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MD Research News

Issue 226

Wednesday 8 April, 2015

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Drug treatment

J Diabetes Complications. 2015 Mar 20. [Epub ahead of print]

Changes in vision related quality of life in patients with diabetic macular edema: Ranibizumab or laser treatment?

Turkoglu EB, Celık E, Aksoy N, Bursalı O, Ucak T, Alagoz G.

PURPOSE: To compare the changes in vision related quality of life (VR-QoL) in patients with diabetic macular edema (DME) undergoing intravitreal ranibizumab (IVR) injection or focal/grid laser.

MATERIAL AND METHODS: In this prospective study, 70 patients with clinically significant macular edema (CSME) were randomized to undergo IVR injection (n=35) and focal/grid laser (n=35). If necessary, the laser or ranibizumab injections were repeated. Distance and near visual acuities, central retinal thickness (CRT) and The 25-item Visual Function Questionnaire (VFQ-25) were used to measure the effectiveness of treatments and VR-QoL before and after 6 months following IVR or laser treatment.

RESULTS: The demographic and clinical findings before the treatments were similar in both main groups. The improvements in distance and near visual acuities were higher in IVR group than the laser group ($p<0.01$). The reduction in CRT in IVR group was higher than that in laser treatment group ($p<0.01$). In both groups, the VFQ-25 composite score tended to improve from baseline to 6 months. And at 6th month, the changes in composite score were significantly higher in IVR group than in laser group ($p<0.05$). The improvements in overall composite scores were 6.3 points for the IVR group compared with 3.0 points in the laser group. Patients treated with IVR and laser had large improvements in composite scores, general vision, near and distance visual acuities in VFQ-25 at 6 months, in comparison with baseline scores, and also mental health subscale in IVR group.

CONCLUSION: Our study revealed that IVR improved not only visual acuity or CRT, but also vision related quality of life more than laser treatment in DME. And these patient-reported outcomes may play an important role in the treatment choice in DME for clinicians.

PMID: 25817172 [PubMed - as supplied by publisher]

J Ophthalmol. 2015;2015:867479. doi: 10.1155/2015/867479. Epub 2015 Mar 4.

Prognostic factors of early morphological response to treatment with ranibizumab in patients with wet age-related macular degeneration.

Chrapek O, Jarkovský J, Šín M, Studnička J, Kolář P, Jirková B, Dušek L, Pitrová Š, Řehák J.

Aim: To assess the significance of age, gender, baseline best corrected visual acuity, baseline macula thickness, and type and size of choroidal neovascularization in early morphological therapeutic response to ranibizumab treatment in patients with the wet form of age-related macular degeneration.

Methods: From 09/2008 to 06/2013 we evaluated 1153 newly diagnosed, treatment-naïve patients treated with ranibizumab. Based on the morphological findings in the macula following the initial 3 injections of ranibizumab, the patients were divided into two groups based on active and inactive choroidal neovascularization.

Results: After the initial 3 injections of ranibizumab, we examined the sample of 841 eyes with active CNV and 312 eyes with inactive CNV. In the inactive group, we found a statistically higher proportion of occult CNV ($P < 0.001$) and lower incidence of CNV greater than 5DA ($P < 0.001$) compared with the active group. We found no statistically significant difference in age, gender, baseline best corrected visual acuity, or baseline macula thickness between the inactive and active groups.

Conclusion: Occult CNV and CNV smaller than 5DA are optimistic factors for a better morphological therapeutic response at the beginning of ranibizumab treatment.

PMID: 25821593 [PubMed] PMCID: PMC4364022

Ophthalmologica. 2015 Mar 26. [Epub ahead of print]

Prospective, Randomized Intervention Study Comparing Retinal Pigment Epithelium-Choroid Graft Surgery and Anti-VEGF Therapy in Patients with Exudative Age-Related Macular Degeneration.

van Zeeburg EJ, Cereda MG, Amarakoon S, van Meurs JC.

PURPOSE: To investigate whether patients with exudative age-related macular degeneration and a submacular hemorrhage, retinal pigment epithelium (RPE) tear or nonresponders to anti-vascular endothelial growth factor (VEGF) benefit more from a free RPE-choroid graft transplantation surgery than from (continuation of) anti-VEGF treatment.

PROCEDURES: A total of 20 patients were included in this prospective, international, multicenter, randomized intervention study.

RESULTS: The change in the mean number of Early Treatment of Diabetic Retinopathy Study (ETDRS) letters in the graft group 1 year postoperatively was -15 (range -54 to +26), whilst 2 patients experienced a gain of >10 letters. The median preoperative visual acuity (VA) was 0.75 logMAR (range 0.46-2.8), and the mean postoperative VA was 1.48 logMAR (range 0.14-2.8). The change in the mean number of ETDRS letters in the anti-VEGF group was -8 (range -26 to +6); no patients experienced a >10 letter gain. The median preoperative VA was 1.36 logMAR (range 0.58-1.6), and the median postoperative VA was 1.42 logMAR (range 0.44-1.66).

CONCLUSIONS: The included patient group is far too small to draw conclusions. However, both gain and loss of VA may be experienced by patients undergoing either treatment method; more gain might be possible for patients with a graft in the absence of complications.

PMID: 25832909 [PubMed - as supplied by publisher]

Cell Physiol Biochem. 2015;35(5):1787-96. Epub 2015 Mar 26.

Inhibition of Ocular Neovascularization by Co-Inhibition of VEGF-A and PLGF.

Huo X, Li Y, Jiang Y, Sun X, Gu L, Guo W, Sun D.

BACKGROUND/AIMS: Age-related macular degeneration (AMD) appears to be a disease with increasing incidence in Western countries and may develop into acquired blindness. Choroidal neovascularization (CNV) is the most frequent cause for AMD, and is commonly induced by regional inflammation. Past studies have highlighted vascular endothelial growth factor A (VEGF-A) as a major trigger for CNV. However, studies on the associated angiogenic factors other than VEGF-A are lacking.

METHODS: Here, we used a well-established laser burn (LB)-induced experimental CNV mouse model to study the molecular mechanisms underlying the development of CNV after ocular injury. We analyzed vessel density by lectin labeling. We isolated macrophages, endothelial cells and other cell types by flow cytometry, and analyzed levels of different angiogenic factors in these populations. We used antisera against VEGF-A (aVEGF) and/or antisera against placental growth factor (PLGF; aPLGF) to antagonize CNV. We used an antibody-driven toxin to selectively eliminate macrophages to evaluate the role of macrophages in CNV. We also examined expression of PLGF in macrophage subtypes.

RESULTS: The choroidal vessel density increased significantly 7 days after LB. LB increased significantly the levels of VEGF-A and PLGF in mouse eyes. Treatment with aVEGF significantly blunted increases in vessel density by LB. Treatment with aPLGF alone did not significantly reduce increases in vessel density. However, aPLGF significantly increased the inhibitory effects of aVEGF on vessel density increases. While VEGF-A was produced by endothelial cells, macrophages and other types at similar levels, PLGF seemed to be predominantly produced by macrophages. Selective macrophage depletion significantly reduced CNV. M2, but M1 macrophages produced high levels of PLGF.

CONCLUSIONS: Together, our data suggest a previously unappreciated role of PLGF in coordination with VEGF-A to regulate CNV during ocular injury. Our study highlights macrophages and their production of PLGF as novel targets for CNV therapy.

