

Issue 317

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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Drug treatment

Retina. 2017 Feb 17. [Epub ahead of print]

LONG-TERM REMISSION OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION WITH AS-NEEDED ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY.

Muftuoglu IK, Alam M, You QS, Gaber R, Ramkumar HL, Mendoza N, Meshi A, Freeman WR.

PURPOSE: To determine the presenting characteristics of patients with neovascular age-related macular degeneration with long-term remission (LTR), which was defined as the absence of intraretinal/subretinal fluid, or hemorrhage, and absence of leakage on fluorescein angiography for longer than 6 months while on as-needed antivascular endothelial growth factor treatment.

METHODS: The presenting characteristics of patients with LTR were compared with a control group including 32 eyes of 28 age-, gender-, and ethnicity-matched patients who did not achieve LTR.

RESULTS: Seventy-four percent of patients in the LTR group had Type 1 choroidal neovascular membrane and 18.5% had retinal angiomatous proliferation. In the control group, 28 eyes had Type 1 choroidal neovascular membrane (87.5%), and none of the patients had retinal angiomatous proliferation; overall, there was a significant difference in lesion types between the 2 groups ($P = 0.036$). Eyes with LTR at presentation had significantly thinner subfoveal choroidal thickness (147 vs. 178 μm , $P = 0.04$). There was more intraretinal fluid and less subretinal fluid at the presentation in the remission group (59.3% intraretinal fluid and 11.1% subretinal fluid) compared with the control group (28.1% intraretinal fluid and 34.4% subretinal fluid, $P = 0.03$).

CONCLUSION: The presence of retinal angiomatous proliferation, thinner choroidal thickness, more intraretinal fluid, and less subretinal fluid at presentation were associated with LTR in patients receiving as-needed treatment for age-related macular degeneration.

PMID: 28221254

Graefes Arch Clin Exp Ophthalmol. 2017 Feb 18. [Epub ahead of print]

Ranibizumab versus aflibercept for macular edema due to central retinal vein occlusion: 18-month results in real-life data.

Chatziralli I, Theodossiadis G, Moschos MM, Mitropoulos P, Theodossiadis P.

PURPOSE: The objective of this study was to compare the anatomical and functional outcomes of

ranibizumab versus aflibercept for the treatment of macular edema due to central retinal vein occlusion (CRVO) in routine clinical practice.

METHODS: Participants in this observational study included 62 treatment-naïve patients with CRVO who received intravitreal injections of either ranibizumab or aflibercept. The demographic data, best-corrected visual acuity (BCVA) and spectral-domain optical coherence tomography (SD-OCT) characteristics were evaluated at baseline and at months 1, 2, 3, 6, 12 and 18 post-treatment.

RESULTS: At month 18, the mean BCVA of ranibizumab-treated eyes increased 7.9 letters, compared to 7.4 letters for eyes receiving aflibercept, with a similar number of injections. There was no statistically significant difference between the two groups in letters or in central subfield thickness at month 18. At the end of the follow-up, 50% of patients in the ranibizumab group and 42.9% in the aflibercept group showed complete resolution of macular edema.

CONCLUSIONS: Ranibizumab and aflibercept demonstrated similar anatomical and functional outcomes over 18-month follow-up in patients with macular edema due to CRVO, with a similar number of injections.

PMID: 28214955

Ophthalmologe. 2017 Feb 20. [Epub ahead of print]

[Adjuvant radiotherapy during anti-VEGF in neovascular age-related macular degeneration]. [Article in German]

Rating P, Freimuth MA, Stuschke M, Bornfeld N.

Abstract: Single adjuvant radiotherapy during anti-VEGF therapy could be in certain indications an alternative to the gold standard of sole intravitreal anti-VEGF drug injection in neovascular age-related macular degeneration. First clinical trials showed efficacy due to reduction of anti-VEGF injection numbers by 100 kV collimated beam radiotherapy. After consideration and performance of adjuvant radiotherapy, results of the course should be centrally registered in order to carry out further analysis.

PMID: 28220249

BMC Ophthalmol. 2017 Feb 20;17(1):16.

Pseudophakic cystoid macular edema prevention and risk factors; prospective study with adjunctive once daily topical nepafenac 0.3% versus placebo.

