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MD Research News

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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

Retina. 2013 Jul 3. [Epub ahead of print]

EFFICIENT CAPTURE OF HIGH-QUALITY DATA ON OUTCOMES OF TREATMENT FOR MACULAR DISEASES: The Fight Retinal Blindness! Project.

Gillies MC, Walton R, Liong J, Arnold JJ, McAllister I, Morlet N, Hunyor A, Guymer R, Keeffe J, Essex R, Herrera-Bond A, Glastonbury B, Simpson JM, Barthelmes D.

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PURPOSE: To describe the development of a web-based high-quality data collection tool to track the outcomes of treatment of macular disease in routine practice.

METHODS: Testing of a larger data collection tool established which fields a clinician would reliably fill out. The program, which was developed using freely available software, consists of modules interacting with a core system. The module for neovascular age-related macular degeneration is described here.

RESULTS: Data for initial visits can be entered within 30 seconds, 15 seconds for follow-up visits. Fifteen centers from Australia, New Zealand, and Switzerland are currently contributing data. Finalized data from 2,052 eyes of 1,693 participants dating from January 2006 were analyzed. Median (25th and 75th percentiles) visual acuity at the index visit was 55 (41, 68) logarithm of the minimum angle of resolution letters with the following lesion types: minimally classic 17.2%, predominantly classic 24.6%, occult 52.0%, idiopathic polypoidal choroidal vasculopathy 1.2%, and retinal angiomatous proliferation 3.2%.

CONCLUSION: This software tool will facilitate the collection of large amounts of data on the routine use of treatments of neovascular age-related macular degeneration. This will allow us to analyze important potentially modifiable variables, such as the effect of different treatment patterns on visual outcomes, and to evaluate new treatments as they are introduced into practice.

PMID: 23836194 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Jul 3. pii: S0161-6420(13)00444-2. doi: 10.1016/j.ophtha.2013.05.018. [Epub ahead of print]

A 4-Year Longitudinal Study of 555 Patients Treated with Ranibizumab for Neovascular Age-Related Macular Degeneration.

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OBJECTIVE: To investigate the visual outcome, pattern of discontinuation, ocular complications, and mortality of patients treated with a variable ranibizumab dosing regimen for neovascular age-related macular degeneration (AMD) for 4 years.

DESIGN: Retrospective chart review supplemented with clinical examination.

PARTICIPANTS: Six hundred eyes of 555 patients initiated intravitreal treatment with vascular endothelial growth factor inhibition for neovascular AMD in 2007 in a community-based hospital.

METHODS: Patient data from a database were retrieved from 2007 through 2011. Descriptive evaluation of the main outcome measures was carried out for the cohort of patients. A group of patients who had been discontinued because of apparent disease inactivity was reexamined.

MAIN OUTCOME MEASURES: Best-corrected visual acuity (BCVA; Snellen), number of intravitreal injections, causes of discontinuations, ocular complications, and standardized mortality rate.

RESULTS: One hundred ninety-two eyes (32%) were still receiving active treatment after 4 years. The mean BCVA in the 192 eyes was unchanged from the start (baseline, 0.30; 4-year follow-up, 0.32; P>0.3). Visual acuity after the third loading dose was associated significantly with the outcome (P < 0.0001) and was a better predictor than baseline acuity. The mean number of injections was 5.5 per year. For 408 eyes (68%), discontinuation of treatment was motivated by the following 4 reasons: lack of apparent treatment response (28%), failure to appear at follow-up (11%), death (9%), and disease inactivity (20%, 120 eyes). Treatment was resumed later in 18% of patients discontinued because of inactivity. Sixty-seven eyes were reexamined in 2012 from the group of patients with disease inactivity. The final visual acuity by then had decreased significantly from the time of discontinuation, from 0.38 to 0.15 (P = 0.001). Endophthalmitis occurred in 2 eyes of 7584 injections. A total of 125 patients had died, corresponding to 75% of the mean mortality in the community.

CONCLUSIONS: One third of the eyes were still receiving active treatment after 4 years and had stable visual acuity. One third of fellow eyes (eyes at risk) started treatment during the 4 years. One fifth of discontinued eyes resumed treatment, indicating that close follow-up should be maintained for patients discontinued because of disease inactivity. The ocular complication rate was 0.2%, and the mortality rate was below expected.

PMID: 23830760 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2013;7:1287-9. doi: 10.2147/OPTH.S47735. Epub 2013 Jun 26.

Retinal pigment epithelium tear after intravitreal aflibercept injection.

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Abstract: To report a case complicated with a retinal pigment epithelium (RPE) tear after intravitreal

aflibercept injection. A 78-year-old man had deteriorated visual acuity in his left eye. Fluorescein angiography showed occult choroidal neovascularization. Optical coherence tomography showed a serous retinal detachment and fibrovascular pigment epithelial detachment. He was diagnosed as typical age-related macular degeneration associated with pigment epithelial detachment and treatment consisting of three consecutive monthly intravitreal injections of aflibercept was planned. A month after the initial injection, his visual acuity had not improved. The red-free photograph showed an area of RPE defect inferior to the fovea. The fundus autofluorescence, fluorescein angiography, and optical coherence tomography clearly demonstrated the presence of an RPE tear. A second injection of aflibercept was performed due to a remaining serous retinal detachment. Although this is a single case and RPE tears may occur as a spontaneous complication of age-related macular degeneration patients, the risk of a tear should be discussed when considering aflibercept treatment for typical age-related macular degeneration patients with pigment epithelial detachment as there might be a risk for developing an RPE tear.

PMID: 23836958 [PubMed] PMCID: PMC3699315

Clin Ophthalmol. 2013;7:1257-67. doi: 10.2147/OPTH.S36443. Epub 2013 Jun 24.

Critical appraisal of ranibizumab in the treatment of diabetic macular edema.