PMID: 25832861 [PubMed - in process]

Retina. 2015 Mar 31. [Epub ahead of print]

ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR NAIVE IDIOPATHIC CHOROIDAL NEOVASCULARIZATION: A Comparative Study.

Sudhalkar A, Yogi R, Chhablani J.

PURPOSE: To determine the clinical characteristics of patients with idiopathic choroidal neovascularization and to compare outcomes between intravitreal bevacizumab (IVB) and ranibizumab as therapy.

METHODS: Retrospective analysis included demographics, the corrected distance visual acuity, details of the ocular examination, imaging, treatment, outcomes, and adverse events. Patients with minimum of 1-year follow-up were included in the study. Primary outcome measure was change in corrected distance visual acuity at the final visit compared with baseline. Secondary outcome measures were change in central macular thickness and subretinal fluid (if present) with treatment and adverse events.

RESULTS: This study included 47 eyes of 45 patients with 30 males. Intravitreal bevacizumab group included 29 eyes (27 patients; with a median age of 39.4 ± 7.3 years). Intravitreal ranibizumab group included 18 eyes (18 patients; median age: 36.8 ± 9.3 years). Median baseline corrected distance visual acuity (logMAR) improved from 0.59 ± 0.38 to 0.2 ± 0.18 (P = 0.03) in intravitreal ranibizumab group and from 0.62 ± 0.41 to 0.18 ± 0.15 logMAR (P = 0.023) in intravitreal bevacizumab group. Median central macular thickness (in micrometers) improved from 315.11 ± 75.24 to 228.24 ± 67 (P = 0.036) in intravitreal bevacizumab group and from 327.24 ± 61.56 to 208 ± 53.42 (P = 0.031) in intravitreal ranibizumab group. There was no significant difference between groups in final corrected distance visual acuity (P = 0.31) or central macular thickness (P = 0.51). No adverse events were noted.

CONCLUSION: Both intravitreal ranibizumab and intravitreal bevacizumab seem equally effective in treating idiopathic choroidal neovascularization with a good safety profile without recurrence.

PMID: 25830696 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Mar 28. [Epub ahead of print]

Influence of the Vitreomacular Interface on Treatment Outcomes in the Comparison of Age-Related Macular Degeneration Treatments Trials.

Cuilla TA, Ying GS, Maguire MG, Martin DF, Jaffe GJ, Grunwald JE, Daniel E, Toth CA; Comparison of Age -Related Macular Degeneration Treatments Trials Research Group.

OBJECTIVE: To assess the association of the vitreomacular interface with outcomes of eyes treated with anti-vascular endothelial growth factor drugs for neovascular age-related macular degeneration (AMD).

DESIGN: Prospective cohort study within a multicenter, randomized clinical trial.

PARTICIPANTS: Patients enrolled in the Comparison of AMD Treatments Trials (CATT).

METHODS: Treatment was assigned randomly as either ranibizumab or bevacizumab and as 3 different regimens for dosing over a 2-year period. Masked readers at a reading center assessed optical coherence tomography (OCT) scans at baseline and follow-up for vitreomacular traction (VMT) and vitreomacular adhesion (VMA), fluid, and central thickness. Visual acuity (VA) was measured by masked, certified examiners.

MAIN OUTCOME MEASURES: Anatomic features and VA at baseline and 1 and 2 years and number of treatments.

RESULTS: At baseline, 143 patient eyes (12.8%) had VMT or VMA. Compared with those with neither (n = 972), patients with VMT or VMA were younger (mean ± standard error, 75.5±0.6 vs. 79.7±0.24 years; P < 0.0001) and more likely to be male (52.4% vs. 36.2%; P = 0.0003), to be cigarette smokers (68.5% vs. 55.3%; P = 0.003), and to have subretinal fluid on OCT (86.7% vs. 81.0%; P = 0.047). Vitreomacular interface status was not associated with VA at baseline or follow-up. Among eyes treated as needed (n = 598) and followed up for 2 years (n = 516), the mean number of injections was 15.4±0.9 for eyes having VMT at baseline or during follow-up (n = 60), 13.8±0.7 for eyes with VMA at baseline or follow-up (n = 79), and 12.9±0.4 (P = 0.02) for eyes without VMT or VMA (n = 377). In addition, the mean number of injections in eyes treated as needed increased from 13.0±0.3 when VMT was not observed to 13.6±1.3 when observed once and to 17±1.2 when observed more than once during follow-up. At 2 years, geographic atrophy developed in a lower percentage of eyes with VMT or VMA at baseline (11.7%) than with neither condition (22.5%; P = 0.005).

CONCLUSIONS: In eyes in the CATT, VMT and VMA were infrequent. At baseline and follow-up, VMT or VMA were not associated with VA. Eyes with VMT or VMA treated as needed required on average 2 more injections over 2 years.

PMID: 25824327 [PubMed - as supplied by publisher]

BMJ. 2015 Apr 1;350:h1654.

Why have UK doctors been deterred from prescribing Avastin?

Cohen D.

No abstract available.

PMID: 25834024

Photodiagnosis Photodyn Ther. 2015 Mar 26. [Epub ahead of print]

The discrepancy between central foveal thickness and best corrected visual acuity in cystoid macular edema secondary to central retinal vein occlusion after intravitreal Lucentis® injection.

Hua R, Li C, Hu Y, Chen L.

PMID: 25818575 [PubMed - as supplied by publisher]

Other treatment & diagnostics

Invest Ophthalmol Vis Sci. 2015 Mar 26. [Epub ahead of print]

The Project MACULA retinal pigment epithelium grading system for histology and optical coherence tomography in age-related macular degeneration.

Curcio CA, Zanzottera EC, Messinger JD, Ach T, Smith RT, Freund KB.

PURPOSE: To seek pathways of retinal pigment epithelium (RPE) fate in age-related macular degeneration via a morphology grading system; provide nomenclature, visualization targets, and metrics for clinical imaging and model systems.

METHODS: Donor eyes with geographic atrophy (GA) or choroidal neovascularization (CNV) and one GA eye with previous clinical spectral domain optical coherence tomography (SDOCT) imaging were processed for histology, photodocumented, and annotated at pre-defined locations. RPE cells contained spindle-shaped melanosomes, apposed a basal lamina or basal laminar deposit (BLamD), and exhibited recognizable morphologies. Thicknesses and unbiased estimates of frequencies were obtained.

RESULTS: In 13 GA eyes (449 locations), Shedding, Sloughed, and Dissociated morphologies were abundant; 22.2% of atrophic locations had Dissociated RPE. In 39 CNV eyes (1363 locations), 37.3% of locations with fibrovascular/fibrocellular scar had Entombed RPE; Sloughed, Dissociated, and Bilaminar morphologies were abundant. Of abnormal RPE, CNV and GA both have ~35% Sloughed/Intraretinal, with more Intraretinal in CNV (9.5% vs 1.8%). Shedding cells associated with granule aggregations in BLamD. The RPE layer did not thin, and BLamD remained thick, with progression. Granule-containing material consistent with three morphologies correlated to SDOCT hyperreflective foci in the previously examined GA patient.

CONCLUSION: RPE morphology indicates multiple pathways in GA and CNV. Atrophic/scarred areas have numerous cells capable of transcribing genes and generating imaging signals. Shed granule aggregates, possibly apoptotic, are visible in SDOCT, as are Dissociated and Sloughed cells. The significance of RPE phenotypes is addressable in longitudinal, high-resolution imaging in clinic populations. Data can motivate future molecular phenotyping studies.