McCafferty S, Harris A, Kew C, Kassm T, Lane L, Levine J, Raven M.

BACKGROUND: Define the effectiveness of a topical non-steroidal anti-inflammatory drug (NSAID) added to topical steroid use after uncomplicated phacoemulsification for the prevention of pseudophakic cystoid macular edema (PCME) using a prospective, randomized, double-masked, placebo-controlled clinical study.

METHODS: Eyes (1000) were randomized to placebo (497) or nepafenac 0.3% (503) used once daily, post-operatively for 5 weeks at two ophthalmology clinics. Diagnosis of PCME was made by clinical, ocular coherence tomography (OCT), and with fluorescein angiography confirmation. Correlation of PCME to NSAID use and the presence of pre-operative risk factors for PCME were assessed including, contralateral PCME, diabetic retinopathy, retinal vein occlusion, macular hole, epiretinal membrane, macular degeneration, retinal detachment repair, and prostaglandin use.

RESULTS: PCME was the most common complication associated with routine cataract surgery (4.2% with PCME risk factors, 2.0% with risk factors excluded). Topical nepafenac 0.3% significantly reduces the

incidence of PCME compared to placebo when used after routine cataract surgery ($p = .0001$). When patients with pre-operative risk factors are excluded, the incidence of PCME between treatment and placebo groups is equivalent ($p = 0.31$). PCME relative risk (RR) was most significant in contralateral PCME (RR 19.5), diabetic retinopathy (RR 13.1), retinal vein occlusion (RR 12.9), macular hole (RR 7.7), and epiretinal membrane (RR 5.7). Prostaglandin use and previous retinal detachment were not shown to increase risk.

CONCLUSION: Pseudophakic cystoid macular edema is common after phacoemulsification cataract surgery. Topical nepafenac 0.3% reduces PCME in patients with pre-operative risk factors for PCME compared to placebo but shows no benefit in patients without pre-operative risk factors.

PMID: 28219426 PMCID: PMC5319126

Ophthalmologica. 2017 Feb 24. [Epub ahead of print]

One-Year Outcomes of 1 + pro re nata versus 3 + pro re nata Intravitreal Aflibercept Injection for Neovascular Age-Related Macular Degeneration.

Takayama K, Kaneko H, Sugita T, Maruko R, Hattori K, Ra E, Kawano K, Kataoka K, Ito Y, Terasaki H.

PURPOSE: We compared 1-year outcomes of 1 + pro re nata (PRN) versus 3 + PRN of intravitreal aflibercept injection (IAI) for age-related macular degeneration (AMD).

METHODS: Forty-two eyes with naïve AMD received 3 + PRN IAI treatment and 47 eyes with naïve AMD received 1 + PRN IAI treatment. Visual acuity (VA), central retinal thickness (CRT), and central choroidal thickness (CCT) and number of administered IAIs during 12 months were compared.

RESULTS: VAs improved, and CRTs reduced significantly at any given month from baseline in both groups ($p < 0.01$, respectively). CCT reduced significantly at 3 months in the 3 + PRN group ($p = 0.024$) but not in the 1 + PRN group. The 1 + PRN group received fewer injections than the 3 + PRN group ($p < 0.01$).

CONCLUSIONS: Aflibercept leads to equivalent VA and morphologic retinal improvement without administering 3 injections.

PMID: 28231566

Ophthalmology. 2017 Mar;124(3):e31-e32.

Re: Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group, et al.: Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials (Ophthalmology 2016;123:1751-1761).

Gillies MC, Daien V, Nguyen V, Barthelmes D.

PMID: 28219517

Clin Ophthalmol. 2017 Feb 7;11:303. eCollection 2017.

Erratum: A single-arm, investigator-initiated study of the efficacy, safety, and tolerability of intravitreal aflibercept injection in subjects with exudative age-related macular degeneration previously treated with ranibizumab or bevacizumab (ASSESS study): 12-month analysis [Corrigendum].

[No authors listed]

Abstract:[This corrects the article on p. 1759 in vol. 9, PMID: 26445522.].