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Abstract: Diabetic retinopathy is the leading cause of blindness among individuals of working age in industrialized nations, with most of the vision loss resulting from diabetic macular edema (DME). The formation of DME depends on the action of several growth factors and inflammatory mediators, but vascular endothelial growth factor (VEGF) appears to be critical for breaking down the blood-retinal barrier and promoting the accumulation of macular edema. Laser photocoagulation has been the standard-of-care for three decades, and although it stabilizes vision, significant gains in visual acuity after treatment are unusual. Several VEGF inhibitors (pegaptanib, aflibercept, and ranibizumab) have been initially developed and tested for the treatment of age-related macular degeneration and subsequently for DME. In Phase I, II, and III trials for DME, ranibizumab has been shown to be superior to macular laser photocoagulation and intraocular triamcinolone acetonide injections for improving visual acuity and drying the macula. As a result, ranibizumab is the only anti-VEGF drug that has been approved by the United States Food and Drug Administration for the treatment of DME. Most experts now consider intravitreal anti-VEGF therapy to be standard-of-care for DME involving the fovea.

PMID: 23836955 [PubMed] ID: PMC3699322

Coll Antropol. 2013 Apr;37 Suppl 1:223-6.

Treatment of submacular haemorrhage in patients with neovascular age related macular degeneration.

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Abstract: To evaluate the efficacy of the pneumatic displacement of the submacular haemorrhage combined with the intravitreal injection of the tissue plasminogen activator. We present a retrospective clinical case series of nine eyes of nine patients that were treated with the intravitreal injection of the tissue plasminogen activator and expansile gas for the submacular haemorrhage due to the age related macular degeneration. We evaluated visual acuities and complications. Selected patients were additionally treated with the intravitreal bevacizumab injections after the procedure. Mean postoperative followup was 19

weeks. Four (4/9) eyes (44%) received additional treatment with the intravitreal bevacizumab during the postoperative period. Statistical analysis was performed using the Student's paired t-test. The mean visual acuity was 1.77 logMAR preoperatively and 1.06 logMAR postoperatively. After the surgery, 4 or more Snellen lines were gained in 7/9 eyes (78%). The improvement of the visual acuity postoperatively was statistically significant (p = 0.002). In 2/9 eyes (22%) the visual acuity did not get better after the procedure. We observed no complications during the follow up period. In our case series, pneumatic displacement of the submacular haemorrhage with the use of the intravitreal tissue plasminogen activator (with or without additional bevacizumab treatment in the selected cases) turned out to be an effective and safe method leading to the improvement of the visual acuity in the majority of cases. To maximise the treatment success, prompt referral to the retinal surgeon is imperative.

PMID: 23837248 [PubMed - in process]

BMC Ophthalmol. 2013 Jul 5;13(1):29. doi: 10.1186/1471-2415-13-29.

Choroidal neovascularization in angioid streaks following microincision vitrectomy surgery: a case report.

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BACKGROUND: Patients with angioid streaks are prone to developing subretinal hemorrhage after ocular or head injury due to the brittleness of Bruch's membrane. However, there have been no reports of any angioid streak patients in whom choroidal neovascularization occurred after vitrectomy surgery. We report herein a patient with angioid streaks who developed choroidal neovascularization after vitrectomy surgery for epiretinal membrane.

CASE PRESENTATION: A 76-year-old man presented with distorted vision in his left eye, with a best corrected visual acuity of 1.2 and 0.6 in his right and left eyes, respectively. Fundus examination showed angioid streaks in both eyes and epiretinal membrane only in the left eye. The patient underwent 23-gauge three-port pars plana vitrectomy with removal of the epiretinal membrane combined with cataract surgery. Internal limiting membrane in addition to the epiretinal membrane were successfully peeled and removed, with indocyanine green dye used to visualize the internal limiting membrane. His left best corrected visual acuity improved to 0.8. An elevated lesion with retinal hemorrhage due to probable choroidal neovascularization was found between the fovea and the optic disc in the left eye at 7 weeks after surgery. Since best corrected visual acuity decreased to 0.15 and the hemorrhage expanded, posterior sub-Tenon injection of triamcinolone acetonide was performed. However, no improvement was observed. Even though intravitreal bevacizumab injection was performed a total of five times, his best corrected visual acuity remained at 0.1. Subsequently, we performed a combination treatment of a standard-fluence photodynamic therapy and intravitreal ranibizumab injection, with additional intravitreal ranibizumab injections performed 3 times after this combination treatment. Best corrected visual acuity improved to 0.5 and the size of the choroidal neovascularization markedly regressed at 4 months after the combined treatment.

CONCLUSION: Development of choroidal neovascularization could possibly occur in elderly patients with angioid streaks after vitrectomy surgery. In such cases, a combination of photodynamic therapy and intravitreal ranibizumab injection may be considered for initial treatment of the choroidal neovascularization.

PMID: 23829451 [PubMed - in process] PMCID: PMC3704727

J Ocul Pharmacol Ther. 2013 Jul 5. [Epub ahead of print]

Can Intravitreal Ranibizumab Alter Retrobulbar Circulation in Eyes with Age-Related Macular

Degeneration?

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Abstract Purpose: To determine the effect of a single intravitreal ranibizumab injection on retrobulbar circulation in cases with neovascular age-related macular degeneration (AMD).

Methods: In this prospective and interventional study, 32 patients with neovascular AMD were enrolled. A single intravitreal ranibizumab dose was in only 1 eye per patient. Peak systolic velocity, end-diastolic velocity, resistive index and pulsatility index values in the common carotid artery, ophthalmic artery, central retinal artery, nasal posterior ciliary artery, and temporal posterior ciliary artery in both injected and uninjected healthy fellow eyes were measured using color Doppler ultrasonography at baseline and 1 week and 1 month after the injection of ranibizumab.

Results: All measurements revealed no statistically significant difference among baseline, first week, and first month after injection measurements for all parameters measured in all arteries in both the injected and uninjected healthy fellow eyes.

Conclusion: A single intravitreal injection of ranibizumab does not significantly affect on retrobulbar circulation of either the injected or the uninjected healthy fellow eyes with neovascular AMD.

PMID: 23829173 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2013 Aug;91(5):e414-e415. doi: 10.1111/aos.12112.

Retinal pigment epithelium tears following intravitreal ranibizumab injection for neovascular age-related macular degeneration.