PMID: 25813989 [PubMed - as supplied by publisher]

Curr Opin Ophthalmol. 2015 May;26(3):188-93.

Current phase 1/2 research for neovascular age-related macular degeneration.

Pecen PE, Kaiser PK.

PURPOSE OF REVIEW: The purpose of this review is to provide an update of phase 1 and 2 clinical trials in neovascular age-related macular degeneration that are either currently underway or recently completed by the end of 2014.

RECENT FINDINGS: Three gene therapy options are currently in early clinical trials, administered via intravitreal (AAV2-sFLT01) or subretinal (AVA-101 and RetinoStat) injection to express angiogenesis inhibitors. Several eye drops are being developed for topical administration for various angiogenic inhibitors, including regorafenib, squalamine lactate, and PAN-90806. Early development of systemic administration options may be intravenous (iSONEP) or oral (X-82). Initial study of local radiation therapy may be via proton beam irradiation or stereotactic radiotherapy. Several intravitreal injections are being

studied including human immuno-conjugate molecule (hl-con1), abicipar pegol, PF582, DE-120, ESBA 1008, and REGN2176-3.

SUMMARY: Numerous treatment options of neovascular age-related macular degeneration are in phase 1/2 clinical trials including gene therapy, eye drops, systemic dosing, localized irradiation, and various intravitreal injections. Future phase 3 trial results will be observed closely to determine which of these therapies will be the next novel treatment of neovascular age-related macular degeneration.

PMID: 25822255 [PubMed - in process]

J Ophthalmol. 2015;2015:201726. Epub 2015 Mar 3.

Gene Therapy with Endogenous Inhibitors of Angiogenesis for Neovascular Age-Related Macular Degeneration: Beyond Anti-VEGF Therapy.

Prea SM, Chan EC, Dusting GJ, Vingrys AJ, Bui BV, Liu GS.

Abstract: Age-related macular degeneration (AMD) is the leading cause of substantial and irreversible vision loss amongst elderly populations in industrialized countries. The advanced neovascular (or "wet") form of the disease is responsible for severe and aggressive loss of central vision. Current treatments aim to seal off leaky blood vessels via laser therapy or to suppress vessel leakage and neovascular growth through intraocular injections of antibodies that target vascular endothelial growth factor (VEGF). However, the long-term success of anti-VEGF therapy can be hampered by limitations such as low or variable efficacy, high frequency of administration (usually monthly), potentially serious side effects, and, most importantly, loss of efficacy with prolonged treatment. Gene transfer of endogenous antiangiogenic proteins is an alternative approach that has the potential to provide long-term suppression of neovascularization and/or excessive vascular leakage in the eye. Preclinical studies of gene transfer in a large animal model have provided impressive preliminary results with a number of transgenes. In addition, a clinical trial in patients suffering from advanced neovascular AMD has provided proof-of-concept for successful gene transfer. In this mini review, we summarize current theories pertaining to the application of gene therapy for neovascular AMD and the potential benefits when used in conjunction with endogenous antiangiogenic proteins.

PMID: 25821585 [PubMed] PMCID: PMC4363820

Retina. 2015 Mar 31. [Epub ahead of print]

MULTIMODAL IMAGING FINDINGS AND MULTIMODAL VISION TESTING IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Sato T, Suzuki M, Ooto S, Spaide RF.

PURPOSE: To investigate the interactions among multimodal imaging findings and multimodal vision testing in neovascular age-related macular degeneration.

METHODS: Patients enrolled in a prospective study of neovascular age-related macular degeneration with at least 3 previous intravitreal anti-vascular endothelial growth factor injections. Each patient underwent multimodal fundus imaging including spectral domain optical coherence tomography and fundus autofluorescence, and multimodal vision testing, including visual acuity, contrast sensitivity, reading speed, and microperimetry.

RESULTS: There were 73 eyes of 49 consecutive patients enrolled. Generalized estimating equations' modelling showed that the significant independent predictors of visual acuity were the area of confluent hypoautofluorescence and involvement of the foveal center with either granular or confluent hypoautofluorescence ($P < 0.001$). Contrast sensitivity was negatively correlated with the area of confluent

hypoautofluorescence (P < 0.001), involvement of the foveal center with granular hypoautofluorescence (P = 0.017), and subfoveal choroidal thickness (P = 0.042). The only significant predictor of reading speed was the size of confluent hypoautofluorescence (P < 0.001). The size of the defect in the ellipsoid zone (P < 0.001) and the presence of intraretinal fluid (P = 0.045) were correlated with microperimetry score.

CONCLUSION: Confluent absence of autofluorescence was a highly significant predictor of vision testing and serves as an easy parameter to obtain in patients with neovascular age-related macular degeneration.

PMID: 25830697 [PubMed - as supplied by publisher]

J Pak Med Assoc. 2014 Sep;64(9):1098-100.

Choroidal neo-vascularization presentation in younger age group (pre-senile).

Shehzad M, Aziz T.

Abstract: Age-related macular degeneration (ARMD) is the most common cause of permanent visual loss in the elderly. Advancing age, as the name suggests, is a major risk factor. Vascular endothelial growth factor. (VEGF) along with other factors could be responsible for the dramatic damage in the eyes. Although uncommon in pre-senile group, this disorder can also occur unrelated to age, such as pathologic myopia in which Fuch's spots can classically be seen. It can also occur following traumatic disruption of the Bruch's membrane. Herein we report a case of a 20-year-old healthy female with no known co-morbidities who presented with complaints of sudden central visual loss in her left eye over the course of a few days (one week) with no preceding history of traumatic event or predisposing factor. To investigate the cause, Optical Coherence Tomography/Fluorescein angiography (OCT/FFA) was ordered which exhibited the classical signs of choroidal neo-vascularization.

PMID: 25823199 [PubMed - in process]

Ophthalmologica. 2015 Mar 26. [Epub ahead of print]

Identification of Underlying Causes of Spontaneous Submacular Hemorrhage by Indocyanine Green Angiography.

Kim H, Lee SC, Kim SM, Lee JH, Koh HJ, Kim SS, Byeon SH, Kim M, Lee CS.

PURPOSE: To investigate the causes of acute spontaneous submacular hemorrhage with indocyanine green angiography (ICGA).

METHODS: Retrospective observation case series. A total of 51 eyes from 51 patients with newly developed spontaneous submacular hemorrhage were enrolled. Best-corrected visual acuity (BCVA), fundus photography, fluorescein angiography, spectral domain optical coherence tomography (OCT), and ICGA at baseline were analyzed. The extent of hemorrhage using fundus photography, height of hemorrhage, and central foveal thickness measured by OCT was analyzed to compare the diagnostic and nondiagnostic groups.

RESULTS: The mean logarithm of the minimum angle of resolution (logMAR) BCVA at presentation was 1.21 ± 0.74 (Snellen equivalent, 20/324); the mean follow-up period was 23.9 ± 23.9 months. The cause of submacular hemorrhage was diagnosed in 43 of 51 eyes (84.3%) based on ICGA at presentation. The initial diagnoses were correct in 93% of eyes. In 3 cases, the initial diagnosis of age-related macular degeneration (AMD) was changed to polypoidal choroidal vasculopathy (PCV) based on follow-up ICGA. The central foveal thickness was significantly greater in the nondiagnostic group (1,102.4 vs. 666.7 μm, respectively; p = 0.008). The most common cause of submacular hemorrhage was neovascular AMD (52.9%), followed by PCV (37.3%), macroaneurysm (5.9%), and lacquer crack (3.9%). The mean final visual acuity was generally worse in patients with submacular hemorrhage with typical AMD (visual acuity 20/618) or PCV (visual acuity 20/240) compared to that in patients with retinal macroaneurysm (visual acuity 20/100) or lacquer crack (visual acuity 20/72).