Erratum for: A single-arm, investigator-initiated study of the efficacy, safety, and tolerability of intravitreal aflibercept injection in subjects with exudative age-related macular degeneration previously treated with ranibizumab or bevacizumab (ASSESS study): 12-month analysis. [Clin Ophthalmol. 2015]

PMID: 28223773 PMCID: PMC5304975

Arch Soc Esp Oftalmol. 2017 Feb 15. [Epub ahead of print]

The diabetic retinopathy clinical research network analysis of the cost-effectiveness of aflibercept, bevacizumab and ranibizumab for the treatment of diabetic macular oedema and its application in Spain. [Article in English, Spanish]

Navarro-Navarro A, Salom D, Martínez-Toldos JJ, Udaondo P, Fernández-Martínez C, Gutiérrez-Arias L, Hervás A, Rodrigo R.

PMID: 28215618

Ophthalmology. 2017 Mar;124(3):e25-e26.

Re: Wells et al.: Aflibercept, Bevacizumab, or Ranibizumab for diabetic macular edema: Two-year results from a comparative effectiveness randomized clinical trial (Ophthalmology 2016;123:1351-1358).

Tornambe P.

PMID: 28219508

Other treatment & diagnosis

Conf Proc IEEE Eng Med Biol Soc. 2016 Aug;2016:6006-6009.

Wearable diagnostic system for age-related macular degeneration.

Mohaghegh N, Zadeh EG, Magierowski S, Mohaghegh N, Zadeh EG, Magierowski S, Mohaghegh N, Zadeh EG, Magierowski S.

Abstract: This paper presents a novel head-mounted point-of-care diagnostic system for detection and continuous monitoring of Age-related Macular Degeneration (AMD). This wearable embedded open-source platform enables accurate monitoring of AMD by taking advantage of multiple standard graphical interface techniques such as Amsler Grid, Threshold Amsler Grid, Macular Computerized Psychophysical Test and Preferential Hyperacuity Perimeter (PHP). Here, we describe the proposed multi-Grid or so-called NGRID software and elaborate on the hardware prototype. This prototype includes a commercially available Oculus HMD incorporated with a single board computer. As the first step towards a fully integrated wearable system, this paper successfully proves the functionality of head-mounted graphical interface device ready for a live demonstration. Participants can experience this device and take a 10-minute AMD eye-exam. Furthermore, NGRID has been approved and permitted for an in-hospital clinical trial.

PMID: 28227879

Optom Vis Sci. 2017 Mar;94(3):423-431.

Outer Retinal Tubulation: A Case Series.

Rousso LA, Rodman JA, Sutton B, Shechtman DL.

PURPOSE: The advent of spectral domain optical coherence tomography has led to superb imaging capabilities in addition to enhanced visualization of the retinal layers. Such advancements have led to the identification of a variety of new retinal conditions, including outer retinal tubulations (ORTs). ORTs are ovoid hyporeflective spaces located in the outer retina. The pathogenesis is unclear but seems to involve sublethal injury to the photoreceptors leading to a compensatory reorganization of the photoreceptor layer with the neighboring ellipsoid zone resulting in a hyperreflective border surrounding a central lumen. Most ORTs have been linked to wet age-related macular degeneration; however, these peculiar structures are now seen in a myriad of retinal disorders.

CASE REPORTS: Our cases will highlight the wide variety of clinical presentations associated with outer retinal tubulations. The clinical presentations include two cases of wet age-related macular degeneration, a case of presumed ocular histoplasmosis syndrome, a case of central areolar choroidal dystrophy, and a case of pathological myopia.

CONCLUSIONS: By correctly differentiating outer retinal tubulations from other masqueraders, unnecessary referrals and interventions can be minimized. Understanding the various disease entities associated with outer retinal tubulation could give further insight into the mechanism and formation of these structures.

PMID: 28225373

Retina. 2017 Feb 17. [Epub ahead of print]

EVALUATION OF MACULAR ISCHEMIA IN EYES WITH BRANCH RETINAL VEIN OCCLUSION: An Optical Coherence Tomography Angiography Study.

Kadomoto S, Muraoka Y, Ooto S, Miwa Y, Iida Y, Suzuma K, Murakami T, Ghashut R, Tsujikawa A, Yoshimura N.

PURPOSE: To quantitatively assess macular morphology and perfusion status using optical coherence tomography, and optical coherence tomography angiography in eyes with branch retinal vein occlusion when macular edema has completely resolved, and to investigate the impact on visual function.