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PMID: 23844861 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Br J Ophthalmol. 2013 Jul 10. doi: 10.1136/bjophthalmol-2013-303219. [Epub ahead of print]

Evaluation of retinal pigment epithelium-Bruch's membrane complex thickness in dry age-related macular degeneration using optical coherence tomography.

Karampelas M, Sim DA, Keane PA, Papastefanou VP, Sadda SR, Tufail A, Dowler J.

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AIM: To compare retinal pigment epithelium-Bruch's membrane (RPE-BM) complex thickness in patients with early and intermediate dry age-related macular degeneration (AMD) and age-matched controls using spectral domain optical coherence tomography (SD-OCT).

METHODS: In this retrospective, cross-sectional study, 25 patients with dry AMD and 25 controls were recruited. SD-OCT scans were manually segmented by two independent investigators. Thickness values

were calculated for the nine Early Treatment Diabetic Retinopathy Study (ETDRS) subfields.

RESULTS: RPE-BM thickness was significantly thicker in the dry AMD group (32.3, 30.6 and 28.4 μm for central, inner and outer subfields, respectively) compared with the normal eyes (22.7, 21.8 and 21.6 μm, respectively). RPE-BM thickness was positively correlated with age in the normal group but not in the AMD group. RPE-BM thickness in the dry AMD group was negatively correlated with visual acuity in the central and inner subfields but not in the outer. We observed good intraobserver and inter-observer reliability for both groups in all ETDRS subfields.

CONCLUSIONS: This study reports novel data concerning RPE-BM segmentation in dry AMD and performs a direct comparison with age-matched normal controls. Our findings confirm the electron and light microscopy derived data and also establish the value of OCT in the quantification of the RPE-BM complex.

PMID: 23843264 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Jul 3. pii: S0002-9394(13)00307-3. doi: 10.1016/j.ajo.2013.04.031. [Epub ahead of print]

Drusen Regression is Associated With Local Changes in Fundus Autofluorescence in Intermediate Age-Related Macular Degeneration.

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PURPOSE: To investigate the association of spontaneous drusen regression in intermediate age-related macular degeneration (AMD) with changes on fundus photography and fundus autofluorescence (FAF) imaging.

DESIGN: Prospective observational case series.

METHODS: Fundus images from 58 eyes (in 58 patients) with intermediate AMD and large drusen were assessed over 2 years for areas of drusen regression that exceeded the area of circle C1 (diameter 125 μm; Age-Related Eye Disease Study grading protocol). Manual segmentation and computer-based image analysis were used to detect and delineate areas of drusen regression. Delineated regions were graded as to their appearance on fundus photographs and FAF images, and changes in FAF signal were graded manually and quantitated using automated image analysis.

RESULTS: Drusen regression was detected in approximately half of study eyes using manual (48%) and computer-assisted (50%) techniques. At year-2, the clinical appearance of areas of drusen regression on fundus photography was mostly unremarkable, with a majority of eyes (71%) demonstrating no detectable clinical abnormalities, and the remainder (29%) showing minor pigmentary changes. However, drusen regression areas were associated with local changes in FAF that were significantly more prominent than changes on fundus photography. A majority of eyes (64%-66%) demonstrated a predominant decrease in overall FAF signal, while 14%-21% of eyes demonstrated a predominant increase in overall FAF signal.

CONCLUSIONS: FAF imaging demonstrated that drusen regression in intermediate AMD was often accompanied by changes in local autofluorescence signal. Drusen regression may be associated with concurrent structural and physiologic changes in the outer retina.

PMID: 23830564 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Jul 4. pii: S0161-6420(13)00485-5. doi: 10.1016/j.ophtha.2013.05.029. [Epub ahead of print]

Optical Coherence Tomography-Based Observation of the Natural History of Drusenoid Lesion in Eyes with Dry Age-Related Macular Degeneration.

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PURPOSE: To use spectral domain optical coherence tomography (SD-OCT) to investigate risk factors predictive for the development of atrophy of drusenoid lesions (DLs) (drusen and drusenoid pigment epithelium detachment) in eyes with non-neovascular age-related macular degeneration (NNVAMD).

DESIGN: Cohort study.

PARTICIPANTS: Forty-one eyes from 29 patients with NNVAMD.

METHODS: Patients with NNVAMD who underwent registered SD-OCT imaging over a minimum period of 6 months were reviewed. Drusenoid lesions that were accompanied by new atrophy onset at 6 months or last follow-up (FUL) were further analyzed. Detailed lesion change was described throughout the study period. Odds ratios (ORs) and risk for new local atrophy onset were calculated.

MAIN OUTCOME MEASURES: Drusenoid lesion features and longitudinal changes in features, including maximum lesion height, lesion diameter, lesion internal reflectivity, and presence and extent of overlying intraretinal hyperreflective foci (HRF). Subfoveal choroidal thickness (SFCT) and choroidal thickness (CT) were measured below each lesion.

RESULTS: A total of 543 individual DLs were identified at baseline, and 28 lesions developed during follow-up. The mean follow-up time was 21.3±8.6 months (range, 6-44 months). Some 3.2% of DLs (18/571) progressed to atrophy within 18.3±9.5 months (range, 5-28 months) of the initial visit. Drusenoid lesions with heterogeneous internal reflectivity were significantly associated with new atrophy onset at 6 months (OR, 5.614; 95% confidence interval [CI], 1.277-24.673) and new atrophy onset at FUL (OR, 7.005; 95% CI, 2.300-21.337). Lesions with the presence of HRF were significant predictors of new atrophy onset at 6 months (OR, 30.161; 95% CI, 4.766-190.860) and FUL (OR, 11.211; 95% CI, 2.513-50.019). Lesions with a baseline maximum height >80 μm or CT ≤135 μm showed a positive association with the new atrophy onset at FUL (OR, 7.886; 95% CI, 2.105-29.538 and OR, 3.796; 95% CI, 1.154-12.481, respectively).

CONCLUSIONS: The presence of HRF overlying DLs, a heterogeneous internal reflectivity of these lesions, was found consistently to be predictive of local atrophy onset in the ensuing months. These findings provide further insight into the natural history of anatomic change occurring in patients with NNVAMD.

