

Issue 15

Monday February 14 , 2011

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

Am J Kidney Dis. 2011 Feb 3. [Epub ahead of print]

Systemic and Kidney Toxicity of Intraocular Administration of Vascular Endothelial Growth Factor Inhibitors.

Pellé G, Shweke N, Duong Van Huyen JP, Tricot L, Hessaïne S, Frémeaux-Bacchi V, Hiesse C, Delahousse M.

Service de néphrologie-transplantation rénale, Hôpital Foch, Suresnes, France.

Abstract

Intravenous injection of angiogenesis-inhibitor drugs is used widely to treat cancers. Associated renal complications primarily involve proteinuria and hypertension, and thrombotic microangiopathies also have been described. Intravitreal anti-vascular endothelial growth factor (VEGF) therapy currently is used by ophthalmologists to treat neovascularization in age-related macular degeneration. However, there is some evidence that intravitreal anti-VEGF injections may result in systemic absorption, with the potential for injury in organs that are reliant on VEGF, such as the kidney. We report the first case to our knowledge of a patient who developed an acute decrease in kidney function, nonimmune microangiopathic hemolytic anemia with schistocytes, and thrombocytopenia after 4 intravitreal injections of ranibizumab. Light microscopy of a kidney biopsy specimen showed segmental duplications of glomerular basement membranes with endothelial swelling and several recanalized arteriolar thrombi. Because of the increasing use of intravitreal anti-VEGF agents, ophthalmologists and nephrologists should be aware of the associated risk of kidney disease. Early detection is crucial so that intravitreal injections can be stopped before severe kidney disease occurs.

PMID: 21295897 [PubMed - as supplied by publisher]

AAPS PharmSciTech. 2011 Feb 11. [Epub ahead of print]

Solution Formulation Development of a VEGF Inhibitor for Intravitreal Injection.

Marra MT, Khamphavong P, Wisniecki P, Gukasyan HJ, Sueda K.

Research Enabling Group, Pfizer Inc, 10777 Science Center Drive, San Diego, California, 92121, USA, michelle.marra@pfizer.com.

Abstract

PF-00337210 is a potent, selective small molecule inhibitor of VEGFRs and has been under consideration

for the treatment of age-related macular degeneration. An ophthalmic solution formulation intended for intravitreal injection was developed. This formulation was designed to maximize drug properties such that the formulation would precipitate upon injection into the vitreous for sustained delivery. As a parenteral formulation with additional constraints dictated by this specialized delivery route, multiple features were balanced in order to develop a successful formulation. Some of these considerations included low dosing volumes (=0.1 mL), a limited repertoire of safe excipients for intravitreal injection, and the unique physical chemical properties of the drug. The aqueous solubility as a function of pH was characterized, buffer stressing studies to select the minimal amount of buffer were conducted, and both chemical and physical stability studies were executed. The selected formulation consisted of an isotonic solution comprised of PF-00337210 free base in a citrate-buffered vehicle containing NaCl for tonicity. The highest strength for regulatory toxicology studies was 60 mg/mL. The selected formulation exhibited sufficient chemical stability upon storage with no precipitation, and acceptable potency and recovery through an intravitreal dosing syringe. Formulation performance was simulated by precipitation experiments using extracted vitreous humor. In simulated injection experiments, PF-00337210 solutions reproducibly precipitated upon introduction to the vitreous so that a depot was formed. To our knowledge, this is the first time that a nonpolymeric in situ-forming depot formulation has been developed for intravitreal delivery, with the active ingredient as the precipitating agent.

PMID: 21312012 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2011 Jan 11;5:81-5.

Freezing adversely affects measurement of vascular endothelial growth factor levels in human aqueous samples.

Balaiya S, Grover S, Murthy RK, Chalam KV.

Department of Ophthalmology, University of Florida College of Medicine, Jacksonville, FL, USA.

PURPOSE: Aqueous levels of vascular endothelial growth factor (VEGF) can be a surrogate marker of intraocular VEGF activity and a measure of efficacy of anti-VEGF treatment in a variety of vasoproliferative retinal disorders, including diabetic retinopathy, age-related macular degeneration, and central retinal vein occlusion. Measurement of the VEGF level may be adversely affected by premeasurement variables, such as freezing and delay, in sample analysis. We aim to evaluate the effect of storage and delayed measurement of human aqueous VEGF levels in these conditions.

METHODS: Aqueous samples collected from patients receiving intravitreal injection of bevacizumab for various retinal diseases were divided into two groups. In Group 1, the VEGF levels were analyzed on the same day; in Group 2, the VEGF levels were analyzed after 21 days of freezer storage (-80°C) using immunobead assay. Statistical comparison using a paired t-test was performed between the two groups.

RESULTS: Thirty-one aqueous humor samples were collected, and the VEGF concentration for fresh samples was 7.8 ± 5.9 pg/mL (mean $\pm$ SD) compared to 6.5 ± 6.0 pg/mL in frozen samples, resulting in a statistically significant difference ($P = 0.03$).

CONCLUSIONS: Accurate measurement of the VEGF level is a vital component of clinical decision-making. Delayed analysis of VEGF levels in aqueous samples may result in significant sample degradation and lower levels of measured VEGF.

PMID: 21311660 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2011 Feb 10. [Epub ahead of print]

Contrast sensitivity outcomes in the ABC trial. A randomized trial of bevacizumab for neovascular age-related macular degeneration.

Patel PJ, Chen FK, Da Cruz L, Rubin GS, Tufail A.

NIHR Biomedical Research Centre for Ophthalmology (Moorfields Eye Hospital and UCL Institute of Ophthalmology).

Purpose: To report the impact of intravitreal bevacizumab therapy on contrast sensitivity in patients with neovascular age-related macular degeneration (nAMD).

Methods: Prospective, multi-center, double-masked, randomized controlled trial of 131 patients with nAMD. Patients with nAMD and received intravitreal bevacizumab (n=65) or standard therapy (n=66) to the study eye with a 6 weekly cycle of assessment. Bevacizumab treatment was 1.25mg/0.05ml given as 3 initial treatments with further retreatment as needed using standardized retreatment criteria and one year (54 week) follow-up. Contrast sensitivity was determined during the study using a Pelli-Robson chart.

