively reviewed clinical charts of 51 patients with AMD. Thirty-one eyes of typical AMD (tAMD) and 20 eyes of polypoidal choroidal vasculopathy (PCV) were evaluated.

RESULTS: The mean logarithm of the minimum angle of resolution (logMAR) vision of all AMD patients was 0.807 at the baseline examination and 0.937 at the 5 year examination. Mean visual acuity letter score loss is similar between patients with tAMD (-7.25) and with PCV (-5.36) at the month 60 examination. The patients with lesions of classic choroidal neovascularization (CNV) had 10.0 letters loss, but the patients with lesions of occult CNV had only 1.43 letters loss. The number of retreatments peaked in year 1 and declined immediately for patients with tAMD, but patients with PCV had significantly more frequent retreatments in the years 3 and 4 than patients with tAMD ($P = 1.48 \times 10^{-2}$, 5.96×10^{-3} , respectively).

CONCLUSION: Visual outcomes in patients with Japanese patients with AMD treated with PDT after 5-year follow up were worse than that in short-term follow up reported previously. In addition, the difference in visual prognosis between tAMD and PCV was not demonstrated after long-term follow-up.

PMID: 23569354 [PubMed - in process] PMCID: PMC3615894

Pathogenesis

J Immunol. 2013 Apr 15;190(8):3839-47. doi: 10.4049/jimmunol.1203200.

Complement in immune and inflammatory disorders: therapeutic interventions.

Ricklin D, Lambris JD.

Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA 19104.

Abstract: With the awareness that immune-inflammatory cross-talk is at the heart of many disorders, the desire for novel immunomodulatory strategies in the therapy of such diseases has grown dramatically. As a prime initiator and important modulator of immunological and inflammatory processes, the complement system has emerged as an attractive target for early and upstream intervention in inflammatory diseases and has moved into the spotlight of drug discovery. Although prevalent conditions such as age-related macular degeneration have attracted the most attention, the diverse array of complement-mediated pathologies, with distinct underlying mechanisms, demands a multifaceted arsenal of therapeutic strategies. Fortunately, efforts in recent years have not only introduced the first complement inhibitors to the clinic but also filled the pipelines with promising candidates. With a focus on immunomodulatory strategies, in this review we discuss complement-directed therapeutic concepts and highlight promising candidate molecules.

PMID: 23564578 [PubMed - in process] PMCID: PMC3623010 [Available on 2014/4/15]

Ophthalmology. 2013 Apr 3. pii: S0161-6420(13)00006-7. doi: 10.1016/j.ophtha.2013.01.004. [Epub ahead of print]

Age-related Macular Degeneration and Modification of Systemic Complement Factor H Production

Macular Disease Foundation Australia Suite 902, 447 Kent Street, Sydney, NSW, 2000, Australia.

Tel: +61 2 9261 8900 | Fax: +61 2 9261 8912 | E: research@mdfoundation.com.au | W: www.mdfoundation.com.au

Through Liver Transplantation.

Khandhadia S, Hakobyan S, Heng LZ, Gibson J, Adams DH, Alexander GJ, Gibson JM, Martin KR, Menon G, Nash K, Sivaprasad S, Ennis S, Cree AJ, Morgan BP, Lotery AJ.

Clinical and Experimental Sciences, Clinical Neurosciences, Faculty of Medicine, University of Southampton, Southampton, UK.

PURPOSE: To investigate whether modification of liver complement factor H (CFH) production, by alteration of liver CFH Y402H genotype through liver transplantation (LT), influences the development of age-related macular degeneration (AMD).

DESIGN: Multicenter, cross-sectional study.

PARTICIPANTS: We recruited 223 Western European patients ≥ 55 years old who had undergone LT ≥ 5 years previously.

METHODS: We determined AMD status using a standard grading system. Recipient CFH Y402H genotype was obtained from DNA extracted from recipient blood samples. Donor CFH Y402H genotype was inferred from recipient plasma CFH Y402H protein allotype, measured using enzyme-linked immunosorbent assays. This approach was verified by genotyping donor tissue from a subgroup of patients. Systemic complement activity was ascertained by measuring levels of plasma complement proteins using an enzyme-linked immunosorbent assay, including substrates (C3, C4), activation products (C3a, C4a, and terminal complement complex), and regulators (total CFH, C1 inhibitor).

MAIN OUTCOME MEASURES: We evaluated AMD status and recipient and donor CFH Y402H genotype.