PMID: 23830761 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Jul 11. pii: iovs.13-12026v1. doi: 10.1167/iovs.13-12026. [Epub ahead of print]

Dual tasking and balance in those with central and peripheral vision losses.

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PURPOSE: To investigate the effects of a secondary task on standing balance in patients with glaucoma or

age-related macular degeneration (AMD) compared with age-similar control subjects.

METHODS: Twelve AMD, 12 glaucoma and 12 control participants underwent posturography under 2 standing conditions (eyes open on a firm or foam rubber surface) and 2 tasks: quiet standing and undertaking a mental arithmetic task. Centre of foot pressure average displacement (root mean square, RMS; mm) was calculated.

RESULTS: The mean [standard deviation] age of the participants in each group was: controls 66.2 [6.4] years, glaucoma 69.2 [4.3] years, AMD 72.2 [5.3] years. There were significant differences in RMS between controls and AMD patients when undertaking the mental arithmetic task standing on the firm surface (mean difference [standard error;SE]: 2.8 [0.8] mm, p = 0.005). There were significant differences between controls and AMD patients when undertaking the mental arithmetic task on the foam surface, with the difference between controls and glaucoma patients approaching significance (mean difference [SE]: control vs AMD = 3.1 [0.9] mm, p = 0.005; control vs glaucoma = 2.2 [0.9] mm, p = 0.06).

CONCLUSION: Postural instability increases with the addition of a secondary task in older persons, which may put them at greater risk of falls. Patients with central losses exhibit greater instability with the addition of a secondary task, particularly during somatosensory pertubations. The negative effects of secondary tasks on balance control in those with peripheral visual losses become more apparent under somatosensory perturbations.

PMID: 23847310 [PubMed - as supplied by publisher]

Coll Antropol. 2013 Apr;37 Suppl 1:153-6.

Binocular refraction in patients with age-related macular degeneration.

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Abstract: We've been finding possible association of central vision damage with binocular vision disorders in our clients suffering from age-related macular degeneration (ARMD), but whose visual acuity still allowed us to examine their binocular vision. Our findings show that there is a significant number of patients with heterophoria in horizontal, as well as vertical direction. The clients rate the vision with prismatic correction as more comfortable, clearer and long-term tolerable. Getting used to prismatic correction was spontaneous and non-problematic. Based on these results we expect to find possibly the most effective rehabilitation of vision in patients suffering from ARMD.

PMID: 23837236 [PubMed - in process]

Coll Antropol. 2013 Apr;37 Suppl 1:111-5.

Visual field.

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Abstract: This article is dedicated to main information about visual field, monocular and binocular ranges of visual field including their defects. Visual field loss may occur to disease of the eye, optic nerve or brain. Typical changes are present at glaucoma and macular degeneration. Visual pathway is also mentioned. The basic medical examinations of visual fields are Amsler grid, kinetic and static perimetry and the other. Newer method is microperimetry which detects the changes directly on the retina. The aim of this poster is

importance and determination of visual field as a preventive ophthalmologic and optometric examination.

PMID: 23837228 [PubMed - in process]

Pathogenesis

PLoS One. 2013 Jun 28;8(6):e67263. doi: 10.1371/journal.pone.0067263. Print 2013.

A2E Induces IL-1ß Production in Retinal Pigment Epithelial Cells via the NLRP3 Inflammasome.

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AIMS:With ageing extracellular material is deposited in Bruch's membrane, as drusen. Lipofuscin is deposited in retinal pigment epithelial cells. Both of these changes are associated with age related macular degeneration, a disease now believed to involve chronic inflammation at the retinal-choroidal interface. We hypothesise that these molecules may act as danger signals, causing the production of inflammatory chemokines and cytokines by the retinal pigment epithelium, via activation of pattern recognition receptors.

METHODS:ARPE-19 cells were stimulated in vitro with the following reported components of drusen: amyloid-ß (1-42), Carboxyethylpyrrole (CEP) modified proteins (CEP-HSA), Nε-(Carboxymethyl)lysine (CML) modified proteins and aggregated vitronectin. The cells were also stimulated with the major fluorophore of lipofuscin: N-retinylidene-N-retinylethanolamine (A2E). Inflammatory chemokine and cytokine production was assessed using Multiplex assays and ELISA. The mechanistic evaluation of the NLRP3 inflammasome pathway was assessed in a stepwise fashion.

RESULTS:Of all the molecules tested only A2E induced inflammatory chemokine and cytokine production. 25 µM A2E induced the production of significantly increased levels of the chemokines IL-8, MCP-1, MCG and MIP-1α, the cytokines IL-1ß, IL-2, IL-6, and TNF-α, and the protein VEGF-A. The release of IL-1ß was studied further, and was determined to be due to NLRP3 inflammasome activation. The pathway of activation involved endocytosis of A2E, and the three inflammasome components NLRP3, ASC and activated caspase-1. Immunohistochemical staining of ABCA4 knockout mice, which show progressive accumulation of A2E levels with age, showed increased amounts of IL-1ß proximal to the retinal pigment epithelium.

CONCLUSIONS:A2E has the ability to stimulate inflammatory chemokine and cytokine production by RPE cells. The pattern recognition receptor NLRP3 is involved in this process. This provides further evidence for the link between A2E, inflammation, and the pathogenesis of AMD. It also supports the recent discovery of NLRP3 inflammasome activation in AMD.

PMID: 23840644 [PubMed - in process] PMCID: PMC3696103

Mol Immunol. 2013 Jul 2. pii: S0161-5890(13)00418-5. doi: 10.1016/j.molimm.2013.06.001. [Epub ahead of print]

Complement factor H related proteins (CFHRs).

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Abstract: Factor H related proteins comprise a group of five plasma proteins: CFHR1, CFHR2, CFHR3, CFHR4 and CFHR5, and each member of this group binds to the central complement component C3b.