METHODS: Thirty consecutive eyes with branch retinal vein occlusion-macular edema that resolved after treatment with intravitreal ranibizumab injections were included. Macular sensitivity was measured by microperimetry; defect length of foveal ellipsoid zone band was measured using optical coherence tomography; foveal avascular zone and parafoveal nonperfusion areas (NPA) were measured by optical coherence tomography angiography.

RESULTS: The logarithm of minimum angle of resolution visual acuity was significantly associated with the defect length of the foveal ellipsoid zone band ($P = 0.005$), the parafoveal NPA in the superficial capillary plexus ($P = 0.007$), and the parafoveal NPA in the deep capillary plexus ($P = 0.006$). Macular sensitivity correlated with parafoveal thickness on the affected side ($P = 0.034$), the defect length of the foveal ellipsoid zone band ($P = 0.048$), parafoveal NPA in the superficial capillary plexus ($P = 0.008$), and parafoveal NPA in the deep capillary plexus ($P = 0.012$). Multivariate analysis where the only significant parameters in the univariate analyses were used as the independent variables showed that parafoveal NPA was most significantly associated with the logarithm of minimum angle of resolution visual acuity ($\beta = 0.500$, $P = 0.005$) and macular sensitivity ($\beta = -0.480$, $P = 0.007$).

CONCLUSION: In eyes with branch retinal vein occlusion-macular edema resolved by intravitreal

ranibizumab treatments, visual function was strongly associated with parafoveal NPA size.

PMID: 28221256

Nan Fang Yi Ke Da Xue Xue Bao. 2016 Feb 20;37(2):165-171.

[Sensitivity and specificity of optical coherence tomography in diagnosing polypoidal choroidal vasculopathy]. [Article in Chinese]

Zhang Y, Yao J, Wang XH, Zhao L, Wang LJ, Wang JM, Zhou AY.

OBJECTIVE: To establish the diagnostic criteria for polypoidal choroidal vasculopathy (PCV) based on spectral-domain optical coherence tomography (SD OCT) by evaluating the sensitivity and specificity of SD OCT in differentiating PCV from wet age-related macular degeneration (wAMD).

METHODS: The clinical data were reviewed for 62 patients (63 eyes) with the initial diagnosis of PCV or wAMD between August, 2012 and June, 2016. Twenty-four patients (25 eyes) were diagnosed to have PCV and 38 (38 eyes) had wAMD based on findings by fundus photography, fluorescein angiography (FFA) and indocyanine green angiography (ICGA). Among the 6 features of SD OCT, namely a sharp RPED peak, double-layer sign, multiple RPED, an RPED notch, a hyporeflective lumen representing polyps, and hyperreflective intraretinal hard exudates, findings of the first two features and at least one of the other features sufficed the diagnosis of PCV; in the absence of the first two features, the diagnosis of PCV was also made when at least 3 of the other features were present simultaneously. The sensitivity and specificity of SD OCT-based diagnosis were estimated by comparison with the gold standard ICGA-based diagnosis.

RESULTS: In the 25 eyes with an established diagnosis of PCV, 23 eyes (92.0%) met the diagnostic criteria based on SD OCT findings; in the 38 eyes with the diagnosis of wAMD, only 4 eyes (10.5%) met the criteria. The sensitivity and specificity of SD OCT-based diagnosis of PCV was 92.0% and 89.5%, respectively.

CONCLUSION: We established the diagnostic criteria for PCV based on SD OCT findings with a high sensitivity and specificity. SD OCT shows a strong capacity for differentiating PCV from wAMD.

PMID: 28219858

J Med Imaging (Bellingham). 2017 Jan;4(1):014503. Epub 2017 Feb 9.

DR HAGIS-a fundus image database for the automatic extraction of retinal surface vessels from diabetic patients.

Holm S, Russell G, Nourrit V, McLoughlin N.