RESULTS: In LT patients, AMD was associated with recipient CFH Y402H genotype ($P = 0.036$; odds ratio [OR], 1.6; 95% confidence interval [CI], 1.0-2.4) but not with donor CFH Y402H genotype ($P = 0.626$), after controlling for age, sex, smoking status, and body mass index. Recipient plasma CFH Y402H protein allotype predicted donor CFH Y402H genotype with 100% accuracy ($n = 49$). Plasma complement protein or activation product levels were similar in LT patients with and without AMD. Compared with previously reported prevalence figures (Rotterdam Study), LT patients demonstrated a high prevalence of both AMD (64.6% vs 37.1%; OR, 3.09; $P < 0.001$) and the CFH Y402H sequence variation (41.9% vs 36.2%; OR, 1.27; $P = 0.014$).

CONCLUSIONS: Presence of AMD is not associated with modification of hepatic CFH production. In addition, AMD is not associated with systemic complement activity in LT patients. These findings suggest that local intraocular complement activity is of greater importance in AMD pathogenesis. The high AMD prevalence observed in LT patients may be associated with the increased frequency of the CFH Y402H sequence variation.

PMID: 23562165 [PubMed - as supplied by publisher]

Cell Metab. 2013 Apr 2;17(4):549-61. doi: 10.1016/j.cmet.2013.03.009.

Impaired cholesterol efflux in senescent macrophages promotes age-related macular degeneration.

Sene A, Khan AA, Cox D, Nakamura RE, Santeford A, Kim BM, Sidhu R, Onken MD, Harbour JW, Hagbi-Levi S, Chowder I, Edwards PA, Baldan A, Parks JS, Ory DS, Apte RS.

Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, Saint Louis, MO 63110, USA.

Abstract: Pathologic angiogenesis mediated by abnormally polarized macrophages plays a central role in common age-associated diseases such as atherosclerosis, cancer, and macular degeneration. Here we demonstrate that abnormal polarization in older macrophages is caused by programmatic changes that

lead to reduced expression of ATP binding cassette transporter ABCA1. Downregulation of ABCA1 by microRNA-33 impairs the ability of macrophages to effectively efflux intracellular cholesterol, which in turn leads to higher levels of free cholesterol within senescent macrophages. Elevated intracellular lipid polarizes older macrophages to an abnormal, alternatively activated phenotype that promotes pathologic vascular proliferation. Mice deficient for Abca1, but not Abcg1, demonstrate an accelerated aging phenotype, whereas restoration of cholesterol efflux using LXR agonists or miR-33 inhibitors reverses it. Monocytes from older humans with age-related macular degeneration showed similar changes. These findings provide an avenue for therapeutic modulation of macrophage function in common age-related diseases.

PMID: 23562078 [PubMed - in process]

Cell Metab. 2013 Apr 2;17(4):471-2. doi: 10.1016/j.cmet.2013.03.010.

Altered cholesterol homeostasis in aged macrophages linked to neovascular macular degeneration.

Chen J, Smith LE.

Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA.

Abstract: Abnormal lipid metabolism has been linked to age-related macular degeneration (AMD); choroidal neovascularization in late AMD commonly causes blindness. Sene et al. (2013) now demonstrate that in aged macrophages decreased ABCA1 expression, regulated by liver X receptor and miR-33, impairs export of intracellular cholesterol, which promotes neovascular AMD.

PMID: 23562072 [PubMed - in process]

Graefes Arch Clin Exp Ophthalmol. 2013 Apr 11. [Epub ahead of print]

Characterization of the effects of retinal pigment epithelium-conditioned media on porcine and aged human retina.

Kolomeyer AM, Sugino IK, Zarbin MA.

The Institute of Ophthalmology and Visual Science, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, 90 Bergen St., DOC6155, Newark, NJ, 07101, USA.

BACKGROUND: Retinal pigment epithelium (RPE) cells produce neurotrophic factors that rescue photoreceptors from degeneration. Previously, we showed that conditioned medium (CM) from fetal vs adult RPE cells resulted in significantly better porcine retinal preservation, and possessed significantly higher levels of hepatocyte growth factor (HGF) and pigment epithelium-derived factor (PEDF). This study aimed to further describe the effects of human fetal RPE-CM on porcine and aged human retina, and to characterize its effects biochemically.

METHODS: RPE-CM was harvested from passage-2 fetal RPE, 7 days after passage, 24-hours after exposure to basal medium. After culture in RPE-CM, porcine retinal morphology was assessed with confocal microscopy. The effects of RPE-CM on porcine and aged human retina survival were assessed by cytotoxicity and apoptosis biochemical assays. To characterize RPE-CM biochemically, effects of heating, digesting with proteinase-K, dilution, concentration, and fractionation were tested. Recombinant proteins and neutralizing antibodies were used to identify proteins that might contribute to the salutary effects of RPE-CM on porcine retina.