Mutations, genetic deletions, duplications or rearrangements in the individual CFHR genes are associated with a number of diseases including atypical hemolytic uremic syndrome (aHUS), C3 glomerulopathies (C3 glomerulonephritis (C3GN), dense deposit disease (DDD) and CFHR5 nephropathy), IgA nephropathy, age related macular degeneration (AMD) and systemic lupus erythematosus (SLE). Although complement regulatory functions were attributed to most of the members of the CFHR protein family, the precise role of each CFHR protein in complement activation and the exact contribution to disease pathology is still unclear. Recent publications show that CFHR proteins form homo- as well as heterodimers. Genetic abnormalities within the CFHR gene locus can result in hybrid proteins with affected dimerization or recognition domains which cause defective functions. Here we summarize the recent data about CFHR genes and proteins in order to better understand the role of CFHR proteins in complement activation and in complement associated diseases.

PMID: 23830046 [PubMed - as supplied by publisher]

J Ophthalmol. 2013;2013:925267. doi: 10.1155/2013/925267. Epub 2013 Jun 4.

Vascular adhesion protein 1 in the eye.

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Abstract: Semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 (SSAO/VAP-1), a dual-function molecule with adhesive and enzymatic properties, is expressed on the surface of vascular endothelial cells of mammals. It also exists as a soluble form (sVAP-1), which is implicated in oxidative stress via its enzymatic activity and can be a prognostic biomarker. Recent evidence suggests that VAP-1 is an important therapeutic target for several inflammation-related ocular diseases, such as uveitis, age-related macular degeneration (AMD), and diabetic retinopathy (DR), by involving in the recruitment of leukocytes at sites of inflammation. Furthermore, VAP-1 plays an important role in the pathogenesis of conjunctival inflammatory diseases such as pyogenic granulomas and the progression of conjunctival lymphoma. VAP-1 may be an alternative therapeutic target in ocular diseases. The in vivo imaging of inflammation using VAP-1 as a target molecule is a novel approach with a potential for early detection and characterization of inflammatory diseases. This paper reviews the critical roles of VAP-1 in ophthalmological diseases which may provide a novel research direction or a potent therapeutic strategy.

PMID: 23840939 [PubMed] PMCID: PMC3687510

Curr Eye Res. 2013 Jul 10. [Epub ahead of print]

Differential Effects of the Estrogen Receptor Agonist Estradiol on Toxicity Induced by Enzymatically-Derived or Autoxidation-Derived Oxysterols in Human ARPE-19 Cells.

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Abstract Purpose/aim of the study: Disturbances in cholesterol metabolism and increased levels of cholesterol oxidation products (oxysterols) in retina may contribute to age-related macular degeneration (AMD). The role of oxysterols or of their target receptors liver X receptors (LXRs) and estrogen receptors (ERs) in the pathogenesis of MD is ill-known. The purpose of this study is to determine the extent to which the oxysterols 27-hydroxycholesterol (27-OHC), 25-hydroxycholesterol (25-OHC) and 7-ketocholesterol (7-KC) affect the transcriptional activity of LXR and ER.

Materials and methods: ARPE-19 cells, untreated or incubated with 27-OHC, 25-OHC or 7-KC for 24 h were harvested. We used Western blot analyses for detecting ERs and LXRs expression, dual luciferase assays for measuring LXRs and ERs transcriptional activity, cytotox-ONE homogeneous membrane integrity assay for measuring cytotoxicity, JC-1 method for measuring mitochondrial membrane potential changes and ELISA for measuring cytokine levels.

Results: Both LXRs and ERs are expressed and are transcriptionally active in ARPE-19 cells. 27-OHC, 25-OHC and 7-KC inhibited ER-mediated transcriptional activity, whereas 27-OHC and 25-OHC increased LXR-mediated transcription. E2 reduced 25-OHC and 27-OHC-induced cytotoxicity, mitochondrial permeability potential decline, and cytokine secretion. The LXR agonist GW3965 or the LXR antagonist 5α-6α-epoxycholesterol-3-sulfate (ECHS) did not offer protection against either 27-OHC and 25-OHC or 7-KC.

Conclusions: Increased levels of oxysterols can decrease ER and increase LXR signaling. ER agonists can offer protection against cytotoxic effects of 27-OHC and 25-OHC, two oxysterols derived by enzymatic reactions. Although they exert similar toxicity, the cellular mechanisms involved in the toxic effects of oxysterols whether derived by enzymatic or autoxidation reactions appear to be different.

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Antioxidant Activity of Galantamine and some of its Derivatives.

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Abstract: Oxidative stress is implicated in the pathogenesis of different human diseases: Alzheimer, Parkinson, Huntington, amyotrophic lateral sclerosis (Lou Gehrig's disease), Down's syndrome, atherosclerosis, vascular disease, cancer, diabetes mellitus type 1 and type 2, age-related macular degeneration, psoriatic arthritis. The aim of the current study is to summarize the scientific evidences for the antioxidant and neuroprotective activity of Galantamine and some of its derivatives. Galantamine is a scavenger of reactive oxygen species and causes neuroprotective effect by lowering the oxidative neuronal damage, through the following pathways: 1) prevention of the activation of P2X7 receptors; 2) protection of mitochondrial membrane potential; 3) prevention of the membrane fluidity disturbances. Another mechanism is the decrease of the overproduction of reactive oxygen species, as a result of the increase of acetylcholine level due to: 1) acethylcholinesterase inhibition; 2) allosteric potentiation of α7-subtype of nicotinic acetylcholine receptors. A close relationship between acethylcholinesterase inhibition and reduced oxidative injury is observed. Through allosteric potentiation of the α7-subtype of nicotinic acetylcholine receptors, the drug leads to induction of phosphorylation of serine-threonine protein kinase, stimulates phosphoinositide 3-kinase and elevates the expression of protective protein Bcl-2. Through activation of these important neuroprotective cascades, Galantamine exerts neuroprotection against a variety of cytotoxic agents (ß-amyloid peptide, glutamate, hydrogen peroxide, and oxygen and glucose deprivation). A new trend in the therapy of Alzheimer's disease will be the investigation and application of compounds such as Galantamine derivatives, which possess acethylcholinesterase and γ-secretase inhibitory activity and antioxidant properties.