Results: At the week 54 examination, bevacizumab treated patients were more likely to gain at least 6 letters or more of contrast sensitivity than the patients receiving standard care (23 [35.4%] versus 10 [15.2%], $P = 0.009$). In addition the bevacizumab treated patients were less likely to lose 6 or more letters with a better mean letter change at week 54 than the patients receiving standard care (3 [4.6%] versus 14 [21.2%], and +4.0 versus -0.7 letters, respectively; $P < 0.05$ for both comparisons).

Conclusion: Consistent with the visual acuity outcomes, bevacizumab improved the chances of a clinically relevant gain in contrast sensitivity in the study population. Given the association between contrast sensitivity and visual disability, the beneficial effects of bevacizumab therapy on contrast sensitivity outcomes are expected to have a favourable impact on patients' daily activities.

PMID: 21310910 [PubMed - as supplied by publisher]

N Engl J Med. 2011 Feb 10;364(6):581-2.

Ranibizumab for age-related macular degeneration.

Trempe C.

Comment on:

N Engl J Med. 2010 Oct 21;363(17):1648-55.

PMID: 21306264 [PubMed - in process]

N Engl J Med. 2011 Feb 10;364(6):582.

Ranibizumab for age-related macular degeneration.

Cheng JW, Wei RL.

Comment on:

N Engl J Med. 2010 Oct 21;363(17):1648-55.

PMID: 21306263 [PubMed - in process]

Am J Ophthalmol. 2011 Feb 8. [Epub ahead of print]

Pharmacotherapy for Neovascular Age-Related Macular Degeneration: An Analysis of the 100% 2008 Medicare Fee-For-Service Part B Claims File.

Brechner RJ, Rosenfeld PJ, Babish JD, Caplan S.

Centers for Medicare and Medicaid Services, Woodlawn, Maryland.

PURPOSE: To describe the usage patterns of pharmacological treatments for neovascular age-related macular degeneration (AMD) in Medicare fee-for-service beneficiaries.

DESIGN: Retrospective review of all Medicare fee-for-service Part B claims for neovascular AMD during 2008.

METHODS: Medicare beneficiaries having undergone treatment were identified. The data collected for each visit for a given beneficiary included age, race, gender, Medicare region, state/zip code of residence, date of visit, whether or not the beneficiary had a treatment, the type and amount of drug, and dollars paid by Medicare. The main outcome measures were the number and rate of treatments, the types of drugs used for treatment, and the payments for these drugs.

RESULTS: Of the 222 886 unique beneficiaries, 146 276 (64.4%) received bevacizumab and 80 929 (35.6%) received ranibizumab. A total of 824 525 injections were performed with 480 025 injections of bevacizumab (58%) and 336 898 injections of ranibizumab (41%). National rates of injections per 100 000 fee-for-service Part B Medicare beneficiaries for bevacizumab and ranibizumab were 1506 and 1057, respectively. Total payments by Medicare were \$20 290 952 for bevacizumab and \$536 642 693 for ranibizumab. In 39 out of 50 states, the rate of injection was higher for bevacizumab compared with ranibizumab.

CONCLUSIONS: In 2008, bevacizumab was used at a higher rate than ranibizumab for the treatment of neovascular AMD. Even though bevacizumab accounted for 58% of all injections, Medicare paid \$516 million more for ranibizumab than bevacizumab. These data suggest that despite its off-label designation, intravitreal bevacizumab is currently the standard-of-care treatment for neovascular AMD in the United States.

PMID: 21310390 [PubMed - as supplied by publisher]

Other treatments & diagnosis

Am J Ophthalmol. 2011 Feb 3. [Epub ahead of print]

Subfoveal Retinal and Choroidal Thickness After Verteporfin Photodynamic Therapy for Polypoidal Choroidal Vasculopathy.

Maruko I, Iida T, Sugano Y, Saito M, Sekiryu T.

Department of Ophthalmology, Fukushima Medical University School of Medicine, Fukushima, Japan.

PURPOSE: To evaluate the morphologic retinal and choroidal changes after verteporfin photodynamic therapy (PDT) with and without ranibizumab for polypoidal choroidal vasculopathy using spectral-domain optical coherence tomography.

DESIGN: Retrospective, comparative series.

METHODS: The enhanced depth imaging optical coherence tomography technique was used in this retrospective, comparative series to measure the subfoveal retinal and choroidal thicknesses before and after treatment.

RESULTS: Twenty-seven eyes with polypoidal choroidal vasculopathy were examined retrospectively. Sixteen eyes were treated with PDT monotherapy (PDT group). Eleven eyes were treated with PDT after intravitreal ranibizumab injection (ranibizumab plus PDT group). The polypoidal lesions regressed in all cases at 3 months. The mean retinal thickness, including the retinal detachment, increased from 401 ± 157 μ m before treatment to 506 ± 182 μ m 2 days after PDT ($P < .001$) and decreased to 365 ± 116 μ m by 1 week after treatment ($P = .03$) and 265 ± 127 μ m by 6 months after treatment ($P < .001$). The mean choroidal thickness increased from 269 ± 107 μ m before treatment to 336 ± 96 μ m 2 days after PDT treatment ($P < .001$ compared with baseline) and decreased to 262 ± 96 μ m by 1 week after treatment ($P = .24$) and 229 ± 104 μ m by 6 months ($P < .001$). Although the choroidal thickness showed a similar trend with both therapies, the retinal thickness in the ranibizumab plus PDT group remained thinner than that in the PDT group until 6 months after treatment.

CONCLUSIONS: PDT was associated with decreased retinal and choroidal thicknesses. Combination therapy reduced the transient exudation after PDT in some cases, and monthly intravitreal ranibizumab injections maintained retinal thinning and seemed to improve vision better than PDT monotherapy.

PMID: 21295766 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2011 Jan 10;5:57-63.

Radiation therapy for neovascular age-related macular degeneration.