RESULTS: Culturing porcine retina in RPE-CM significantly preserved outer nuclear layer width and the number of nuclei in cross-section, and significantly decreased photoreceptor axon retraction. RPE-CM

decreased porcine retinal death by 17-34 % ($p < 0.05$) compared to basal medium. Human retina from age-related macular degeneration (AMD) and non-AMD donors responded similarly after culture in RPE-CM. Heating, proteinase-K digestion, and dilution significantly diminished RPE-CM-mediated preservation of porcine retina, whereas concentrating RPE-CM significantly enhanced its preservation of porcine retina. Molecular cut filtration identified retina-preserving activity in the 3-100 kDa filtrate. PEDF or HGF at 90 % receptor occupancy significantly improved retinal preservation over 48 h of culture compared to basal medium. Neutralizing PEDF in RPE-CM decreased its ability to reduce retinal apoptosis by 23-27 % ($p < 0.05$).

CONCLUSION: RPE-CM reduced biochemically and histologically measured degeneration in porcine retinae. This effect was concentration-dependent, and can be attributed to a protein component(s) in a 3-100 kDa molecular cut fraction. Human retina (including non-AMD and AMD Caucasian and non-AMD African-American) responds to culture in RPE-CM similarly to porcine retina. Receptor occupancy calculations and retinal viability data indicate that PEDF may be one of the components that contribute to retina preservation by RPE-CM.

PMID: 23575949 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Apr 11. pii: iovs.12-10341v1. doi: 10.1167/iov.12-10341. [Epub ahead of print]

Lack of Lymphatics and Lymph Node-mediated Immunity in Choroidal Neovascularization.

Nakao S, Zandi S, Kohno R, Sun D, Nakama T, Ishikawa K, Yoshida S, Enaida H, Ishibashi T, Hafezi-Moghadam A.

Department of Ophthalmology, Kyushu University, Graduate School of Medical Sciences, Fukuoka, Japan.

Purpose: Inflammation and immune cells regulate choroidal neovascularization (CNV) and could become therapeutic targets in age-related macular degeneration (AMD). Lymphangiogenesis is a key component of various inflammatory diseases. Whether lymphangiogenesis and lymph node-mediated immunity are involved in the pathogenesis of AMD is not understood.

Methods: To investigate lymphangiogenesis in AMD, we generated choroidal neovascularization (CNV) in animals by laser and studied surgically removed CNV membranes from uveitis and AMD patients. Immunohistochemistry was performed with LYVE-1 and podoplanin antibodies. VEGF-C and VEGFR-3 expressions were examined with immunohistochemistry and western blotting. To examine the role of lymph node in CNV, we lasered lymphotoxin alpha deficient mice ($LT\alpha^{-/-}$) and measured the CNV volume.

Results: Immunohistochemistry showed that LYVE-1(+) macrophages infiltrated in acutely induced CNV, however, lymphatic tubes did not form. CNV membranes from patients did not show LYVE-1(+)podoplanin (+) vessels, suggesting lack of lymphangiogenesis in AMD and uveitis. Western blots and immunostaining revealed VEGF-C and VEGFR-3 expression in CNV lesions, mainly in macrophages and angiogenic endothelial cells. Using fluorescent microsphere tracers, we show a path for cellular migration from the eye to the cervical lymph nodes (LN) during CNV. However, CNV injury did not cause LN swelling. CNV volume did not differ between WT and LN deficient mice, suggesting that LN is not a key component of early CNV formation.

Conclusions: Laser-induced CNV is not primarily dependent on acquired immunity, nor does the fundus injury affect peripheral LNs. Our results reveal a previously unknown cellular connection between the ocular fundus and the cervical LNs. This connection that in function resembles lymphatics is actively utilized in CNV.

PMID: 23580489 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2013 Apr 10. [Epub ahead of print]

Endothelial Progenitor Cells and Plasma Vascular Endothelial Growth Factor and Stromal Cell-Derived Factor-1 During Ranibizumab Treatment for Neovascular Age-Related Macular Degeneration.

Grierson R, Meyer-Rüsenberg B, Kunst F, Berna MJ, Richard G, Thill M.

Department of Ophthalmology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Abstract Purpose: To evaluate endothelial progenitor cell [late outgrowth endothelial progenitor cells (OECs)], vascular endothelial growth factor (VEGF), and stromal cell-derived factor 1 α (SDF-1 α) plasma levels as potential biomarkers before and during ranibizumab (Lucentis®) treatment for neovascular age-related macular degeneration (nvAMD).