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Aging (Albany NY). 2013 Jun 17. [Epub ahead of print]

Deficiency in the metabolite receptor SUCNR1 (GPR91) leads to outer retinal lesions.

Favret S, Binet F, Lapalme E, Leboeuf D, Carbadillo J, Rubic T, Picard E, Mawambo G, Tetreault N, Joyal JS, Chemtob S, Sennlaub F, Sangiovanni JP, Guimond M, Sapieha P.

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Abstract: Age-related macular degeneration (AMD) is a prominent cause of blindness in the Western world. To date, its molecular pathogenesis as well as the sequence of events leading to retinal degeneration remain largely ill-defined. While the invasion of choroidal neovessels in the retina is the primary mechanism that precipitates loss of sight, an earlier dry form precedes it. Here we provide the first evidence for the protective role of the Retinal Pigment Epithelium (RPE)-resident metabolite receptor, succinate receptor 1 (SUCNR1; G-Protein coupled Receptor-91 (GPR91), in preventing dry AMD-like lesions of the outer retina. Genetic analysis of 925 patients with geographic atrophy and 1199 AMD-free peers revealed an increased risk of developing geographic atrophy associated with intronic variants in theSUCNR1 gene. In mice, outer retinal expression of SUCNR1 is observed in the RPE as well as microglial cells and decreases progressively with age. Accordingly, Sucnr1-/- mice show signs of premature sub-retinal dystrophy with accumulation of oxidized-LDL, abnormal thickening of Bruch's membrane and a buildup of subretinal microglia. The accumulation of microglia in Sucnr1-deficient mice is likely triggered by the inefficient clearance of oxidized lipids by the RPE as bone marrow transfer of wild-type microglia into Sucnr1-/- mice did not salvage the patho-phenotype and systemic lipolysis was equivalent between wild-type and control mice. Our findings suggest that deficiency in SUCNR1 is a possible contributing factor to the pathogenesis of dry AMD and thus broaden our understanding of this clinically unmet need.

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Patients with early age-related macular degeneration exhibit signs of macro- and micro-vascular disease and abnormal blood glutathione levels.

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BACKGROUND: This pilot study aimed to investigate systemic and retinal vascular function and their relationship to circulatory markers of cardiovascular risk in early age-related macular degeneration (AMD) patients without any already diagnosed systemic vascular pathologies.

METHODS: Fourteen patients diagnosed with early AMD and 14 age- and gender-matched healthy controls underwent blood pressure, carotid intima-media thickness (C-IMT) and peripheral arterial stiffness measurements. Retinal vascular reactivity was assessed by means of dynamic retinal vessel analysis (DVA) using a modified protocol. Blood analyses were conducted for glutathione levels and plasma levels of total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG).

RESULTS: The AMD patients showed significantly greater C-IMT ($p = 0.029$) and augmentation index (AIx) ($p = 0.042$) than the age-matched controls. In addition, they demonstrated a shallower retinal arterial dilation slope (Slope AD) ($p = 0.005$) and a longer retinal venous reaction time (RT) to flickering light ($p = 0.026$). Blood analyses also revealed that AMD patients exhibited higher oxidized glutathione (GSSG) ($p = 0.024$), lower redox index ($p = 0.043$) and higher LDL-C ($p = 0.033$) levels than the controls. Venous RT parameter correlated positively with blood GSSG levels ($r = 0.58$, $p = 0.038$) in AMD subjects, but not in the controls ($p > 0.05$).

CONCLUSIONS: Patients diagnosed with early AMD exhibit signs of systemic and retinal vascular alterations that correlated with known risk markers for future cardiovascular morbidity.

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Epidemiology

Br J Ophthalmol. 2013 Jul 5. [Epub ahead of print]

Examining the association between age-related macular degeneration and motor vehicle collision involvement: a retrospective cohort study.

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BACKGROUND: Little is known about motor vehicle collision (MVC) risk in older drivers with age-related macular degeneration (AMD). The purpose of this study is to examine associations between MVC involvement and AMD presence and severity.

METHODS: In a retrospective cohort study pooling the samples from four previous studies, we examined associations between MVC rate and older drivers with early, intermediate or advanced AMD as compared with those in normal eye health. MVC data were based on accident reports obtained from the state agency that compiles this information.

RESULTS: MVC rate was highest among those in normal eye health and progressively declined among those with early and intermediate disease, and then increased for those with advanced AMD. However, only for drivers with intermediate AMD was the MVC rate significantly different (lower) as compared with those in normal eye health, regardless of whether the rate was defined in terms of person-years (RR 0.34, 95% CI 0.13 to 0.89) or person-miles (RR 0.35, 95% CI 0.13 to 0.91) of driving.

CONCLUSIONS: These results suggest that older drivers with intermediate AMD have a reduced risk of collision involvement. Further research should investigate whether self-regulatory driving practices by these drivers (avoiding challenging driving situations) underlies this reduced risk.

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Clin Ophthalmol. 2013;7:1325-32. doi: 10.2147/OPTH.S45248. Epub 2013 Jul 1.

Assessing quality of life in the treatment of patients with age-related macular degeneration: clinical research findings and recommendations for clinical practice.

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BACKGROUND: The importance of incorporating quality-of-life (QoL) assessments into medical practice is growing as health care practice shifts from a "disease-based" to a "patient-centered" model. The prevalence of age-related macular degeneration (AMD) is increasing in today's aging population. The purpose of this paper is: (1) to discuss, by reviewing the current literature, the impact of AMD on patients' QoL and the utility of QoL assessments in evaluating the impact of AMD and its treatment; and (2) to make a recommendation for incorporating QoL into clinical practice.

METHODS: We conducted a PubMed and an open Internet search to identify publications on the measurement of QoL in AMD, as well as the impact of AMD and the effect of treatment on QoL. A total of 28 articles were selected.

RESULTS: AMD has been found to cause a severity-dependent decrement in QoL that is comparable to systemic diseases such as cancer, ischemic heart disease, and stroke. QoL impairment manifests as greater social dependence, difficulty with daily living, higher rates of clinical depression, increased risk of

falls, premature admission to nursing homes, and suicide. The National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) is the most widely used eye disease-specific QoL instrument in AMD. It has been shown to correlate significantly with visual acuity (VA). QoL reflects aspects of AMD including psychological well-being, functional capacity, and the ability to perform patients' valued activities, which are not captured by a single, numerical VA score.