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Abstract

Antivascular endothelial growth factor (anti-VEGF) therapies represent the standard of care for most patients presenting with neovascular (wet) age-related macular degeneration (neovascular AMD). Anti-VEGF drugs require repeated injections and impose a considerable burden of care, and not all patients respond. Radiation targets the proliferating cells that cause neovascular AMD, including fibroblastic, inflammatory, and endothelial cells. Two new neovascular AMD radiation treatments are being investigated: epimacular brachytherapy and stereotactic radiosurgery. Epimacular brachytherapy uses beta radiation, delivered to the lesion via a pars plana vitrectomy. Stereotactic radiosurgery uses low voltage X-rays in overlapping beams, directed onto the lesion. Feasibility data for epimacular brachytherapy show a greatly reduced need for anti-VEGF therapy, with a mean vision gain of 8.9 ETDRS letters at 12 months. Pivotal trials are underway (MERLOT, CABERNET). Preliminary stereotactic radiosurgery data suggest a mean vision gain of 8 to 10 ETDRS letters at 12 months. A large randomized sham controlled stereotactic radiosurgery feasibility study is underway (CLH002), with pivotal trials to follow. While it is too early to conclude on the safety and efficacy of epimacular brachytherapy and stereotactic radiosurgery, preliminary results are positive, and these suggest that radiation offers a more durable therapeutic effect than intraocular injections.

PMID: 21311657 [PubMed - in process]

Genetics

Curr Eye Res. 2011 Feb 10. [Epub ahead of print]

Splicing Factor Polymorphisms, the Control of VEGF Isoforms and Association with Angiogenic Eye Disease.

Carter JG, Cherry J, Williams K, Turner S, Bates DO, Churchill AJ.

Unit of Ophthalmology, University of Bristol, Bristol, UK.

Purpose: Alternative splicing of the last exon (exon 8) of vascular endothelial growth factor (VEGF) pre-mRNA is a key element in the balance of pro- and anti-angiogenic VEGF isoforms in exudative age-related macular degeneration (exAMD) and proliferative diabetic retinopathy (PDR). Three splicing factors, SRp40, ASF/SF2, and SRp55 are predicted to control alternative splicing by binding to exonic splice enhancers (ESE) in VEGF exon 8. This pilot study examines whether there is an association between angiogenic eye disease and splicing factor polymorphisms, and whether there are sequence variations in the alternative splice sites of the VEGF gene.

Materials and Methods: A case:control pilot study comparing 163 individuals with angiogenic eye disease (94 exAMD and 69 PDR patients) with 95 age-matched controls. Splicing factor polymorphisms were genotyped by Restriction Fragment Length Polymorphism (RFLP) and sequencing, and the VEGF alternatively spliced region was assessed by denaturing High Performance Liquid Chromatography (dHPLC) using a transgenomic WAVE heteroduplex analyzer.

Results: No variations were observed in the alternatively spliced region of VEGF exon 8. ASF/SF2 polymorphisms showed no association with exAMD or PDR. For PDR, we observed a trend in SRp40 (rs6573908) where the 5136CC genotype was more frequent in controls ($p=0.0517$) and a significant association of the SRp55 (rs2235611), where the 2994C allele was more common in the PDR group ($p=0.03$). This remained strong, but not significant, after logistic regression for age, sex, disease type, and duration ($p=0.06$).

Conclusions: The lack of variation in the VEGF alternatively spliced region suggests the importance of sequence conservation in this area in maintaining the balance of pro- and anti-angiogenic VEGF isoforms. The link between PDR and the SRp55 2994 polymorphism suggests a disease-specific association between factors controlling VEGF splicing and ocular angiogenesis.

PMID: 21309690 [PubMed - as supplied by publisher]

Gene Ther. 2011 Feb 10. [Epub ahead of print]

Adenovirus-mediated delivery of CD46 attenuates the alternative complement pathway on RPE: implications for age-related macular degeneration.

Sweigard JH, Cashman SM, Kumar-Singh R.

1] Department of Ophthalmology and Neuroscience, Sackler School of Graduate Biomedical Sciences, Tufts University School of Medicine, Boston, MA, USA [2] Program in Cell, Molecular and Developmental Biology, Sackler School of Graduate Biomedical Sciences, Tufts University School of Medicine, Boston, MA, USA.

Abstract

Activation of the alternative pathway of the complement system has been implicated in the pathogenesis of age-related macular degeneration. Membrane attack complex (MAC) has been identified mainly on the Bruch's membrane and drusen underlying the retinal pigment epithelium (RPE). Membrane cofactor protein (CD46) preferentially regulates the alternative pathway of complement. The aim of this study was to evaluate the potential of increasing CD46 expression on RPE cells using an adenovirus as a gene therapy approach to reduce alternative pathway-mediated damage to RPE cells. We generated a recombinant adenovirus vector expressing human CD46 (hCD46) and delivered the vector to murine hepatocytes and RPE cells in vitro. After incubation in human serum in conditions in which the classical pathway of complement was blocked, we measured alternative pathway-mediated damage of these cells by quantifying lysis and MAC formation. Adenovirus expressing hCD46 was delivered to the subretinal space of adult mice, and 1 week later, ocular flat mounts were challenged with human serum and the levels of complement-mediated damage was quantified. Adenovirus-mediated delivery of hCD46 localizes to the basal and lateral surfaces of RPE cells where it offers protection from alternative pathway-mediated damage, but not classical, allowing the classical pathway to function unhindered. Gene Therapy advance online publication, 10 February 2011; doi:10.1038/gt.2011.6.

PMID: 21307887 [PubMed - as supplied by publisher]

Pathogenesis & epidemiology

Nature. 2011 Feb 6. [Epub ahead of print]

DICER1 deficit induces Alu RNA toxicity in age-related macular degeneration.

Kaneko H, Dridi S, Tarallo V, Gelfand BD, Fowler BJ, Cho WG, Kleinman ME, Ponicsan SL, Hauswirth WW, Chiodo VA, Karikó K, Yoo JW, Lee DK, Hadziahmetovic M, Song Y, Misra S, Chaudhuri G, Buaas FW, Braun RE, Hinton DR, Zhang Q, Grossniklaus HE, Provis JM, Madigan MC, Milam AH, Justice NL, Albuquerque RJ, Blandford AD, Bogdanovich S, Hirano Y, Witta J, Fuchs E, Littman DR, Ambati BK, Rudin CM, Chong MM, Provost P, Kugel JF, Goodrich JA, Dunaief JL, Baffi JZ, Ambati J.