Methods: Thirty-one patients with untreated nvAMD presenting for 3 consecutive intravitreal ranibizumab injections and a follow-up visit at 4 weeks intervals were enrolled. Peripheral blood was collected before each injection and at the follow-up visit and OEC clusters were cultured and evaluated according to previously published protocols. VEGF and SDF-1 α plasma levels were measured by enzyme-linked immunosorbent assay and compared to values from healthy young and old control.

Results: Patients with a high OEC count before treatment presented significantly more often with a short symptom duration and a smaller choroidal neovascularization size. VEGF plasma levels were significantly higher in nvAMD (282.4 ± 195.2 pg/mL) compared to young (45.5 ± 6.8 pg/mL) and old control (46.1 ± 8.5 pg/mL). OEC levels decreased nonsignificantly during ranibizumab treatment, returning to baseline levels after the third injection. VEGF and SDF-1 α plasma levels decreased significantly during treatment toward control values. Patients needing retreatment after 3 ranibizumab injections had significantly higher VEGF plasma levels at pretreatment compared to patients not needing further treatment.

Conclusions: The results presented here suggest that VEGF plasma levels may warrant further evaluation regarding biological, therapeutic, and predictive implications in nvAMD.

PMID: 23573802 [PubMed - as supplied by publisher]

Exp Eye Res. 2013 Apr 3. pii: S0014-4835(13)00077-8. doi: 10.1016/j.exer.2013.03.017. [Epub ahead of print]

Retinal deimination and PAD2 levels in retinas from donors with age-related macular degeneration (AMD).

Bonilha VL, Shadrach KG, Rayborn ME, Li Y, Pauer GJ, Hagstrom SA, Bhattacharya SK, Hollyfield JG.

Department of Ophthalmology, The Cole Eye Institute(i31), Cleveland Clinic Lerner College of Medicine, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Electronic address: bonilhav@ccf.org.

Abstract: Deimination is a form of protein posttranslational modification carried out by the peptidyl arginine deiminases (PADs) enzymes. PAD2 is the principal deiminase expressed in the retina. Elevated levels of PAD2 and protein deimination are present in a number of human neurological diseases, with or without ocular manifestation. To define the association of deimination with the pathogenesis of age-related macular degeneration (AMD), we studied protein deimination and PAD2 levels in retinas of AMD donor eyes compared to age-matched non-AMD retinas. Eyes from non-AMD and AMD donors were fixed in 4% paraformaldehyde and 0.5% glutaraldehyde in phosphate buffer. Retina and retinal pigment epithelium (RPE) from donor eyes were processed for immunohistochemical detection and western blotting using antibodies to PAD2 and citrulline residues. The ganglion cell, inner plexiform, inner nuclear and outer nuclear layers were labeled by both PAD2 and citrulline antibodies. Changes in the localization of deiminated residues and PAD2 were evident as the retinal layers were remodeled coincident with

photoreceptor degeneration in AMD retinas. Immunodetection of either PAD2 or citrulline residues could not be evaluated in the RPE layer due to the high autofluorescence levels in this layer. Interestingly, higher deimination immunoreactivity was detected in AMD retinal lysates. However, no significant changes in PAD2 were detected in the AMD and non-AMD retinas and RPE lysates. Our observations show increased levels of protein deimination but not PAD2 in AMD retinas and RPE, suggesting a reduced rate of turnover of deiminated proteins in these AMD retinas.

PMID: 23562679 [PubMed - as supplied by publisher]

Structure. 2013 Apr 2. pii: S0969-2126(13)00077-4. doi: 10.1016/j.str.2013.03.001. [Epub ahead of print]

Molecular Organization and ATP-Induced Conformational Changes of ABCA4, the Photoreceptor-Specific ABC Transporter.

Tsybovsky Y, Orban T, Molday RS, Taylor D, Palczewski K.

Department of Pharmacology, School of Medicine, Case Western Reserve University, Cleveland, OH 44106, USA. Electronic address: yxt76@case.edu.

Abstract: ATP-binding cassette (ABC) transporters use ATP to translocate various substrates across cellular membranes. Several members of subfamily A of mammalian ABC transporters are associated with severe health disorders, but their unusual complexity and large size have so far precluded structural characterization. ABCA4 is localized to the discs of vertebrate photoreceptor outer segments. This protein transports N-retinylidene-phosphatidylethanolamine to the outer side of disc membranes to prevent formation of toxic compounds causing macular degeneration. An 18 Å-resolution structure of ABCA4 isolated from bovine rod outer segments was determined using electron microscopy and single-particle reconstruction. Significant conformational changes in the cytoplasmic and transmembrane regions were observed upon binding of a nonhydrolyzable ATP analog and accompanied by altered hydrogen/deuterium exchange in the Walker A motif of one of the nucleotide-binding domains. These findings provide an initial view of the molecular organization and functional rearrangements for any member of the ABCA subfamily of ABC transporters.