CONCLUSIONS: ICGA at initial presentation helps identify causes of submacular hemorrhage, allowing differential treatment approaches that may improve outcomes and safety.

PMID: 25833061 [PubMed - as supplied by publisher]

J Med Assoc Thai. 2014 Oct;97 Suppl 10:S115-9.

Spontaneous bilateral retinal pigment epithelium rips with good visual acuity.

Sinawat S, Bhoomibunchoo C, Yospaiboon Y, Sinawat S.

Abstract: Retinal pigment epithelium (RPE) rips commonly occur in retinochoroidal disorders including age-related macular degeneration, idiopathic polypoid alchoroidal vasculopathy, central serous chorioretinopathy, high myopia andchoroidal neovascularization. Most patients have unilateral involvement and poor visual prognosis. A 55-year-old female presented with decreased vision in her right eye for one week. Her best-corrected visual acuity was 6/12 in the right eye and 6/6-2 in the left. Fundus examination revealed a large juxtafoveal RPE rip in the right eye and multiple small pigment epithelium detachments in the left. No abnormal hyperfluorescent lesions were detected byfundus angiography. High-dose oral antioxidant was prescribed. A pigment epithelium detachment (PED) in the left eye grew larger over the follow-up period. Ultimately, a RPE rip also occurred in the left eye in the 17th week offollow-up. Her best-corrected visual acuity was 6/9. Although reinvestigation was done, no other choroidal abnormalities were demonstrated by optical coherence tomography (OCT) and fundus angiography. During the observation, RPE tears were reattached spontaneously in both eyes. A considerable amount of RPE proliferation, migration, and repopulation was also demonstrated by OCT and fundus autofluorescence. After 2.5 years of follow-ups, her best-corrected visual acuity was 6/9 in the right eye and 6/6 in the left. We hypothesize that the increased surface tension of RPE is the etiology of RPE rips in this case. Furthermore, the underlying chorioretinal abnormality directly affects the visual prognosis and further studies are needed in prevention, pathogenesis and treatment.

PMID: 25816547 [PubMed - in process]

BioDrugs. 2015 Mar 27. [Epub ahead of print]

Pharmacologic Vitreolysis with Ocriplasmin: Rationale for Use and Therapeutic Potential in Vitreo-Retinal Disorders.

Khoshnevis M, Sebag J.

Abstract: With increased knowledge about the origins and pathophysiology of vitreo-retinal disorders-and, in particular, the central role of anomalous posterior vitreous detachment in vitreo-maculopathies-a paradigm shift from surgery to pharmacotherapy is taking place with the development of pharmacologic vitreolysis. The first approved agent for pharmacologic vitreolysis therapy is ocriplasmin, a truncated form of the nonspecific serine protease plasmin. Twelve studies comprise the current ocriplasmin clinical trial program, demonstrating the efficacy and safety of a single intravitreal injection of ocriplasmin for the treatment of patients with symptomatic vitreo-macular adhesion or vitreo-macular traction, including patients with macular holes. Although post-approval implementation of ocriplamsin in clinical practice has shown success rates of up to 78 %, there have been recent case reports of acute, transient visual dysfunction. There are thus new initiatives to further refine clinical indications for case selection and to identify possible untoward effects. Although more studies are warranted, it appears that ocriplasmin offers a good alternative to surgery. The future lies in pharmacologic vitreolysis, and the future of pharmacologic vitreolysis lies in prevention. Thus, long-term studies are needed to define a role for pharmacologic vitreolysis, in particular with ocriplasmin, in the prevention of progressive diabetic retinopathy and age-related macular degeneration.

PMID: 25812991 [PubMed - as supplied by publisher]

Methods Cell Biol. 2015;127:75-92. Epub 2015 Feb 14.

Cilia in photoreceptors.

Li L, Anand M, Rao KN, Khanna H.

Abstract: Retina is a neurosensory tissue lining the back of the eye and is responsible for light detection and relaying the signal to the visual cortex in the brain. Mammalian retina consists of six major types of neurons (including photoreceptors; rods and cones) and one type of glial cells arranged in distinct layers. Photoreceptors are the most abundant cell types accounting for approximately 60% of all cells in the retina. Owing to their unique structure and function as ciliated neurons and their vast majority, dysfunction and degeneration of photoreceptors is associated with several inherited blindness disorders, such as retinitis pigmentosa, cone-rod degeneration, and age-related macular degeneration. Therefore, it is imperative to examine the structure and function of photoreceptors so that better understanding of the pathogenesis of associated diseases can be obtained for designing therapeutic modalities. In this chapter, we will provide detailed methods for analyzing photoreceptor function (electroretinography), structure, and biochemical analysis of sensory cilia of photoreceptors using mammalian retina as model system. These methods are widely used to assess photoreceptor development and degeneration during disease.

PMID: 25837387 [PubMed - in process]

Ophthalmologe. 2015 Apr 4. [Epub ahead of print]

[Forms of age-related macular degeneration].[Article in German]

Schargus M.

Abstract: Age-related macular degeneration (AMD) is the major reason for blindness affecting about 50 % of blind people in Germany. Early forms of AMD with drusen and pigment epithelium changes can be detected in 20 % of patients over 65 years old. The dry form of AMD causes slow deterioration of visual acuity, which cannot currently be adequately treated. In contrast development of a choroidal neovascularization (CNV) membrane results in rapid visual loss which will become permanent if treatment is not started immediately. Using anti-vascular endothelial growth factor (VEGF) agents stabilization and improvement of visual acuity is possible. Special types of AMD, such as retinal angiomatous proliferation and polypoidal choroidal vasculopathy are much less common. The natural course of the diseases can be very different, end stages often result in scarring and anti-VEGF agents are only weakly effective.

PMID: 25837316 [PubMed - as supplied by publisher]

Pathogenesis

Curr Eye Res. 2015 Apr 2:1-8. [Epub ahead of print]

Lactoferrin Reduces Chorioretinal Damage in the Murine Laser Model of Choroidal Neovascularization.

Montezuma SR, Dolezal LD, Rageh AA, Mar K, Jordan M, Ferrington DA.

PURPOSE: To determine whether lactoferrin, specifically endogenous mouse lactoferrin and exogenous intraperitoneal lactoferrin treatment, plays a role in reducing the chorioretinal damage in the laser-induced model of choroidal neovascularization.

MATERIALS AND METHODS: Four 532-nm argon laser spots were placed between the retinal vessels of each eye. At Day 7, Fluorescein Angiography was performed to grade the lesions. The mice were perfused with fluorescein-labeled tomato lectin and sacrificed. The retinal pigment epithelium-choroid-sclera complex

was flat-mounted and analyzed with a confocal microscope to measure the volume of the lesions. The effect of endogenous lactoferrin was studied by comparing lactoferrin knockout and wild-type (WT) mice. The effect of exogenous lactoferrin treatment was studied by comparing lactoferrin knockout and WT mice treated with lactoferrin for seven days to their respective controls.