1] Department of Ophthalmology & Visual Sciences, University of Kentucky, Lexington, Kentucky 40506, USA [2].

Abstract

Geographic atrophy (GA), an untreatable advanced form of age-related macular degeneration, results from retinal pigmented epithelium (RPE) cell degeneration. Here we show that the microRNA (miRNA)-processing enzyme DICER1 is reduced in the RPE of humans with GA, and that conditional ablation of Dicer1, but not seven other miRNA-processing enzymes, induces RPE degeneration in mice. DICER1 knockdown induces accumulation of Alu RNA in human RPE cells and Alu-like B1 and B2 RNAs in mouse RPE. Alu RNA is increased in the RPE of humans with GA, and this pathogenic RNA induces human RPE cytotoxicity and RPE degeneration in mice. Antisense oligonucleotides targeting Alu/B1/B2 RNAs prevent DICER1 depletion-induced RPE degeneration despite global miRNA downregulation. DICER1 degrades Alu RNA, and this digested Alu RNA cannot induce RPE degeneration in mice. These findings reveal a miRNA-independent cell survival function for DICER1 involving retrotransposon transcript degradation, show that Alu RNA can directly cause human pathology, and identify new targets for a major cause of blindness.

PMID: 21297615 [PubMed - as supplied by publisher]

J Vis Exp. 2011 Jan 23;(47). pii: 2455. doi: 10.3791/2455.

BMC Public Health. 2011 Feb 4;11(1):80. [Epub ahead of print]

Prevalence and progression of visual impairment in patients newly diagnosed with clinical type 2 diabetes: a 6-year follow up study.

de Fine Olivarius N, Siersma V, Juul Almind G, Vesti Nielsen N.

BACKGROUND: Many diabetic patients fear visual loss as the worst consequence of diabetes. In most studies the main eye pathology is assigned as the cause of visual impairment. This study analysed a broad range of possible ocular and non-ocular predictors of visual impairment prospectively in patients newly diagnosed with clinical type 2 diabetes.

METHODS: Data were from a population-based cohort of 1,241 persons newly diagnosed with clinical, often symptomatic type 2 diabetes aged 40 years or over. After 6 years, 807 patients were followed up. Standard eye examinations were done by practising ophthalmologists.

RESULTS: At diabetes diagnosis median age was 65.5 years. Over 6 years, the prevalence of blindness (visual acuity of best seeing eye ≤ 0.1) rose from 0.9% (11/1,241) to 2.4% (19/807) and the prevalence of moderate visual impairment (>0.1 ; <0.5) rose from 5.4% (67/1,241) to 6.7% (54/807). The incidence (95% confidence interval) of blindness was 40.2 (25.3-63.8) per 10,000 patient-years. Baseline predictors of level of visual acuity (age, age-related macular degeneration (AMD), cataract, living alone, low self-rated health, and sedentary life-style) and speed of continued visual loss (age, AMD, diabetic retinopathy (DR), cataract, living alone, and high fasting triglycerides) were identified.

CONCLUSIONS: In a comprehensive assessment of predictors of visual impairment, even in a health care system allowing self-referral to free eye examinations, treatable eye pathologies such as DR and cataract emerge together with age as the most notable predictors of continued visual loss after diabetes diagnosis. Our results underline the importance of eliminating barriers to efficient eye care by increasing patients' and primary care practitioners' awareness of the necessity of regular eye examinations and timely surgical treatment.

PMID: 21294871 [PubMed - as supplied by publisher]

J Alzheimers Dis. 2011 Feb 1. [Epub ahead of print]

Age-Related Macular Degeneration (AMD): Alzheimer's Disease in the Eye?

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Department of Ophthalmology, Kuopio University Hospital, Kuopio, Finland.

Abstract

Age-related macular degeneration (AMD) is a late-onset, neurodegenerative retinal disease that shares several clinical and pathological features with Alzheimer's disease (AD), including stress stimuli such as oxidative stress and inflammation. In both diseases, the detrimental intra- and extracellular deposits have many similarities. Aging, hypercholesterolaemia, hypertension, obesity, arteriosclerosis, and smoking are risk factors to develop AMD and AD. Cellular aging processes have similar organelle and signaling association in the retina and brain tissues. However, it seems that these diseases have a different genetic background. In this review, differences and similarities of AMD and AD are thoroughly discussed.

PMID: 21297256 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Feb 4. [Epub ahead of print]

The Effect of Bilateral Macular Scotomas from Age-related Macular Degeneration on Reach-to-grasp Hand Movement.

Timberlake GT, Omoscharka E, Quaney BM, Grose SA, Maino JH.

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Purpose. Vision plays a critical role in reaching and grasping objects. Consequently bilateral macular scotomas from Age-related Macular Degeneration (AMD) may affect reach-to-grasp movements. The purpose of this work was to investigate changes in reach-to-grasp movement dynamics and to relate those changes to the characteristics of subjects' Preferred Retinal Loci (PRL), scotomas, and visual acuities.

Methods. Three-dimensional positions of the index finger and thumb were recorded while subjects with bilateral scotomas and subjects with normal vision reached for and grasped blocks of three widths at two distances under binocular and monocular viewing conditions. Reach-dynamic parameters and the grip aperture (thumb-index finger distance) were calculated. Retinal locations and sizes of subjects' scotomas and PRLs were mapped with a Scanning Laser Ophthalmoscope. **Results.** Scotoma subjects' hand trajectories had longer movement durations, lower maximum velocities, and longer visual reaction times than controls. With monocular viewing Maximum Grip Aperture (MGA) increased as a function of block width at a significantly higher rate for scotoma subjects than controls. MGA decreased with increasing PRL bivariate normal ellipse area, and visual reaction time increased with decreasing acuity of the eye tested. **Conclusions.** In comparison to normally sighted subjects, subjects with bilateral macular scotomas from AMD have reach-to-grasp movements with longer trajectories, longer visual reaction times, lower velocities, and altered MGA-block width scaling. Visual reaction time and MGA are directly related to PRL

characteristics. Deficits in reach-to-grasp movement due to macular scotomas are greater in degree than those reported by others for real or artificial peripheral scotomas.