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J Biol Chem. 2013 Apr 9. [Epub ahead of print]

Photoreceptor proteins initiate microglial activation via Toll-like receptor 4 in retinal degeneration mediated by all-trans-retinal.

Kohno H, Chen Y, Kevany BM, Pearlman E, Miyagi M, Maeda T, Palczewski K, Maeda A.

Case Western Reserve University, United States.

Abstract: Although several genetic and biochemical factors are associated with the pathogenesis of retinal degeneration, it has yet to be determined how these different impairments can cause similar degenerative phenotypes. Here, we report microglial/macrophage activation in both a Stargardt disease and age-related macular degeneration mouse model caused by delayed clearance of all-trans-retinal from the retina, and in a retinitis pigmentosa mouse model with impaired retinal pigment epithelium (RPE) phagocytosis. Mouse microglia displayed RPE cytotoxicity and increased production of inflammatory chemokines/cytokines, Ccl2, Il1b and Tnf, after co-incubation with ligands that activate innate immunity. Notably, phagocytosis of photoreceptor proteins increased the activation of microglia/macrophages and RPE cells isolated from model mice as well as wild-type mice. The mRNA levels of Tlr2 and Tlr4, which can recognize proteins as their ligands, were elevated in mice with retinal degeneration. Bone marrow-derived macrophages from Tlr4

-deficient mice did not increase Ccl2 after co-incubation with photoreceptor proteins. Tlr4-/-Abca4-/-Rdh8-/- mice displayed milder retinal degenerative phenotypes than Abca4-/-Rdh8-/- mice. Additionally, inactivation of microglia/macrophages by pharmacological approaches attenuated mouse retinal degeneration. This study demonstrates an important contribution of TLR4-mediated microglial activation by endogenous photoreceptor proteins in retinal inflammation that aggravates retinal cell death. This pathway is likely to represent an underlying common pathology in degenerative retinal disorders.

PMID: 23572532 [PubMed - as supplied by publisher]

Middle East Afr J Ophthalmol. 2013 Jan;20(1):26-37. doi: 10.4103/0974-9233.106384.

Nanotechnology approaches for ocular drug delivery.

Department of Ophthalmology, Center for Nanomedicine, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.

Abstract: Blindness is a major health concern worldwide that has a powerful impact on afflicted individuals and their families, and is associated with enormous socio-economical consequences. The Middle East is heavily impacted by blindness, and the problem there is augmented by an increasing incidence of diabetes in the population. An appropriate drug/gene delivery system that can sustain and deliver therapeutics to the target tissues and cells is a key need for ocular therapies. The application of nanotechnology in medicine is undergoing rapid progress, and the recent developments in nanomedicine-based therapeutic approaches may bring significant benefits to address the leading causes of blindness associated with cataract, glaucoma, diabetic retinopathy and retinal degeneration. In this brief review, we highlight some promising nanomedicine-based therapeutic approaches for drug and gene delivery to the anterior and posterior segments.

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Epidemiology

Indian J Ophthalmol. 2013 Apr 10. [Epub ahead of print]

Prevalence and determinants of age-related macular degeneration in the 50 years and older population: A hospital based study in Maharashtra, India.

Kulkarni SR, Aghashe SR, Khandekar RB, Deshpande MD.

Department of Non Communicable Diseases Surveillance and Control, Eye and Ear Health Care, Ministry of Health, Muscat, Oman.

Background: We present the magnitude and determinants of age-related macular degeneration (ARMD) among the 50 year and older population that visited our hospital.

Materials and Methods: This was a cohort of eye patients with ARMD, seen from 2006 to 2009. Optometrist noted the best-corrected vision. Ophthalmologists examined eyes using a slit-lamp bio-microscope. The ARMD was confirmed by fluoresceine angiography and optical coherent tomography. The age, sex, history of smoking, sun exposure, family history of ARMD, diet, body mass index (BMI), hypertension, and diabetes were associated with ARMD.

Result: Of the 19,140 persons of ≥ 50 years of age-attending eye clinic in our hospital, 302 persons had ARMD in at least one eye. The proportion of overall ARMD was 1.38% (95% CI 1.21--1.55). The proportion of age-related maculopathy (ARM) and late ARMD was 1.14% (95% CI 0.99--1.29) and 0.24% (95% CI 0.21-0.24) respectively. ARM was unilateral and bilateral in 64 (29.2%) and 155 (70.8%) persons

respectively. Dry ARMD was found in 47.8%. On regression analysis, old age (OR = 1.05), male (OR = 0.54), and history of smoking (OR = 2.32) were significant risk factors of ARMD. A total of 4.2% of persons with ARMD were blind (vision <3/60). Only 43% of persons with ARMD had J6 grade of the best-corrected near vision.