RESULTS: Lactoferrin knockout mice demonstrated 47% larger lesion volumes than WT mice ($p < 0.001$). Intraperitoneal treatment with Lactoferrin reduced the lesion volume in Lactoferrin knockout mice by 26% ($p < 0.04$). Regarding the fluorescein angiography, lesions indicating the greatest damage (grade 2B) occurred more frequently in control lactoferrin knockout mice compared with control WT mice (16% versus 5%). Intraperitoneal treatment with Lactoferrin reduced the grade 2B lesions from16% to 2% in Lactoferrin knockout mice.

CONCLUSION: The endogenous lactoferrin present in WT mice appears to reduce the choroidal neovascularization in the laser-induced choroidal neovascularization model in mice. Treatment with exogenous lactoferrin is capable of reducing the choroidal neovascularization in lactoferrin knockout mice but does not add a significant protective effect to WT.

PMID: 25835346 [PubMed - as supplied by publisher]

Antioxid Redox Signal. 2015 Apr 1. [Epub ahead of print]

Do Beta 2-Glycoprotein I Disulfide Bonds Protect the Human Retina in the setting of Age Related Macular Degeneration?

Qi M, Abdelatti M, Krilis M, Madigan MC, Weaver J, Guymer RH, McCluskey P, Wang Y, Zhou S, Krilis S, Giannakopoulos B.

Abstract: Age-related macular degeneration (AMD) affects the region of the retina responsible for high resolution vision. It is a major cause of blindness in the ageing population. This is the first study to examine the association of redox modified, cysteine based, post-translational forms of beta 2-glycoprotein I (β2GPI) in the plasma of individuals with early and late stages of patients with AMD compared to controls. Exploration is also undertaken to assess whether the free thiol form of β2GPI versus the oxidized disulfide form have distinct functional properties in the setting of hydrogen peroxide mediated cell death of an immortalized human retinal pigment epithelium (RPE) cell line. We demonstrate β2GPI in the retina and choroid of patients with AMD. Free thiol β2GPI is shown to protect the immortalized human RPE cell line against H2O2 induced cell death, whereas the oxidized form of β2GPI and free thiol bovine serum albumin were not protective. Free thiol β2GPI levels were significantly decreased in patients with late AMD compared to early AMD and healthy controls. Our observations lead to the hypothesis that free thiol β2GPI may protect against oxidative stress injury to RPE cells in the early stages of AMD.

PMID: 25827171 [PubMed - as supplied by publisher]

J Ophthalmic Inflamm Infect. 2014 Oct 15;4:26. eCollection 2014.

Update on intravitreal anti-tumor necrosis factor alpha therapies for ocular disorders.

Pascual-Camps I, Hernández-Martínez P, Monje-Fernández L, Dolz-Marco R, Gallego-Pinazo R, Wu L, Arévalo JF, Díaz-Llopis M.

Abstract: Tumor necrosis factor alpha (TNF-?) is an important pro-inflammatory cytokine associated with a variety of ocular diseases. The currently available TNF-? inhibitors are etanercept, infliximab, adalimumab, golimumab, and certolizumab. Experimental and clinical studies on the intravitreal use of these agents have been reported with etanercept, infliximab, and adalimumab: etanercept has shown limited efficacy in scarce reports; infliximab has been associated with local safety concerns but appears to benefit certain cases; adalimumab has shown no efficacy in cases of age-related macular degeneration (AMD) or diabetic

macular edema (DME), but the combination with bevacizumab may be effective in refractory cases of macular diseases. Further preclinical and clinical studies are warranted in order to be able to obtain a more robust conclusion on the use of intravitreal TNF-? inhibitors.

PMID: 25825604 [PubMed] PMCID: PMC4372686

Sci Rep. 2015 Mar 30;5:9497.

Association of PEDF polymorphisms with age-related macular degeneration and polypoidal choroidal vasculopathy: a systematic review and meta-analysis.

Ma L, Tang SM, Rong SS, Chen H, Young AL, Kumaramanickavel G, Pang CP, Chen LJ.

Abstract: This study assesses the association of the pigment epithelium-derived factor (PEDF) gene with age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV). Publications in MEDLINE and EMBASE up to 21/08/2014 were searched for case-control association studies of PEDF with AMD and/or PCV. Reported studies giving adequate genotype and/or allele information were included. Pooled odds ratios (OR) and 95% confidence intervals (CI) of each polymorphism were estimated. Our literature search yielded 297 records. After excluding duplicates and reports with incomplete information, 8 studies were eligible for meta-analysis, involving 2284 AMD patients versus 3416 controls, and 317 PCV patients versus 371 controls. Four PEDF polymorphisms were meta-analyzed: rs1136287, rs12150053, rs12948385 and rs9913583, but none was significantly associated with AMD or PCV. The most-investigated polymorphism, rs1136287, had a pooled-OR of 1.02 (95% CI: 0.94-1.11, P = 0.64) for AMD. In subgroup analysis by ethnicity, no significant association was identified. Polymorphisms present in single report showed no association. Therefore, existing data in literature does not support the role of PEDF in the genetic susceptibility of AMD and PCV, although replication in specific populations is warranted. Since the pooled-sample size for PCV was small, there is a need of PEDF genotyping in larger samples of PCV.

PMID: 25820866 [PubMed - in process]

Exp Eye Res. 2015 Apr;133:126-131.

Role of tyrosine-sulfated proteins in retinal structure and function.

Kanan Y, Al-Ubaidi MR.

Abstract: The extracellular matrix (ECM) plays a significant role in cellular and retinal health. The study of retinal tyrosine-sulfated proteins is an important first step toward understanding the role of ECM in retinal health and diseases. These secreted proteins are members of the retinal ECM. Tyrosine sulfation was shown to be necessary for the development of proper retinal structure and function. The importance of tyrosine sulfation is further demonstrated by the evolutionary presence of tyrosylprotein sulfotransferases, enzymes that catalyze proteins' tyrosine sulfation, and the compensatory abilities of these enzymes. Research has identified four tyrosine-sulfated retinal proteins: fibulin 2, vitronectin, complement factor H (CFH), and opticin. Vitronectin and CFH regulate the activation of the complement system and are involved in the etiology of some cases of age-related macular degeneration. Analysis of the role of tyrosine sulfation in fibulin function showed that sulfation influences the protein's ability to regulate growth and migration. Although opticin was recently shown to exhibit anti-angiogenic properties, it is not yet determined what role sulfation plays in that function. Future studies focusing on identifying all of the tyrosine-sulfated retinal proteins would be instrumental in determining the impact of sulfation on retinal protein function in retinal homeostasis and diseases.

PMID: 25819460 [PubMed - as supplied by publisher] PMCID: PMC4379419

Exp Eye Res. 2015 Apr;133:100-111.

The dynamic sclera: Extracellular matrix remodeling in normal ocular growth and myopia development.

Harper AR, Summers JA.

Abstract: Myopia is a common ocular condition, characterized by excessive elongation of the ocular globe. The prevalence of myopia continues to increase, particularly among highly educated groups, now exceeding 80% in some groups. In parallel with the increased prevalence of myopia, are increases in associated blinding ocular conditions including glaucoma, retinal detachment and macular degeneration, making myopia a significant global health concern. The elongation of the eye is closely related to the biomechanical properties of the sclera, which in turn are largely dependent on the composition of the scleral extracellular matrix. Therefore an understanding of the cellular and extracellular events involved in the regulation of scleral growth and remodeling during childhood and young adulthood will provide future avenues for the treatment of myopia and its associated ocular complications.