PMID: 21296817 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Feb 4. [Epub ahead of print]

Determinants of Macular Pigment Optical Density and its Relation to Age-Related Maculopathy -- Results from the Muenster Aging and Retina Study (MARS).

Dietzel M, Zeimer M, Heimes B, Claes B, Pauleikhoff D, Hense HW.

Institute of Epidemiology and Social Medicine, University Muenster, Germany;

Purpose: A protective effect of macular pigment (MP), consisting of lutein (L) and zeaxanthin (Z) in age related maculopathy (ARM) and its late stage, age-related macular degeneration (AMD) is controversially discussed. We investigated determinants of MP optical density (MPOD) and its relation to ARM.

Methods: We assessed MPOD at eccentricities of 0.5° and 2.0° from the fovea in 369 participants of the 2.6 year follow-up examination of the prospective Muenster Aging and Retina Study using dual-wavelength analysis of autofluorescence images. ARM was graded from standardized fundus photographs according to the International Classification System.

Results: MPOD at 0.5° and 2.0° between pairs and within single eyes were strongly correlated ($p < 0.001$). Smoking and body mass index showed moderately inverse associations with MPOD at 2.0° while age was positively related to MPOD at both eccentricities. Serum L, measured at the baseline examination, was significantly associated with MPOD measured at follow-up. Likewise, use of L/Z containing supplements raised MPOD. Crude mean MPOD increased with ascending stage of ARM. However, adjustment for influential factors and exclusion of L supplement users removed differences of mean MPOD between ARM stages. Considering further the accompanying eye, study eyes with ARM had significantly higher MPOD when the contralateral eye had AMD.

Conclusions: MPOD levels show a high degree of intra-individual concordance and inter-individual variability. Long-standing serum L levels, and in particular L supplementation, were the strongest determinants of MPOD. The hypothetical inverse association between MPOD and ARM stage was not confirmed.

PMID: 21296816 [PubMed - as supplied by publisher] Coll Antropol. 2010 Apr;34 Suppl 2:65-7.

The circulatory influence on development of age-related macular degeneration and hearing and equilibrium impairments.

Caljkusic-Mance T, Kovacevic D, Sepic T, Strenja-Linic I, Alpeza-Dunato Z, Vojnikovic B.

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Abstract

This study attempts to answer the question if any level of head and neck circulation takes a part in development of Age-Related Macular Degeneration (ARMD) and hearing and equilibrium impairments. Condition of large blood vessels was examined by Color-Doppler ultrasound, and carotid and ophthalmic arteries were included. The microcirculatory changes were examined directly by fundus photography and fluorescein angiography and indirectly testing hearing and equilibrium. The study group included 40 patients (21 females, 19 males) aging from 53 to 84 years with different stages of ARMD. The control group included 40 patients (18 females, 22 males) aging from 51 to 82 years without ARMD. Patients were inhabitants of Primorsko-Goranska County. There was no relationship between ARMD and condition of

large blood vessels because significant stenosis of carotid arteries was found in 2 patients (5%) in study group and 3 patients (7.5%) in the control group ($p > 0.05$). On the contrary, we found correlation between ARMD and hearing ($p = 0.0127$) and equilibrium impairments ($p = 0.0242$). Fluorescein angiograms shows raised number of ischemic retinal capillaries in patients with ARMD ($p = 0.0053$). Results lead to conclusion that circulatory disorders on microcirculatory level take a great part in development of ARMD and hearing and equilibrium impairments in the elderly. The key is damage of sensory cells of the retina and inner ear caused by microcirculatory disorders. Interesting data was noticed that 9 patients with more serious ARMD on one side of head had greater hearing loss on the same side. If we find a new treatment for microcirculatory disorders, maybe we can treat both sensory impairments in earlier stage.

PMID: 21302704 [PubMed - in process]

Coll Antropol. 2010 Apr;34 Suppl 2:57-9.

Epidemiological study of sun exposure and visual field damage in children in Primorsko-Goranska County--the risk factors of earlier development of macular degeneration.

Vojnikovic B, Synek S, Micovic V, Telezar M, Linsak Z.

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Abstract

The aim of this study was to examine the possible harmful effects of solar exposure on visual field damage in children living in Primorsko-Goranska County. Our previous work has shown noxious influence on visual field in children with anamnesis long term exposure to sunlight. This is an extended study, including children in Novi Vinodolski and Gorski kotar. We measured possible defect in isopterical visual field and macular-meridian thresholds. In the area of island of Rab these changes were the biggest, subsequently is Novi Vinodolski and at least Gorski kotar with the smallest range of eye complicates according to exposure to sunlight. These damages correlate with the areas of great solar emission. Damages in periphery isopters of visual field have shown the characteristics of periphery defect invagination, while increased macular thresholds in complete visual field was from 5 to 15Asb. We can conclude that there is direct connection between increased sunlight and long-term exposure to sunlight on one side, and on the other side, damages of retinal perception. Increased sun exposure may represent very important factors in early occurrence and develop of Age-Related Macular Degeneration (AMD). It is recommended the children protection in summer months, as well as taking derivatives of vitamin A and antioxidants. Nowadays, AMD is one of the most important causes of damaged visual field, pretend to be national problem if we don't use the adequate prevention. World Health Organization has to begin with prevention of AMD, including these risk factors.

PMID: 21302703 [PubMed - in process]

Coll Antropol. 2010 Apr;34 Suppl 2:25-8.

Epidemiology and quality of life of patients with age-related macular degeneration.

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Abstract

It is well known that age-related macular degeneration (AMD), besides glaucoma and diabetic retinopathy, represents a major cause of low vision and blindness throughout the world. In this study, specific causal factors of AMD are analyzed, emphasizing the causal role and effects of sunlight, no matter which part of its

spectrum, in a longer exposition through life. The accent is also put on the influence of lifestyle as well as vitamin and antioxidants supplementation in development or prevention of AMD.

PMID: 21302701 [PubMed - in process]

Coll Antropol. 2010 Apr;34 Suppl 2:5-8.

Benedictine monastery on the Island of Rab hides the mystery of sunlight influence on development of macular degeneration (AMD). Is a harmful sunlight, risk factor or cause of macular degeneration?