Abstract: A database of retinal fundus images, the DR HAGIS database, is presented. This database consists of 39 high-resolution color fundus images obtained from a diabetic retinopathy screening program in the UK. The NHS screening program uses service providers that employ different fundus and digital cameras. This results in a range of different image sizes and resolutions. Furthermore, patients enrolled in such programs often display other comorbidities in addition to diabetes. Therefore, in an effort to replicate the normal range of images examined by grading experts during screening, the DR HAGIS database consists of images of varying image sizes and resolutions and four comorbidity subgroups: collectively defined as the diabetic retinopathy, hypertension, age-related macular degeneration, and Glaucoma image set (DR HAGIS). For each image, the vasculature has been manually segmented to provide a realistic set of images on which to test automatic vessel extraction algorithms. Modified versions of two previously published vessel extraction algorithms were applied to this database to provide some baseline measurements. A method based purely on the intensity of images pixels resulted in a mean segmentation

accuracy of 95.83% ([Formula: see text]), whereas an algorithm based on Gabor filters generated an accuracy of 95.71% ([Formula: see text]).

PMID: 28217714 PMCID: PMC5299858 [Available on 2018-02-09]

Pathogenesis

Mol Immunol. 2017 Feb 16. [Epub ahead of print]

Potential influences of complement factor H in autoimmune inflammatory and thrombotic disorders.

Ferluga J, Kouser L, Murugaiah V, Sim RB, Kishore U.

Abstract: Complement system homeostasis is important for host self-protection and anti-microbial immune surveillance, and recent research indicates roles in tissue development and remodelling. Complement also appears to have several points of interaction with the blood coagulation system. Deficiency and altered function due to gene mutations and polymorphisms in complement effectors and regulators, including Factor H, have been associated with familial and sporadic autoimmune inflammatory - thrombotic disorders, in which autoantibodies play a part. These include systemic lupus erythematosus, rheumatoid arthritis, atypical haemolytic uremic syndrome, anti-phospholipid syndrome and age-related macular degeneration. Such diseases are generally complex - multigenic and heterogeneous in their symptoms and predisposition/susceptibility. They usually need to be triggered by vascular trauma, drugs or infection and non-complement genetic factors also play a part. Underlying events seem to include decline in peripheral regulatory T cells, dendritic cell, and B cell tolerance, associated with alterations in lymphoid organ microenvironment. Factor H is an abundant protein, synthesised in many cell types, and its reported binding to many different ligands, even if not of high affinity, may influence a large number of molecular interactions, together with the accepted role of Factor H within the complement system. Factor H is involved in mesenchymal stem cell mediated tolerance and also contributes to self-tolerance by augmenting iC3b production and opsonisation of apoptotic cells for their silent dendritic cell engulfment via complement receptor CR3, which mediates anti-inflammatory-tolerogenic effects in the apoptotic cell context. There may be co-operation with other phagocytic receptors, such as complement C1q receptors, and the Tim glycoprotein family, which specifically bind phosphatidylserine expressed on the apoptotic cell surface. Factor H is able to discriminate between self and nonself surfaces for self-protection and anti-microbe defence. Factor H, particularly as an abundant platelet protein, may also modulate blood coagulation, having an anti-thrombotic role. Here, we review a number of interaction pathways in coagulation and in immunity, together with associated diseases, and indicate where Factor H may be expected to exert an influence, based on reports of the diversity of ligands for Factor H.

PMID: 28216098

Epidemiology

Clin Ophthalmol. 2017 Feb 9;11:317-322. eCollection 2017.

Idiopathic polypoidal choroidal vasculopathy in Thai patients with clinical and angiographic choroidal neovascularization.

Bhoomibunchoo C, Yospaiboon Y, Thoongsuwan S, Rojanaporn D, Watanachai N, Jirarattanasopa P, Wongcumchang N, Amphornphruet A, Vongkulsiri S, Arayangkoon E.

OBJECTIVE: This study aimed to study the prevalence and characteristics of idiopathic polypoidal choroidal vasculopathy (IPCV) in Thai patients with clinical and angiographic choroidal neovascularization (CNV).

PATIENTS AND METHODS: A consecutive case study of 140 patients presenting with CNV was conducted in nine large referral eye centers throughout Thailand. The demographic data, fundus photographs, fundus fluorescein angiography and indocyanine green angiography of the patients were analyzed.