CONCLUSION: The literature shows that the adverse impact of AMD on QoL is comparable to serious systemic disease. Eye disease-specific instruments for measuring QoL, such as the NEI VFQ-25, have shown a significant correlation of QoL decrement with measures of disease severity, as well as significant QoL improvement with treatment. The NEI VFQ-25 and other validated instruments provide a wide-ranging assessment of vision-related functioning that is important to patients and complementary to VA measurement. We strongly recommend the incorporation of QoL assessment into routine clinical practice.

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Prevalence of myelinated retinal nerve fibres in adult Indians: the Central India Eye and Medical Study.

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Purpose: To determine the prevalence of myelinated retinal nerve fibers in the adult Indian population.

Methods: The Central India Eye and Medical Study performed in rural Central India included 4711 participants aged 30+ years. The participants underwent a detailed ophthalmic and medical examination.

Results: Readable fundus photographs were available for 8645 eyes of 4485 (95.2%) subjects. Myelinated retinal nerve fibers were detected in 52 eyes (46 subjects) with a prevalence rate of 0.58 ± 0.08 per 100 eyes [95% confidence interval (CI): 0.42, 0.74] and 1.03 ± 0.15 per 100 subjects (95%CI: 0.73, 1.32). Prevalence of myelinated retinal nerve fibers was significantly associated hyperopic refractive error (p = 0.008; OR: 1.31; 95%CI: 1.07, 1.59). It was not significantly associated with age (p = 0.11), best corrected visual acuity (logMAR; p = 0.33), intraocular pressure (p = 0.09), amount of nuclear cataract (p = 0.93), optic disc area (p = 0.60), presence of glaucomatous optic nerve atrophy (p = 0.62), and early age-related macular degeneration (p = 0.53).

Conclusions: Myelinated retinal nerve fibers are present in about 10 out of 1000 adult Indians in rural Central India, with a higher prevalence in hyperopic eyes. Prevalence of myelinated retinal nerve fibers was not associated with age, visual acuity, glaucoma and macular degeneration.

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Genetics

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Interaction of complement factor h and fibulin3 in age-related macular degeneration.

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Abstract: Age-related macular degeneration (AMD) is a major cause of vision loss. It is associated with development of characteristic plaque-like deposits (soft drusen) in Bruch's membrane basal to the retinal pigment epithelium (RPE). A sequence variant (Y402H) in short consensus repeat domain 7 (SCR7) of complement factor H (CFH) is associated with risk for "dry" AMD. We asked whether the eye-targeting of this disease might be related to specific interactions of CFH SCR7 with proteins expressed in the aging human RPE/choroid that could contribute to protein deposition in drusen. Yeast 2-hybrid (Y2H) screens of a retinal pigment epithelium/choroid library derived from aged donors using CFH SCR7 baits detected an interaction with EFEMP1/Fibulin 3 (Fib3), which is the locus for an inherited macular degeneration and also accumulates basal to macular RPE in AMD. The CFH/Fib3 interaction was validated by co-immunoprecipitation of native proteins. Quantitative Y2H and ELISA assays with different recombinant protein constructs both demonstrated higher affinity for Fib3 for the disease-related CFH 402H variant. Immuno-labeling revealed colocalization of CFH and Fib3 in globular deposits within cholesterol-rich domains in soft drusen in two AMD donors homozygous for CFH 402H (H/H). This pattern of labeling was quite distinct from those seen in examples of eyes with Y/Y and H/Y genotypes. The CFH 402H/Fib3 interaction could contribute to the development of pathological aggregates in soft drusen in some patients and as such might provide a target for therapeutic intervention in some forms of AMD.

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Haplotypes in IL-8 Gene Are Associated to Age-Related Macular Degeneration: A Case-Control Study.

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BACKGROUND: Age-related macular degeneration (AMD) is the main cause of blindness in the developed world. The etiology of AMD is multifactorial due to the interaction between genetic and environmental factors. IL-8 has a role in inflammation and angiogenesis; we report the genetic characterization of IL-8 allele architecture and evaluate the role of SNPs or haplotypes in the susceptibility to wet AMD, case-control study.

METHODS: Case-control study including 721 AMD patients and 660 controls becoming from Italian population. Genotyping was carried out by Real Time-PCR. Differences in the frequencies were estimated by the chi-square test. Direct sequencing was carried out by capillary electrophoresis trough ABI3130xl.

RESULTS: rs2227306 showed a p-value of 4.15*10-5 and an Odds Ratio (OR) for T allele of 1.39 [1.19-1.62]. After these positive results, we sequenced the entire IL-8 regulatory and coding regions of 60 patients and 30 controls stratified for their genotype at rs2227306. We defined two different haplotypes involving rs4073 (A/T), rs2227306 (C/T), rs2227346 (C/T) and rs1126647 (A/T): A-T-T-T (p-value: 2.08*10-9; OR: 1.68 [1.43-1.97]) and T-C-C-A (p-value: 7.07*10-11; OR: 0.60 [0.51-0.70]). To further investigate a potential functional role of associated haplotypes, we performed an expression study on RNA extracted from whole blood of 75 donors to verify a possible direct correlation between haplotype and gene expression, failing to reveal significant differences.

CONCLUSIONS: These results suggest a possible secondary role of IL-8 gene in the development of the disease. This paper outlines the importance of association between inflammation and AMD. Moreover IL-8 is a new susceptibility genomic biomarker of AMD.

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Evaluating the Association between Pathological Myopia and SNPs in RASGRF1. ACTC1 and GJD2 Genes at Chromosome 15q14 and 15q25 in a Chinese Population.

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Abstract Background: This study investigated the association of the 27 SNPs located in RASGRF1. GJD2, and ACTC1 genes with pathological myopia in a Chinese Han population.