Vojnikovic B, Vojnikovic D.

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Abstract

Benedictine Monastery of St. Andrew is probably the oldest existing Benedictine monastery in this area. According to hundreds of years of legend, it was founded in 1018 year. In clinical examination about the possibility of the macular degeneration occurrence in 15 Benedictine sisters, we found the age-related macular degeneration (AMD) in two cases only. In 13 other sisters aging 27, 60, 67years, the fundus picture was like in a baby, vision, visual field and meridian thresholds were normal. What is the explanation for this phenomenon? Two sisters with AMD work and live as the farm workers, but the other sisters live in closed monastery with very low natural sunlight, approximately 300-500 lx. In conclusion, the earlier author's experimental and clinical works follow the consequence that without exposure of eyes to harmful higher doses of sunlight, it is not possible to develop AMD. The harmful cumulative dose of sunlight is not the risk factor but the cause, including the inheritance, for AMD development.

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Dissection of human vitreous body elements for proteomic analysis.

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Abstract

The vitreous is an optically clear, collagenous extracellular matrix that fills the inside of the eye and overlies the retina. (1,2) Abnormal interactions between vitreous substructures and the retina underlie several vitreoretinal diseases, including retinal tear and detachment, macular pucker, macular hole, age-related macular degeneration, vitreomacular traction, proliferative vitreoretinopathy, proliferative diabetic retinopathy, and inherited vitreoretinopathies. (1,2) The molecular composition of the vitreous substructures is not known. Since the vitreous body is transparent with limited surgical access, it has been difficult to study its substructures at the molecular level. We developed a method to separate and preserve these tissues for proteomic and biochemical analysis. The dissection technique in this experimental video shows how to isolate vitreous base, anterior hyaloid, vitreous core, and vitreous cortex from postmortem human eyes. One-dimensional SDS-PAGE analyses of each vitreous component showed that our dissection technique resulted in four unique protein profiles corresponding to each substructure of the human vitreous body. Identification of differentially compartmentalized proteins will reveal candidate molecules underlying various vitreoretinal diseases.

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Distribution of age-related macular degeneration in Primorsko-Goranska County.

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Abstract

The aim of this study is to show what part of our County has the most population with age-related macular degeneration (ARMD) and how some types frequently appear in same parts. The County includes 3 different geographic areas: Gorski Kotar, Coast and Islands. ARMD is the leading cause of visual impairment and blindness in developed countries. There are two categories of ARMD: atrophic or "dry" ARMD and exudative or "wet" ARMD. Our epidemiological study group includes 60 patients (33 females, 27 males) with both types of ARMD and they mostly spent their life times in our County. Patients were examined and treated in our Clinic during 2008 and 2009. We also examined which contribution factor (age, genetics, UV-exposure, diet, iris and macular pigment) is more common and found a links with occupation, residence and habits. Our study shows that ARMD in our County is most frequent in interval of 61-80 years. Incidence of ARMD is mild increased in female (55%). Significant incidence of ARMD is connected with patients who work outdoor more than 5 hours daily (70 %). There were no significant difference between patients in different areas[-Gorski Kotar and Coast ($p = 0.9260$), Gorshi Kotar and Islands ($p = 0.8382$) and Coast and Islands ($p = 0.8546$) connected with occupations. Regions Coast and Islands had more cases of ARMD than Gorski Kotar, but in Gorski Kotar patients had greater percent of "wet" type. Difference is statistically significant between areas Gorski Kotar and Islands ($\chi^2 = 4.675$, $p = 0.0306$). Also, there were statistically significant difference in nutrition between Gorski Kotar and Islands ($\chi^2 = 4.17$, $p = 0.0411$). Incidence of ARMD is related with less iris and macular pigment--47 patients (77%). There was an increased risk for exudative type in Trsce and Cabar in Gorski Kotar

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Solar spectral lines ("solar halo")--healing or harmful for the retina?

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Abstract

The sungazing method has been known for thousands of years as healing method based on chromotherapeutic principle. Our examinations on the island of Rab show that it is acceptable only if applied 10 min before the sunset. Gazing has to be directed towards the green-yellow part of the spectrum, since the remaining part of the sun halo contains harmful energy. However, authors suggest that it would be preferable to use spectacles with medical filters transmitting wavelight of green-yellow colour, especially for treatment of macular degeneration.

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Coll Antropol. 2010 Apr;34 Suppl 2:1-3.

Medical perspective: macular degeneration (AMD) and human sight in the future.

Vojnikovic B.

Abstract

The author concisely presents the results of his 30-year investigations about the harmful influence of the higher sun radiation on the eyes. The investigations were carried out among the population of the Island of Rab, situated in the northern part of the Adriatic sea. This geographical region has been characterized by higher doses of the global sun radiation compared with the remaining part of the Republic of Croatia, and partly with the rest of the Mediterranean. The author proved it by his own measurements of UV-B, UV-A and the global sun radiation. The number of the diseased from the macular degeneration (AMD), cataract and precancerous pterygium has been significantly increased in those inhabitants being more exposed to the sun radiation. Investigating the retinal threshold, of the macula and peripherally--meridian thresholds, even the children more exposed to the sun radiation without protection, are established to have the increased excitation threshold of the retina, making later the basis and risk factor for the earlier AMD development. The author also points out that the periphery of retina and the macula are damaged in AMD. Later stages of macular degeneration transfer to the clinical form of the optic nerve atrophy. The author pathohistologically proved that the whole retina has been degeneratively involved in AMD, not only the photoreceptors and the retinal pigment. Therefore, the author pleads for the idea of children protection from the higher sun radiation to become a national problem of each country, and the coordination must be with the World Health Organization (WHO).

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Chromotherapy of macular degeneration with transitions lenses and green-yellow medical filters and special programme for psychoorganic disturbances.