PMID: 25819458 [PubMed - as supplied by publisher] PMCID: PMC4379420

Exp Eye Res. 2015 Apr;133:3-18.

Structure and function of the interphotoreceptor matrix surrounding retinal photoreceptor cells.

Ishikawa M, Sawada Y, Yoshitomi T.

Abstract: The interphotoreceptor matrix (IPM) is a highly organized structure with interconnected domains surrounding cone and rod photoreceptor cells and extends throughout the subretinal space. Based on known roles of the extracellular matrix in other tissues, the IPM is thought to have several prominent functions including serving as a receptor for growth factors, regulating retinoid transport, participating in cytoskeletal organization in surrounding cells, and regulation of oxygen and nutrient transport. In addition, a number of studies suggest that the IPM also may play a significant role in the etiology of retinal degenerative disorders. In this review, we describe the present knowledge concerning the structure and function of the IPM under physiological and pathological conditions.

PMID: 25819450 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Mar 26. [Epub ahead of print]

Time Dependent Changes of Cell Proliferation after Laser Photocoagulation in Mouse Chorioretinal Tissue.

Lee SH, Kim HD, Park YJ, Ohn YH, Park TK.

PURPOSE: This study investigated the time course of cell proliferation after laser photocoagulation and analyzed the cell types of proliferating cells.

METHODS: C57BL/6J mice received unilateral laser photocoagulation. Intraperitoneal 5-bromo-2-deoxyuridine (BrdU) injection was performed, and mice were divided into two groups according to the injection paradigm: group 1 with continuous injection and group 2 with periodical injection. Each group was again divided into 4 subgroups according to injection period: 0-3 days (n=11), 0-7 days (n=14), 0-14 days (n=6), and 0-28 days (n=6) after laser photocoagulation for group 1; and 0-3 days (n=11), 4-7 days (n=6), 8 -14 days (n=6), and 15-28 days (n=6) after laser photocoagulation for group 2. The eyes were examined with immunohistochemistry using anti-BrdU antibody and other various antibodies for identification of proliferating cells. Manual cell counting and flow cytometry were performed for quantification.

RESULTS: In group 1, the number of BrdU+ cells showed marked increase during the first 3 days of laser

lesioning, reaching its maximum after 7 days (P<0.05). Group 2 also demonstrated peak proliferation during the first 3 days, but significantly reduced number of BrdU+ cells were detected during 4-7 days, 8-14 days, and 15-28 days of laser treatment (P<0.05). BrdU+ cells colocalized with CD11b, F4/80, iba1, RPE65, CD31, and GFAP labeling, and CD11b+, F4/80+, and iba1+ cells constituted the main fraction of BrdU+ cells.

CONCLUSIONS: Laser photocoagulation induced cell proliferation mostly during the first 3 days, and many proliferating cells were identified as inflammatory cells, RPE cells, endothelial cells, and Müller cells.

PMID: 25813995 [PubMed - as supplied by publisher]

Epidemiology

Pol Merkur Lekarski. 2015 Feb 25;38(225):144-9.

[Does acetylsalicylic acid and vitamin K antagonists are risk factors of macular degeneration related with age?].[Article in Polish]

Jończyk-Skórka K1, Śliwczyńska-Rodziewicz D1, Jarmak A1, Kowalski J2.

AIM: The aim of this study was to evaluate the effects of chronic use of acetylsalicylic acid (ASA) and vitamin K antagonists (VKA) on the incidence of age related macular degeneration (AMD).

MATERIALS AND METHODS: The study included 292 individuals (187 women, 105 men, aged 45-94 (mean 73.2 ± 10.2 years). All individuals completed a survey and underwent a full eye examination. Patients were divided into four groups according to the presence or absence of degenerative changes at the bottom of an eye: group D - 80 patients with drusen (23 men and 57 women), 27,4% of studied population, group GA - 25 patients with geographic atrophy (10 men, 15 women), 8,56% of studied population, group CNV - 52 patients with neovascular form of AMD (28 men, 24 women), 17,81% of studied population, group Z - 135 healthy people (44 men, 91 women), 46,23% of studied population. Among study group 79 patients (27,1%) used aspirin, 32 people (11%) used vitamin K antagonists (acenocoumarol or warfarin), 181 people (61,9%) didn't use any drug.

RESULTS: Patients from D and CNV group took ASA and VKA more often than patients from GA and Z group. The percentages were: in a group Z - 30,37%, in group D - 46,25%, in group GA - 32%, in group CNV - 48,08% (p=0,0407). There was no relationship between belonging to a group and use of ASA (p=0,3169). A statistically significant relationship between belonging to a group and use of VKA was discovered. The number of people using VKA in group D and CNV was statistically significantly higher than in the healthy control group and percentage were as follows: in group Z - 8,15%, in group D - 17,5%, in group GA 0%, in group CNV - 13,46% (p=0,0159). Patient groups differed statistically significantly due to age (p=0,0043), sex (p=0,0197), family history of macular diseases (p <0,0001), smoking (p=0,011), prevalence of hypercholesterolemia (p=0,0437), ischemic heart disease (p= 0,0173). The consumption of fish at least once a week and eating fruits and vegetables more often than once a day was associated with a reduced incidence of AMD p=0,0009, p=0,0003. Patients without AMD assessed their quality of life at a higher level than people with AMD (p<0,0001). ASA and VKA intake was found not to be an independent risk factor for AMD. Positive family history was an independent risk factor for AMD in all groups. Also age ≥75, fish consumption > 1 week, male gender were independent risk factors for AMD in specified groups.

CONCLUSIONS: Patients with drusen and exudative form of AMD took ASA and VKA more often than healthy people and patients with geographic atrophy. ASA or VKA intake was found not to be an independent risk factor for AMD. Positive family history was an independent risk factor for AMD in all groups. In selected groups: age ≥75, male gender and reduced consumption of fish was found to be an independent risk factor for AMD. Number of people taking ASA and VKA is increasing and further studies are needed to assess their impact on the organ of vision.

PMID: 25815614 [PubMed - in process]

JAMA Ophthalmol. 2015 Apr 2. [Epub ahead of print]

Incidence, Progression, and Associated Risk Factors of Medium Drusen in Age-Related Macular Degeneration: Findings From the 15-Year Follow-up of an Australian Cohort.

Joachim ND, Mitchell P, Kifley A, Wang JJ.

Importance: The natural course and prognosis of medium drusen and risk factors associated with the incidence and progression of this lesion type in age-related macular degeneration (AMD) are not well understood.

Objective: To assess the 15-year incidence and progression of medium drusen and associated risk factors.

Design, Setting, and Participants: Population-based cohort in the Blue Mountains region, west of Sydney, Australia. Included in the study were 3654 participants 49 years or older who attended baseline examinations of the Blue Mountains Eye Study (1992-1994), and 75.8%, 76.7%, and 56.1% of survivors who attended the 5-year, 10-year, and 15-year follow-up examinations, respectively.

Main Outcomes and Measures: Color retinal fundus photographs were obtained at each examination. The incidence and progression of medium drusen (maximum diameter, 63 to <125 µm) were assessed using Kaplan-Meier product-limit survival methods, controlling for competing risk of death. Factors associated with a 15-year incidence of medium drusen were assessed using discrete logistic regression models after adjusting for age, sex, smoking status, serum lipid levels, systemic and dietary factors, and CFH rs1061170 and ARMS2 rs10490924 polymorphisms. Associations between lesion characteristics and the progression to late AMD were assessed using generalized estimating equation models and eye-specific data.