Conclusion: ARMD does not seem to be of public health magnitude in the study area. Early stages of ARMD were common among patients. Age, being male, and history of smoking were significant risk factors for ARMD.

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Genetics

Ann Hum Genet. 2013 May;77(3):215-31. doi: 10.1111/ahg.12011.

Genetic factors in nonsmokers with age-related macular degeneration revealed through genome-wide gene-environment interaction analysis.

Naj AC, Scott WK, Courtenay MD, Cade WH, Schwartz SG, Kovach JL, Agarwal A, Wang G, Haines JL, Pericak-Vance MA.

Department of Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Abstract: Relatively little is known about the interaction between genes and environment in the complex etiology of age-related macular degeneration (AMD). This study aimed to identify novel factors associated with AMD by analyzing gene-smoking interactions in a genome-wide association study of 1207 AMD cases and 686 controls of Caucasian background with genotype data on 668,238 single nucleotide polymorphisms (SNPs) after quality control. Participants' history of smoking at least 100 cigarettes lifetime was determined by a self-administered questionnaire. SNP associations modeled the effect of the minor allele additively on AMD using logistic regression, with adjustment for age, sex, and ever/never smoking. Joint effects of SNPs and smoking were examined comparing a null model containing only age, sex, and smoking against an extended model including genotypic and interaction terms. Genome-wide significant main effects were detected at three known AMD loci: CFH ($P = 7.51 \times 10^{-30}$), ARMS2 ($P = 1.94 \times 10^{-23}$), and RDBP/CFB/C2 ($P = 4.37 \times 10^{-10}$), while joint effects analysis revealed three genomic regions with $P < 10^{-5}$. Analyses stratified by smoking found genetic associations largely restricted to nonsmokers, with one notable exception: the chromosome 18q22.1 intergenic SNP rs17073641 (between SERPINB8 and CDH7), more strongly associated in nonsmokers (OR = 0.57, $P = 2.73 \times 10^{-5}$), with an inverse association among smokers (OR = 1.42, $P = 0.00228$), suggesting that smoking modifies the effect of some genetic polymorphisms on AMD risk.

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Exome sequencing reveals CCDC111 mutation associated with high myopia.

Zhao F, Wu J, Xue A, Su Y, Wang X, Lu X, Zhou Z, Qu J, Zhou X.

School of Ophthalmology and Optometry and Eye Hospital, Wenzhou Medical College, 270 Xueyuan Road, Wenzhou, 325003, Zhejiang, People's Republic of China, striveswzmc@163.com.

Abstract: Myopia is a refractive error of the eye that is prevalent worldwide. The most extreme form, high myopia, is usually associated with other ocular disorders such as retinal detachment, macular

degeneration, cataract, and glaucoma, and is one of leading causes of blindness. The etiology is complex and has not been fully elucidated. In this study, we identified a novel missense variant of the CCDC111 gene (NM_152683.2: c.265T > G; p.Y89D) in a high myopia family by exome sequencing. The variant was identified in 4 patients from an additional 270 sporadic high myopia patients, but not found in 270 controls. The amino acid is highly conserved across species, and variants giving rise to amino acid substitutions are predicted to be functionally damaging. The CCDC111 gene was ubiquitously expressed in primary cell cultures from human eye tissue, including corneal epithelial cells, choroidal melanoma cells, scleral fibroblasts, retinal epithelial cells, retinal Müller cells, and lens capsule epithelial cells. In summary, our results suggested that the CCDC111 may be a susceptibility gene for high myopia.

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J Int Med Res. 2013 Feb 5. [Epub ahead of print]

Association between vascular endothelial growth factor +936 C/T gene polymorphism and age-related macular degeneration.

Jiang Y, Liang G, Wang L, Jiang J, Du G, Huang Y.

Department of Ophthalmology, Chinese PLA General Hospital, Beijing, China.

OBJECTIVES: The pathogenesis of age-related macular degeneration (AMD) remains unknown. Vascular endothelial growth factor (VEGF) is an important regulator of angiogenesis and a target for inhibition therapy in wet AMD. This study investigated the association between the VEGF +936 C/T gene polymorphism and AMD, in a Chinese Han population.

METHODS: Patients with AMD, and age- and sex-matched controls were enrolled. Restriction fragment length polymorphism was used to analyse the VEGF +936 polymorphism in the promoter and the 3' untranslated region of the gene.