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Abstract

Optical spectrum of the sunlight consists of visible or chromatic spectrum, with the range of wavelengths of electromagnetic vibrations from 7700 to 3900 AU, and the invisible spectrum: infrared and ultraviolet. Chromatic spectrum gives rise to the sensation of colour, capable for simulating specialized retinal photoreceptors and is perceptible as light. This rule of perception of the particular range of the optical spectrum goes mainly for man, while particular deviations, more or less, are applicable to the rest of animal and plant life. The optical part of the spectrum belongs to nonionizing radiation. It created the life on the Earth, maintaining it nowadays and even threatening the human organ of vision, because the retina had not been yet adequately accommodated through evolution with its photoreactive metabolism. Human retina is very sensitive about possible harmful influence of ultraviolet and blue light even today in evolution, but also phototoxic on complete strong visible light. In their clinical and experimental work on animals, the authors prove with their own patent (P 20020077A)-Vojnikovic B&D, and in collaboration with Essilor Optic Austria GmbH, that particular medical filters in the range of green-yellow colour especially (565 to 570 nm), and in combination with "Transitions" successfully threat macular degeneration-AMD, slowing down its progression and having positive psychoorganic effect on the depressive mood of such patients with threatened sight. Full attention has been paid to the design of medical filter, so the periphery of the lens plays a positive role in blood concentration of melatonin, while the central part stimulates the sight and the concentration of serotonin. Thus the physiological balance of melatonin and serotonin and the stability of psychophysical disturbances have been achieved.

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Coll Antropol. 2010 Apr;34 Suppl 2:45-8.

What associates Charles Bonnet syndrome with age-related macular degeneration?

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Abstract

Charles Bonnet syndrome (CBS) is a condition related to patients with visual loss due to age related macular degeneration or glaucoma that are having complex visual hallucinations. The CBS was first described by Swiss physician Charles Bonnet in 1760. Affected patients, who are otherwise mentally healthy people with significant visual loss, have vivid, complex recurrent visual hallucinations (VHs). One characteristic of these hallucinations is that they usually are "Lilliputian hallucinations" as patients experience micropsia (hallucinations in which the characters or objects are distorted and much smaller than normal). The prevalence of Charles Bonnet Syndrome has been reported to be between 10% and 40%; a recent Australian study has found the prevalence to be 17.5%. The high incidence of non-reported CBS is thought to be as a result of patient's fear to report the symptoms as they could be labeled as mentally insane since those type of visual hallucinations could be found in variety of psychiatric and neurological disorders such as drug or alcohol abuse (delirium tremens), Alice in Wonderland syndrome (AIWS), psychosis, schizophrenia, dementia, narcolepsy, epilepsy, Parkinson disease, brain tumors, migraine, as well as, in long term sleep deprivation. VHs can also be presented as the initial sign of the Epstein-Barr virus infection in infectious mononucleosis. Patients who suffer from CBS usually possess insight into the unreality of their visual experiences, which are commonly pleasant but may sometimes cause distress. The hallucinations consist of well-defined, organized, and clear images over which the subject has little control. It is believed that they represent release phenomena due to deafferentation of the visual association areas of the cerebral cortex, leading to a form of phantom vision. Cognitive defects, social isolation, and sensory deprivation have also been implicated in the etiology of this condition. This study was conducted on 350 patients diagnosed with Age-Related Macular Degeneration (AMD) and shows incidence of CBS in 13% of patients with AMD. Furthermore, we have found higher incidence of CBS in patients with massive loss of vision in peripheral visual field which is not age related.

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Computational Quantification of Complex Fundus Phenotypes in Age-Related Macular Degeneration and Stargardt's Disease.

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Purpose. To describe an automated method for quantification of specific fundus phenotypes and evaluate its performance to differentiate drusen, the hallmark lesions of age-related macular degeneration (AMD), from similar-looking bright lesions, the pisciform deposits or "flecks", typical for Stargardt disease (SD).

Methods. Fundus macular images, from thirty eyes of thirty subjects, were studied. Fifteen subjects had a clinical diagnosis of AMD with at least 10 intermediate and/or 1 large drusen, and the other fifteen had SD. As a test of bright lesion separation, AMD and SD subjects were chosen from the heterogeneous phenotypes of each disorder, to be as visually similar as possible. Drusen and fleck properties were quantified from the color images using an automated method, and a shape classifier was used to divide the images as characteristic of either AMD or SD. Image membership performance was quantified using area under the Receiver Operating Characteristics curve (AUC).

Results. All SD subjects demonstrated at least one disease-associated variant of the ABCA4 gene. The method achieved an AUC of 0.936 for differentiating AMD from SD.

Conclusions. Automated quantification of fundus phenotypes was achieved, and the results show that our method can differentiate AMD from SD subjects, two distinctly different genetically-associated disorders, by quantifying the properties of the bright lesions (drusen and flecks) in their fundus images, even when the images were visually selected to be similar. Quantification of fundus phenotypes may allow recognition of new phenotypes, correlation with new genotypes, and may measure disease-specific biomarkers to improve management of patients with AMD and SD.

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Interactive expressions of HtrA1 and VEGF in human vitreous humors and fetal RPE cells.

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Purpose: High temperature requirement factor A1 (HtrA1) is associated with exudative age-related macular degeneration (AMD), an angiogenic retinal disease related to vascular endothelial growth factor (VEGF). This study investigates the interactive relationship between the expressions of HtrA1 and VEGF.

Methods: The vitreous humor levels of HtrA1, VEGF and PEDF were determined in 55 unrelated Han Chinese patients who underwent ocular surgeries. Expressions of HTRA1 and VEGFA were studied interactively and under stress conditions in primary human fetal retinal pigment epithelial (RPE) cells to evaluate their regulations.

Results: Vitreous levels of HtrA1 were significantly associated with that of VEGF in vitreous samples from all patients (Pearson's correlation coefficient test; $r = 0.650$, $p = 7.91 \times 10^{-8}$) and from patients with retinal detachment ($r = 0.835$, $p = 2.14 \times 10^{-7}$). Upon stress induction, HTRA1 and VEGFA were upregulated in human fetal RPE cells treated by tunicamycin and dithiothreitol (DTT), but reduced after treatment by MG132. However, HtrA1 and VEGF did not regulate each other in their expressions.

Conclusions: Our results revealed an association between HtrA1 and VEGF in human vitreous humors and RPE cells. They are both related to stress and inflammatory conditions.

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Prevalence and Risks Factors of Age-Related Macular Degeneration in Oklahoma Indians The Vision Keepers Study.

Butt AL, Lee ET, Klein R, Russell D, Ogola G, Warn A, Kingsley RM, Yeh J.