Methods: Myopia patients were stratified according to whether they did (n = 274) or did not (n = 131) have myopic macular degeneration (MMD). The SNPbrowser software was used to identify specific SNPs for analysis and minimal allele frequency of >20%, and a pairwise r2 < 0.85 were genotyped using MALDI-TOF mass spectrometry.

Results: Before controlling for false discovery rate, the frequency of the rs1867315 C/C genotype compared with healthy controls was lower in the myopia group (p = 0.006) and in myopia patients without macular degeneration (p = 0.019). The frequency of the rs670957A/A genotype was also lower in patients without MMD compared with controls (p = 0.045). For rs2070664, the frequency of the A allele was higher in the patients with MMD compared to those without MMD (p = 0.032). After controlling for a false discovery rate of 5%, there was no significant difference in genotype and allele frequencies between these groups.

Conclusion: In this study, there was no association of the analyzed SNPs located in RASGRF1. GJD2, and ACTC1 with pathological myopia, suggesting that SNPs included in our study have no or a limited role in causing pathologic myopia in this Chinese Han population.

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GENETIC FACTORS ASSOCIATED WITH RESPONSE TO INTRAVITREAL RANIBIZUMAB IN KOREAN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To investigate the association between genetic risk variants for age-related macular degeneration (AMD) and response to intravitreal ranibizumab in Korean patients with neovascular AMD.

METHODS: This prospective study included 273 treatment-naive patients (273 eyes) who underwent 5 monthly injections (Months 0, 1, 2, 3, and 4) of intravitreal ranibizumab for neovascular AMD. Patients were genotyped for 23 single-nucleotide polymorphisms within 12 AMD-relevant genes. For each polymorphism, genotypic association with good response at Month 5, predetermined as visual improvement of ≥8 Early Treatment Diabetic Retinopathy Study letters from baseline, was investigated with logistic regression analysis adjusted for age, gender, smoking, baseline Early Treatment Diabetic Retinopathy Study letter, central retinal thickness, lesion area, and type of choroidal neovascularization.

RESULTS: At Month 5, visual acuity improved by 9.1 ± 17.6 letters from baseline, and 136 patients (49.8%) were classified as good responders. In logistic regression, no tested polymorphism showed statistically significant association with favorable visual outcome at Month 5. When unadjusted for multiple tests, AA

genotype for VEGF rs699947 had an increased chance of good response compared with other genotypes (odds ratio, 3.61; 95% confidence interval, 1.42-9.18; P = 0.0071).

CONCLUSION: In this Korean neovascular AMD cohort, there was no statistically significant effect of genotype on early visual outcome after ranibizumab treatment.

PMID: 23842101 [PubMed - as supplied by publisher]

Diet

Zhongguo Zhong Xi Yi Jie He Za Zhi. 2013 Apr;33(4):531-7.

[Prevention and treatment of age-related macular degeneration by extract of Fructus lycii and its constituents lutein/zeaxanthin: an in vive and in vitro experimental research].

[Article in Chinese]

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OBJECTIVE: To investigate the in vivo inhibition of extract of Fructus lycii (FL) on the expressions of cathepsin B (Cat B) and cystatin C (Cys C) in high-fat diet and hydroquinone (HQ) induced model mice with age-related macular degeneration (AMD), and to explore the in vitro effects of lutein and zeaxanthin on hydrogen peroxide (H2O2,) induced expressions of matrix metalloproteinase 2 (MMP-2) and tissue inhibitor of metalloproteinase 2 (TIMP-2) on ARPE-19 cells.

METHODS: Fifty female 8-month-old C57BL/6 mice were recruited in this research. Ten mice fed with regular diet was taken as the age control group. The rest 40 mice were fed with high fat diet for 6 months, followed by adding HQ (0. 8%) in the drinking water for 3 consecutive months. Then the modeled mice were randomly divided into the model control group (n =10), the high (at the daily dose of 3.75 g/kg), middle (at the daily dose of 2.50 g/kg), and low dose (at the daily dose of 1.25 g/kg) FL groups, 10 in each group. The extract of FL at each dose was respectively administered to mice by gastrogavage for 3 successive months. By the end of the experiment, the mice were killed and their eyeballs were removed. The protein expressions of Cat B and Cys C were observed by immunohistochemical assay. The mRNA and protein expressions of Cat B and Cys C were detected by real-time PCR and Western blot respectively. The drug concentrations of H2O2, lutein, and zeaxanthin were screened and detected using the activity of cell proliferation. The protein expressions of MMP-2 and TIMP-2 were detected using Western blot.

RESULTS: Compared with the age control group, the mRNA and protein expressions of Cat B and Cys C were significantly higher in the in vivo model control group (P <0.05, P <0.01). The mRNA expressions of Cat B and Cys C were weaker in the middle and high dose FL groups than in the model control group (P <0. 05, P <0. 01). In in vitro cells, lutein and zeaxanthin could down-regulate the protein expressions of MMP-2 and TIMP-2 in H202 induced ARPE-19 cells (P <0. 05, P <0. 01).

CONCLUSIONS: Extract of FL could down-regulate the high protein expressions of Cat B and Cys C in high-fat diet and HQ induced model mice. Lutein and zeaxanthin could down-regulate the protein expressions of MMP-2 and TIMP-2 in H202 induced ARPE-19 cells.

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Botanical compounds: effects on major eye diseases.

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Abstract: Botanical compounds have been widely used throughout history as cures for various diseases and ailments. Many of these compounds exhibit strong antioxidative, anti-inflammatory, and antiapoptotic properties. These are also common damaging mechanisms apparent in several ocular diseases, including age-related macular degeneration (AMD), glaucoma, diabetic retinopathy, cataract, and retinitis pigmentosa. In recent years, there have been many epidemiological and clinical studies that have demonstrated the beneficial effects of plant-derived compounds, such as curcumin, lutein and zeaxanthin, danshen, ginseng, and many more, on these ocular pathologies. Studies in cell cultures and animal models showed promising results for their uses in eye diseases. While there are many apparent significant correlations, further investigation is needed to uncover the mechanistic pathways of these botanical compounds in order to reach widespread pharmaceutical use and provide noninvasive alternatives for prevention and treatments of the major eye diseases.

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