RESULTS: The study included 200 AMD patients and 200 control subjects. There was a significantly higher prevalence of the TT genotype among AMD patients (9.0%) compared with controls (3.5%); the odds ratio for this genotype in AMD patients was 2.73 (95% confidence intervals 1.11, 6.68). There were no significant associations between any genotype and AMD subphenotypic categories (early, geographic atrophy, choroidal neovascularization).

CONCLUSIONS: The present study findings suggested that the VEGF +936 TT genotype was associated with AMD among Han Chinese patients.

PMID: 23569009 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Apr 5. pii: S0161-6420(13)00045-6. doi: 10.1016/j.ophtha.2013.01.030. [Epub ahead of print]

Investigation of Genetic Variation in Scavenger Receptor Class B, Member 1 (SCARB1) and Association with Serum Carotenoids.

McKay GJ, Loane E, Nolan JM, Patterson CC, Meyers KJ, Mares JA, Yonova-Doing E, Hammond CJ, Beatty S, Silvestri G.

Centre for Public Health, Royal Victoria Hospital, Queen's University Belfast, Belfast, Northern Ireland. Electronic address: g.j.mckay@qub.ac.uk.

OBJECTIVE: To investigate association of scavenger receptor class B, member 1 (SCARB1) genetic variants with serum carotenoid levels of lutein (L) and zeaxanthin (Z) and macular pigment optical density

(MPOD).

DESIGN: A cross-sectional study of healthy adults aged 20 to 70.

PARTICIPANTS: We recruited 302 participants after local advertisement.

METHODS: We measured MPOD by customized heterochromatic flicker photometry. Fasting blood samples were taken for serum L and Z measurement by high-performance liquid chromatography and lipoprotein analysis by spectrophotometric assay. Forty-seven single nucleotide polymorphisms (SNPs) across SCARB1 were genotyped using Sequenom technology. Association analyses were performed using PLINK to compare allele and haplotype means, with adjustment for potential confounding and correction for multiple comparisons by permutation testing. Replication analysis was performed in the TwinsUK and Carotenoids in Age-Related Eye Disease Study (CAREDS) cohorts.

MAIN OUTCOME MEASURES: Odds ratios for MPOD area, serum L and Z concentrations associated with genetic variations in SCARB1 and interactions between SCARB1 and gender.

RESULTS: After multiple regression analysis with adjustment for age, body mass index, gender, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, smoking, and dietary L and Z levels, 5 SNPs were significantly associated with serum L concentration and 1 SNP with MPOD ($P < 0.01$). Only the association between rs11057841 and serum L withstood correction for multiple comparisons by permutation testing ($P < 0.01$) and replicated in the TwinsUK cohort ($P = 0.014$). Independent replication was also observed in the CAREDS cohort with rs10846744 ($P = 2 \times 10^{-4}$), an SNP in high linkage disequilibrium with rs11057841 ($r^2 = 0.93$). No interactions by gender were found. Haplotype analysis revealed no stronger association than obtained with single SNP analyses.

CONCLUSIONS: Our study has identified association between rs11057841 and serum L concentration (24% increase per T allele) in healthy subjects, independent of potential confounding factors. Our data supports further evaluation of the role for SCARB1 in the transport of macular pigment and the possible modulation of age-related macular degeneration risk through combating the effects of oxidative stress within the retina.

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CC Chemokine receptor-3 as new target for age related macular degeneration.

Sharma NK, Gupta A, Prabhakar S, Singh R, Bhatt AK, Anand A.

Department of Neurology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

Abstract: CC Chemokine receptor-3 (CCR3) is involved in angiogenic processes. Recently, CCR3 was accounted to participate in choroidal neovascularization (CNV) and CCR3 targeting was reported to be superior to standard anti vascular endothelial growth factor-A (VEGF-A) administration when tested in an artificially induced CNV in animals. As human CCR3 studies are lacking in age-related macular degeneration (AMD) patients we sought to determine if CCR3 has any association with inflammatory processes that occur in CNV. Total 176 subjects were included on the basis of inclusion criteria. Real time PCR was used to analyze the single nucleotide polymorphism in CCR3 of AMD (115) and normal controls ($n=61$). Genotype frequency was adjusted for possible confounders like cigarette smoking, alcohol, meat consumption and other risk factors. Chi-square test was used for analysis of polymorphism. The genotype distribution of CCR3 (rs3091250) polymorphism was significantly different in AMD patients in the Indian population. GT (Heterozygous) and TT (homozygous) at the rs3091250 SNP increased risk of AMD as compared to the GG genotypes (OR =4.8, CI 95%=2.2-10.8 and OR=4.1, CI 95%=1.6-10.1 respectively). Subgroup analysis of AMD patients in wet and dry revealed no significant differences. There was no

significant difference for rs3091312 in AMD and control group. A significant association between AMD and CCR3 (rs3091250) polymorphism localized on chromosome 3p21.3 was detected. The results suggest the possible contribution of rs3091250, a new predisposing allele in AMD.