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OBJECTIVE: To determine the prevalence of age-related macular degeneration (AMD) and to identify its risk factors in an Oklahoma Indian population.

DESIGN: Cross-sectional study design.

PARTICIPANTS: Included 1019 Oklahoma Indians who participated in baseline and second examinations

of the Strong Heart Study.

METHODS: Retinal photographs of at least 1 eye were obtained and graded for AMD by the University of Wisconsin Ocular Epidemiology Reading Center. Retinal photographs of 986 participants were considered gradable and were included in the study.

MAIN OUTCOME MEASURES: Age-related macular degeneration (early and late).

RESULTS: The overall prevalence of AMD in the study was 35.2%, including a prevalence of 0.81% for late AMD. The prevalence of early AMD increased from 30.6% in those aged 48 to 59 years to 46.1% in those 70 to 82 years of age. When potential risk factors were analyzed individually (univariate analyses), men with hypertension had a significantly higher prevalence of AMD ($P = 0.02$) than those without hypertension. In women, high-density lipoprotein cholesterol and sun exposure were associated positively with the prevalence of AMD ($P = 0.01$), whereas a history of using multivitamins was associated with lower AMD prevalence ($P = 0.005$). When multiple risk factors were analyzed simultaneously using logistic regression, only age showed significant association with AMD in both men ($P = 0.02$) and women ($P < 0.0001$) and was the only significant risk factor in men. In women, multivitamin use and total cholesterol had a significant inverse association with AMD, whereas sun exposure and high-density lipoprotein cholesterol had a positive association. When men and women were combined, age and high-density lipoprotein cholesterol had significant positive associations, whereas total cholesterol, multivitamin use, and current alcohol use showed a significant inverse association with AMD.

CONCLUSIONS: This study was the first to report a detailed prevalence of AMD in Oklahoma Indians and its risk factors. The prevalence seemed to be relatively high compared with that in other ethnic groups. Some of the modifiable risk factors identified confirmed previous findings and can be used to design preventive programs to reduce the burden of AMD, although longitudinal data are still needed.

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NBHA Reduces Acrolein-Induced Changes in ARPE-19 Cells: Possible Involvement of TGF?

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Purpose: Acrolein, a toxic, reactive aldehyde formed metabolically and environmentally, has been implicated in the damage to and dysfunction of the retinal pigment epithelium (RPE) that accompanies age-related macular degeneration (AMD). Our purpose was to investigate the potential of acrolein to influence the release of transforming growth factor beta-2 (TGF β 2) and vascular endothelial growth factor (VEGF), to assess the ability of N-benzylhydroxylamine (NBHA) to prevent the effect of acrolein on cytokine release and reduction of viable cells, and to explore the pathway by which acrolein might be causing the increase of VEGF.

Materials and Methods: Confluent ARPE-19 cells were treated with acrolein and/or NBHA. They were also pretreated with SIS3, a specific inhibitor of SMAD 3, and ZM39923, a JAK3 inhibitor, before being treated with acrolein. Viable cells were counted; ELISA was used to measure the TGF β 2 and/or VEGF in the conditioned media.

Results: Acrolein was shown to reduce the number of viable ARPE-19 cells and to upregulate the release of the proangiogenic cytokines TGF β 2 and VEGF. Co-treatment with 200 μ M NBHA significantly reduced the effects of acrolein on viable cell number and TGF β 2 release. Pretreatment of the cells with SIS3 partially blocked the action of acrolein on decreased viable cell number and VEGF upregulation, suggesting that part of the effects of acrolein are mediated by the increased levels of TGF β and its signaling.

Conclusions: Our results suggest that the action of acrolein on the reduction of viability and VEGF increase

by ARPE-19 cells is partially mediated by TGF β 2. By reducing the effects of acrolein, NBHA and SIS3 could be potential pharmacological agents in the prevention and progression of acrolein-induced damage to the RPE that relates to AMD.

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Diet

Sci Transl Med. 2011 Feb 9;3(69):69ra12.

5-Lipoxygenase Metabolite 4-HDHA Is a Mediator of the Antiangiogenic Effect of ω -3 Polyunsaturated Fatty Acids.

Sapieha P, Stahl A, Chen J, Seaward MR, Willett KL, Krah NM, Dennison RJ, Connor KM, Aderman CM, Licican E, Carughi A, Perelman D, Kanaoka Y, Sangiovanni JP, Gronert K, Smith LE.

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Abstract

Lipid signaling is dysregulated in many diseases with vascular pathology, including cancer, diabetic retinopathy, retinopathy of prematurity, and age-related macular degeneration. We have previously demonstrated that diets enriched in ω -3 polyunsaturated fatty acids (PUFAs) effectively reduce pathological retinal neovascularization in a mouse model of oxygen-induced retinopathy, in part through metabolic products that suppress microglial-derived tumor necrosis factor- α . To better understand the protective effects of ω -3 PUFAs, we examined the relative importance of major lipid metabolic pathways and their products in contributing to this effect. ω -3 PUFA diets were fed to four lines of mice deficient in each key lipid-processing enzyme (cyclooxygenase 1 or 2, or lipoxygenase 5 or 12/15), retinopathy was induced by oxygen exposure; only loss of 5-lipoxygenase (5-LOX) abrogated the protection against retinopathy of dietary ω -3 PUFAs. This protective effect was due to 5-LOX oxidation of the ω -3 PUFA lipid docosahexaenoic acid to 4-hydroxy-docosahexaenoic acid (4-HDHA). 4-HDHA directly inhibited endothelial cell proliferation and sprouting angiogenesis via peroxisome proliferator-activated receptor γ (PPAR γ), independent of 4-HDHA's anti-inflammatory effects. Our study suggests that ω -3 PUFAs may be profitably used as an alternative or supplement to current anti-vascular endothelial growth factor (VEGF) treatment for proliferative retinopathy and points to the therapeutic potential of ω -3 PUFAs and metabolites in other diseases of vasoproliferation. It also suggests that cyclooxygenase inhibitors such as aspirin and ibuprofen (but not lipoxygenase inhibitors such as zileuton) might be used without losing the beneficial effect of dietary ω -3 PUFA.

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