Results: Among 1317 participants at risk, the 15-year cumulative incidence of medium drusen was 13.9% (n = 281). Increasing age (per decade older) (odds ratio [OR], 1.4; 95% CI, 1.2-1.8) and the presence of at least 3 risk alleles of the CFH rs1061170 or ARMS2 rs10490924 genes (OR, 2.1; 95% CI, 1.1-4.1) were associated with a higher incidence. There was no association between past smoking (OR, 0.8; 95% CI, 0.6-1.1) or current smoking (OR, 0.6; 95% CI, 0.4-1.1) and the development of medium drusen. The progression rate to late AMD in eyes with both medium drusen and retinal pigmentary abnormalities was 4-fold higher than that in eyes with medium drusen alone. Larger total area and central location of medium drusen were associated with a greater likelihood of the progression to worse stages of AMD.

Conclusions and Relevance: Older age and the presence of CFH and ARMS2 risk alleles are 2 main risk factors associated with the development of medium drusen. The copresence of medium drusen plus retinal pigment epithelium abnormalities signals a greater risk of the progression to late AMD than the presence of medium drusen alone.

PMID: 25838066 [PubMed - as supplied by publisher]

Genetics

Mol Vis. 2015 Mar 15;21:285-92. eCollection 2015

Analysis of rare variants in the CFH gene in patients with the cuticular drusen subtype of age-related macular degeneration.

Duvvari MR, Saksens NT, van de Ven JP, de Jong-Hesse Y, Schick T, Nillesen WM, Fauser S, Hoefsloot LH, Hoyng CB, de Jong EK, den Hollander AI.

PURPOSE: Age-related macular degeneration (AMD) and cuticular drusen (CD), a clinical subtype of AMD, have been linked to genetic variants in the complement factor H (CFH) gene. In this study, we aimed to investigate the frequency of rare variants in the CFH gene in 180 cases with CD. In addition, we aimed to determine the frequency of a previously reported rare, highly penetrant CFH variant (p.Arg1210Cys) in a

Dutch-German non-CD-type AMD case-control cohort, and to describe the phenotype of patients carrying the p.Arg1210Cys variant.

METHODS: Study subjects were selected from the European Genetic Database (EUGENDA), a joint AMD database of the Radboud University Medical Centre and the University Hospital of Cologne, and graded at the Cologne Image Reading Centre and Laboratory (CIRCL). Additionally, two CD cases were recruited from the VU Medical Centre in Amsterdam. The CFH gene was analyzed in 180 CD cases with Sanger sequencing. All identified variants were analyzed for potential damaging effects with prediction software tools Sorting Intolerant from Tolerant (SIFT) and Polymorphism Phenotyping (PolyPhen). In addition, we genotyped the p.Arg1210Cys variant in 813 non-CD type AMD cases and 1175 controls.

RESULTS: Sequencing identified 11 rare, heterozygous missense variants, one frameshift variant, and one splice acceptor site variant in 16 CD cases. The p.Arg1210Cys variant was identified in two CD cases but was not identified in our Dutch-German non-CD-type AMD case-control cohort.

CONCLUSIONS: The present study identified the presence of rare variants in the CFH gene in 16 (8.8%) of 180 patients with the CD subtype of AMD. The carriers of rare CFH variants displayed a significantly earlier age at onset than non-carriers (p=0.016). The rare missense variant p.Arg1210Cys was identified in two CD cases, but was not detected in 813 non-CD type AMD cases or in the 1,175 controls of our Dutch-German cohort. The current study suggests that the p.Arg1210Cys variant may be restricted to a subset of patients with the CD subtype of AMD. Detailed clinical phenotyping, including fluorescein angiography, of patients with AMD carrying the p.Arg1210Cys variant in other cohorts is required to confirm this finding.

PMID: 25814826 [PubMed - in process] PMCID: PMC4360166

Mol Vis. 2015 Mar 13;21:264-72. eCollection 2015

CFH Y402H polymorphism is associated with elevated vitreal GM-CSF and choroidal macrophages in the postmortem human eye.

Wang JC, Cao S, Wang A, To E, Law G, Gao J, Zhang D, Cui JZ, Matsubara JA.

PURPOSE: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in people 50 years of age or older in developed countries. The homozygous CC genotype in the complement factor H (CFH) Y402H single nucleotide polymorphism (SNP; rs1061170) is widely recognized as a risk factor for the development of AMD. In this study, we examined vitreal levels of granulocyte macrophage colony-stimulating factor (GM-CSF), a hematopoietic cytokine, and macrophages in the choroid of postmortem human eyes genotyped for the CFH Y402H SNP.

METHODS: Twenty-two pairs of postmortem, non-diseased, human donor eyes were obtained. The vitreous and retinal tissues of the left eyes were collected for GM-CSF level measurement and CFH Y402H genotyping, respectively. The right eyes were paraffin-embedded and sectioned for immunohistochemistry using a macrophage and microglia marker, CD68. Cell cultures of RPE cells were stimulated with complement C3a, C5a, 4-hydroxynonenal (HNE), or tumor necrosis factor alpha (TNF-α), and GM-CSF expression was measured with a suspension assay or quantitative PCR.

RESULTS: Eyes genotyped with the CC or the CT risk variant of the CFH Y402H SNP showed significantly increased levels of GM-CSF in the vitreous compared to eyes with the protective TT variant (mean ± standard error of mean, 607.54±85.83 pg/ml or 656.32±15.20 pg/ml versus 286.69±81.96 pg/ml, p<0.05). The choroid of eye tissues genotyped with the CC variant showed higher levels of CD68 immunoreactivity than the tissues genotyped with the TT variant (p<0.05). The GM-CSF levels detected in the supernatant of RPE cells in culture treated with HNE or TNF-α were significantly higher compared to the non-treated control (145.88±5.06 pg/ml and 149.32±3.76 pg/ml versus 123.27±4.05 pg/ml, p<0.05). Furthermore, the gene expression of GM-CSF detected in the lysate of RPE cells stimulated with complement C3a or C5a showed significantly increased fold changes compared to the non-treated control (C3a: 2.38±0.31 fold,

p<0.05; C5a: 2.84±0.54 fold, p<0.01).

CONCLUSIONS: Our data showed a relationship between the CFH Y402H polymorphism and GM-CSF levels in the vitreous and accumulation of choroidal macrophages in the postmortem eye. These data suggest that the at-risk variant of the CFH gene may contribute to the dysregulation of proinflammatory cytokines locally in the eye.

PMID: 25814824 [PubMed - in process] PMCID: PMC4360164

Nat Commun. 2015 Mar 30;6:6817.

Corrigendum: New loci and coding variants confer risk for age-related macular degeneration in East Asians.

Cheng CY, Yamashiro K, Jia Chen L, et al

PMID: 25817435 [PubMed - in process]

Diet, lifestyle and low vision

PLoS One. 2015 Mar 30;10(3):e0122548. eCollection 2015.

Smoking, Antioxidant Supplementation and Dietary Intakes among Older Adults with Age-Related Macular Degeneration over 10 Years.

Gopinath B, Flood VM, Kifley A, Liew G, Mitchell P.