PMID: 23566847 [PubMed - as supplied by publisher]

Am J Epidemiol. 2013 Apr 9. [Epub ahead of print]

RE: "THE ASSOCIATION BETWEEN COMPLEMENT COMPONENT 2/COMPLEMENT FACTOR B POLYMORPHISMS AND AGE-RELATED MACULAR DEGENERATION: A HuGE REVIEW AND META-ANALYSIS"

Hughes AE, Bradley DT.

Centre for Public Health, School of Medicine, Dentistry, and Biomedical Sciences, Queen's University Belfast, Belfast BT12 6BL, United Kingdom.

PMID: 23572050 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2013 Apr 9;1-2. doi: 10.1001/jamaophthalmol.2013.589. [Epub ahead of print]

Coding Variants in ARMS2 and the Risk of Age-Related Macular Degeneration.

Wang G, Scott WK, Agarwal A, Haines JL, Pericak-Vance MA.

PMID: 23572227 [PubMed - as supplied by publisher]

Diet

Nutrients. 2013 Apr 9;5(4):1169-85. doi: 10.3390/nu5041169.

Dietary sources of lutein and zeaxanthin carotenoids and their role in eye health.

Abdel-Aal el-SM, Akhtar H, Zaheer K, Ali R.

Guelph Food Research Centre, Agriculture and Agri-Food Canada, Guelph, ON N1G 5C9, Canada. elsayed.abdelaal@agr.gc.ca.

Abstract: The eye is a major sensory organ that requires special care for a healthy and productive lifestyle. Numerous studies have identified lutein and zeaxanthin to be essential components for eye health. Lutein and zeaxanthin are carotenoid pigments that impart yellow or orange color to various common foods such as cantaloupe, pasta, corn, carrots, orange/yellow peppers, fish, salmon and eggs. Their role in human health, in particular the health of the eye, is well established from epidemiological, clinical and interventional studies. They constitute the main pigments found in the yellow spot of the human retina which protect the macula from damage by blue light, improve visual acuity and scavenge harmful reactive oxygen species. They have also been linked with reduced risk of age-related macular degeneration (AMD) and cataracts. Research over the past decade has focused on the development of carotenoid-rich foods to boost their intake especially in the elderly population. The aim of this article is to review recent scientific evidences supporting the benefits of lutein and zexanthin in preventing the onset of two major age-related eye diseases with diets rich in these carotenoids. The review also lists major dietary sources of lutein and zeaxanthin and refers to newly developed foods, daily intake, bioavailability and physiological effects in relation to eye health. Examples of the newly developed high-lutein functional foods are also underlined.

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Acta Ophthalmol. 2013 Apr 10. doi: 10.1111/aos.12067. [Epub ahead of print]

Relationship between macular pigment and visual acuity in eyes with early age-related macular degeneration.

Puell MC, Palomo-Alvarez C, Barrio AR, Gómez-Sanz FJ, Pérez-Carrasco MJ.

Applied Vision Research Group, Complutense University, Madrid, Spain Hospital del Henares, Madrid, Spain.

Purpose: Today the extent to which MP impacts visual function in early AMD remains unclear. This study examines the relationship between macular pigment optical density (MPOD) and high-contrast visual acuity (HC-VA) and low-contrast visual acuity (LC-VA) in eyes with early age-related macular degeneration (AMD).

Methods: Measurements were made in 22 subjects with early AMD and 27 healthy control subjects. Distance best-corrected VA was measured using HC (96%) and LC (10%) Bailey-Lovie logMAR letter charts under photopic luminance conditions. MPOD was determined at the fovea through apparent motion photometry using the cathode ray tube-based Metropsis psychophysical vision test (Cambridge Research Systems).

Results: No significant differences in foveal MPOD were detected between the control eyes (0.30 ± 0.24 log units) and eyes with early AMD (0.27 ± 0.15 log units). Neither were differences detected between the two groups in mean HC- and LC-VA. Foveal MPOD showed significant correlation with both photopic HC-VA ($r = -0.47$, $p = 0.0008$) and LC-VA ($r = -0.46$, $p = 0.0008$) such that as MPOD increased, photopic HC-VA and LC-VA improved (lower logMAR values).

Conclusions: Low MP levels were related to worse visual function in both healthy eyes and eyes with early AMD. Our findings provide direction for future studies designed to improve retinal function through the use of oral supplements known to increase MP levels, especially in eyes with AMD and a low MPOD.

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