Abstract: We aimed to compare the micronutrient usage and other lifestyle behaviors over 10 years among those with and without age-related macular degeneration (AMD). 1612 participants aged 49+ years at baseline were re-examined over 10 years, west of Sydney, Australia. AMD was assessed from retinal photographs. Dietary data were collected using a semi-quantitative food frequency questionnaire. Smoking status was self-reported. 56 participants had any AMD at baseline, of these 25% quit smoking at 5 years and were still not smoking at 10-year follow-up. Among participants who had below the recommended intake of vitamins A, C or E supplements at baseline, those who did compared to those who did not develop late AMD over 10 years were more likely to report vitamins A (total), C or E supplement intake above the recommended intake at 10-year follow-up: multivariable-adjusted OR 4.21 (95% CI 1.65-10.73); OR 6.52 (95% CI 2.76-15.41); and OR 5.71 (95% CI 2.42-13.51), respectively. Participants with compared to without AMD did not appreciably increase fish, fruit and vegetable consumption and overall diet quality. Adherence to smoking and dietary recommendations was poor among older adults with AMD. However, uptake of antioxidant supplements increased significantly among those with late AMD.

PMID: 25822372 [PubMed - in process]

Biomed Res Int. 2015;2015:564738. Epub 2015 Mar 1

Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age-related macular degeneration.

Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lin XM.

Purpose: To compare the 2-year effect of multiple doses of lutein/zeaxanthin on serum, macular pigmentation, and visual performance on patients with early age-related macular degeneration (AMD).

Methods: In this randomized, double-blinded, and placebo-controlled trial, 112 early AMD patients randomly received either 10 mg lutein, 20 mg lutein, a combination of lutein (10 mg) and zeaxanthin (10 mg), or

placebo daily for 2 years. Serum concentration of lutein/zeaxanthin, macular pigment optical density (MPOD), visual functions including best-spectacle corrected visual acuity (BCVA), contrast sensitivity (CS), flash recovery time (FRT), and vision-related quality of life (VFQ25) was quantified.

Results: Serum lutein concentration and MPOD significantly increased in all the active treatment groups. Supplementation with 20 mg lutein was the most effective in increasing MPOD and CS at 3 cycles/degree for the first 48 weeks. However, they both significantly increased to the same peak value following supplementation with either 10 mg or 20 mg lutein during the intervention. No statistical changes of BCVA or FRT were observed during the trial.

Conclusions: Long-term lutein supplementation could increase serum lutein concentration, MPOD, and visual sensitivities of early AMD patients. 10 mg lutein daily might be an advisable long-term dosage for early AMD treatment.

PMID: 25815324 [PubMed - in process] PMCID: PMC4359817

Rocz Panstw Zakl Hig. 2015;66(1):55-60.

Dietary sources of lutein in adults suffering eye disease (AMD/cataracts).

Sulich A, Hamułka J, Nogal D.

BACKGROUND: Epidemiological studies indicate that by consuming 6-14 mg lutein daily, the risk of acquiring eye diseases like age-related macular degeneration (AMD) or cataracts becomes reduced. Their symptoms can also by such means be alleviated and treatment improved.

OBJECTIVES: To estimate dietary intakes of lutein obtained from foodstuffs and supplements along with determining its main sources in selected groups of adults suffering from eye disease and healthy controls.

MATERIAL AND METHODS: The study was performed in Warsaw and its neighbourhoods during 2008-12. Subjects were 375 adults aged 50-97 years, of whom half had been diagnosed with AMD and/or cataracts; constituting the test group. Dietary intakes of lutein were assessed by Food Frequency Questionnaire Method whilst interview questionnaires assessed the intake of supplements.

RESULTS: Overall, the average dietary intake of lutein from foodstuffs was 2.5 mg daily, with the test group being significantly higher than healthy controls (2.9 vs 2.1 mg daily). Women's intakes were also higher than in men (2.9 vs 2.1 mg daily), as were those possessing higher or secondary education compared to the others with primary or vocational education (2.7 vs 2.3 mg daily). Fresh vegetables were found to be the main dietary sources of lutein that included green leafy vegetables and frozen vegetables, constituting respectively 63% and 13% of the dietary intake. Dietary supplements containing lutein were taken by 109 subjects of whom most had eye disease (over 80%); where the average daily consumption of lutein from this source was 6.5 mg.

CONCLUSIONS: For older people, the dietary intake of lutein from foodstuffs may be insufficient to prevent eye disease. Taking daily dietary supplements would thus be indicated to make up such deficiencies of lutein.

PMID: 25813074 [PubMed - in process]

Oxid Med Cell Longev. 2015;2015:804054. Epub 2015 Feb 28.

Association of age-related macular degeneration with erythrocyte antioxidant enzymes activity and serum total antioxidant status.

Plestina-Borjan I, Katusic D2, Medvidovic-Grubisic M3, Supe-Domic D4, Bucan K1, Tandara L4, Rogosic V1.

Abstract: The aim was to estimate association of the oxidative stress with the occurrence of age-related macular degeneration (AMD). The activities of erythrocyte antioxidant enzymes: superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) and additionally serum total antioxidant status (TAS) were used as indicators of the oxidative stress level. 57 AMD patients (32 early and 25 late AMD) and 50 healthy, age and gender matched controls were included. GPx activity ($P < 0.001$) and serum TAS ($P = 0.015$) were significantly lower in AMD patients. The difference was not significant for SOD or CAT activities. Significant interaction between GPx and SOD was detected ($P = 0.003$). At high levels of SOD activity (over 75th percentile), one standard deviation decrease in GPx increases the odds for AMD for six times (OR = 6.22; $P < 0.001$). ROC analysis revealed that combined values of GPx activity and TAS are significant determinants of AMD status. Accuracy, sensitivity, specificity, and positive and negative predictive values were 75%, 95%, 52%, 69%, and 90%, respectively. The study showed that low GPx activity and TAS are associated with AMD. SOD modulates the association of GPx and AMD. The results suggest that erythrocyte antioxidant enzymes activity and serum TAS could be promising markers for the prediction of AMD.

PMID: 25815109 [PubMed - in process] PMCID: PMC4359814

Contemp Clin Trials. 2015 Mar 24. [Epub ahead of print]

The macular degeneration and aging study: Design and research protocol of a randomized trial for a psychosocial intervention with macular degeneration patients.

Sörensen S, White K, Mak W, Zanibbi K, Tang W, O'Hearn A, Hegel MT.

Abstract: Age-related Macular Degeneration (AMD) is the leading cause of irreversible and predictable blindness among older adults and creates serious physical and mental health consequences for this population. Visual impairment is associated with negative future outlook and depression and has serious consequences for older adults' quality of life and, by way of depression, on long-term survival. Psychosocial interventions have the potential to alleviate and prevent depression symptoms among older AMD patients. We describe the protocol of the Macular Degeneration and Aging Study, a randomized clinical trial of a psychosocial Preventive Problem-Solving Intervention. The intervention is aimed at enhancing well-being and future planning among older adults with macular degeneration by increasing preparation for future care. Adequate randomization and therapeutic fidelity were achieved. Current retention rates were acceptable, given the vulnerability of the population. Acceptability (adherence and satisfaction) is high. Given the high public health significance and impact on quality of life among older adults with vision loss, this protocol contributes a valid test of a promising intervention for maintaining mental and physical health in this population.

PMID: 25812482 [PubMed - as supplied by publisher]