RESULTS: Of 129 patients with clinical and angiographic CNV, IPCV was diagnosed in 100 patients (77.52%), idiopathic CNVs in 16 patients (12.40%) and age-related macular degeneration (AMD) in 12 patients (9.30%). Of the 107 eyes with IPCV, 90 eyes (84.11%) had both branching venous networks (BVNs) and polypoidal lesions. Most IPCV patients (93%) had unilateral involvement and were at a younger age than AMD patients. In all, 79 eyes (73.83%) had lesions found in the macular area, 14 eyes (13.08%) in the temporal to vascular arcades, ten eyes (9.35%) in the peripapillary area and four eyes (3.74%) in both macular and peripapillary areas. The clinical manifestations of IPCV at presentation were categorized into two patterns. There were 95 eyes (88.79%) of a hemorrhagic pattern and 12 eyes (11.21%) of an exudative pattern.

CONCLUSION: IPCV is the most common macular disease in Thai patients with CNV. Most IPCVs have both BVNs and polypoidal lesions located in the macular area and present with a hemorrhagic pattern.

PMID: 28223776 PMCID: PMC5308571

Genetics

Immunity. 2017 Feb 21;46(2):167-169.

Compliments of Factor H: What's in it for AMD?

Mattapallil MJ, Caspi RR.

Abstract: Genetic variations in complement factor H (CFH) confer greater risk for age-related macular degeneration (AMD). In this issue of Immunity, Calippe et al. (2017) uncover a non-canonical role for CFH in the inhibition of mononuclear phagocyte elimination from sub-retinal lesions, providing insight into the pathophysiology of AMD associated with CFH variants.

PMID: 28228273

Nat Commun. 2017 Feb 21;8:14500.

In vivo genome editing with a small Cas9 orthologue derived from Campylobacter jejuni.

Kim E, Koo T, Park SW, Kim D, Kim K, Cho HY, Song DW, Lee KJ, Jung MH, Kim S, Kim JH, Kim JH, Kim JS.

Abstract: Several CRISPR-Cas9 orthologues have been used for genome editing. Here, we present the smallest Cas9 orthologue characterized to date, derived from Campylobacter jejuni (CjCas9), for efficient genome editing in vivo. After determining protospacer-adjacent motif (PAM) sequences and optimizing single-guide RNA (sgRNA) length, we package the CjCas9 gene, its sgRNA sequence, and a marker gene in an all-in-one adeno-associated virus (AAV) vector and produce the resulting virus at a high titer. CjCas9 is highly specific, cleaving only a limited number of sites in the human or mouse genome. CjCas9, delivered via AAV, induces targeted mutations at high frequencies in mouse muscle cells or retinal pigment epithelium (RPE) cells. Furthermore, CjCas9 targeted to the Vegfa or Hif1a gene in RPE cells reduces the size of laser-induced choroidal neovascularization, suggesting that in vivo genome editing with CjCas9 is a new option for the treatment of age-related macular degeneration.

PMID: 28220790

Immunity. 2017 Feb 21;46(2):261-272.

Complement Factor H Inhibits CD47-Mediated Resolution of Inflammation.

Calippe B, Augustin S, Beguier F, et al

Abstract: Variants of the CFH gene, encoding complement factor H (CFH), show strong association with age-related macular degeneration (AMD), a major cause of blindness. Here, we used murine models of AMD to examine the contribution of CFH to disease etiology. Cfh deletion protected the mice from the pathogenic subretinal accumulation of mononuclear phagocytes (MP) that characterize AMD and showed accelerated resolution of inflammation. MP persistence arose secondary to binding of CFH to CD11b, which obstructed the homeostatic elimination of MPs from the subretinal space mediated by thrombospondin-1 (TSP-1) activation of CD47. The AMD-associated CFH(H402) variant markedly increased this inhibitory effect on microglial cells, supporting a causal link to disease etiology. This mechanism is not restricted to the eye, as similar results were observed in a model of acute sterile peritonitis. Pharmacological activation of CD47 accelerated resolution of both subretinal and peritoneal inflammation, with implications for the treatment of chronic inflammatory disease.

PMID: 28228282

Stem cells

Acta Biomater. 2017 Feb 18. [Epub ahead of print]

Langmuir-Schaefer film deposition onto honeycomb porous films for retinal tissue engineering.

Calejo MT, Ilmarinen T, Vuorimaa-Laukkanen E, Talvitie E, Hakola HM, Skottman H, Kellomäki M.

Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss in senior citizens in the developed world. The disease is characterised by the degeneration of a specific cell layer at the back of the eye - the retinal pigment epithelium (RPE), which is essential in retinal function. The most promising therapeutic option to restore the lost vision is considered to be RPE cell transplantation. This work focuses on the development of biodegradable biomaterials with similar properties to the native Bruch's membrane as carriers for RPE cells. In particular, the breath figure (BF) method was used to create semi-permeable microporous films, which were thereafter used as the substrate for the consecutive Langmuir-Schaefer (LS) deposition of highly organised layers of collagen type I and collagen type IV. The newly developed biomaterials were further characterised in terms of surface porosity, roughness, hydrophilicity, collagen distribution, diffusion properties and hydrolytic stability. Human embryonic stem cell-derived RPE cells (hESC-RPE) cultured on the biomaterials showed good adhesion, spreading and morphology, as well as the expression of specific protein markers. Cell function was additionally confirmed by the assessment of the phagocytic capacity of hESC-RPE. Throughout the study, microporous films consistently showed better results as cell culture materials for hESC-RPE than dip-coated controls. This work demonstrates the potential of the BF-LS combined technologies to create biomimetic prosthetic Bruch's membranes for hESC-RPE transplantation.

STATEMENT OF SIGNIFICANCE: Age-related macular degeneration (AMD) is a leading cause of central blindness in developed countries, associated with the degeneration of the retinal pigment epithelium (RPE), a specific cell layer at the back of the eye. Transplantation of RPE cells derived from stem cells is considered the best option to treat these patients. In this work, we developed a cell carrier for human embryonic stem cell-derived RPE that resembled the upper layers of the membrane that naturally supports the RPE cells in the retina. The new combination of technologies employed in this study resulted in very promising materials as confirmed by our studies on cell proliferation, morphology and function.

PMID: 28223209

Diet, lifestyle & low vision

Foods. 2016 Jan 12;5(1).

Can Xanthophyll-Membrane Interactions Explain Their Selective Presence in the Retina and Brain?

Widomska J, Zareba M, Subczynski WK.

Abstract: Epidemiological studies demonstrate that a high dietary intake of carotenoids may offer protection against age-related macular degeneration, cancer and cardiovascular and neurodegenerative diseases. Humans cannot synthesize carotenoids and depend on their dietary intake. Major carotenoids that have been found in human plasma can be divided into two groups, carotenes (nonpolar molecules, such as β -carotene, α -carotene or lycopene) and xanthophylls (polar carotenoids that include an oxygen atom in their structure, such as lutein, zeaxanthin and β -cryptoxanthin). Only two dietary carotenoids, namely lutein and zeaxanthin (macular xanthophylls), are selectively accumulated in the human retina. A third carotenoid, meso-zeaxanthin, is formed directly in the human retina from lutein. Additionally, xanthophylls account for about 70% of total carotenoids in all brain regions. Some specific properties of these polar carotenoids must explain why they, among other available carotenoids, were selected during evolution to protect the retina and brain. It is also likely that the selective uptake and deposition of macular xanthophylls in the retina and brain are enhanced by specific xanthophyll-binding proteins. We hypothesize that the high membrane solubility and preferential transmembrane orientation of macular xanthophylls distinguish them from other dietary carotenoids, enhance their chemical and physical stability in retina and brain membranes and maximize their protective action in these organs. Most importantly, xanthophylls are selectively concentrated in the most vulnerable regions of lipid bilayer membranes enriched in polyunsaturated lipids. This localization is ideal if macular xanthophylls are to act as lipid-soluble antioxidants, which is the most accepted mechanism through which lutein and zeaxanthin protect neural tissue against degenerative diseases.

PMID: 28231102

Conf Proc IEEE Eng Med Biol Soc. 2016 Aug;2016:4979-4982.

Inertial sensor based gait analysis discriminates subjects with and without visual impairment caused by simulated macular degeneration.

Kanzler CM, Barth J, Klucken J, Eskofier BM, Kanzler CM, Barth J, Klucken J, Eskofier BM, Barth J, Klucken J, Eskofier BM, Kanzler CM.

Abstract: Macular degeneration is the third leading cause of blindness worldwide and the leading cause of blindness in the developing world. The analysis of gait parameters can be used to assess the influence of macular degeneration on gait. This study examines the effect of macular degeneration on gait using inertial sensor based 3D spatio-temporal gait parameters. We acquired gait data from 21 young and healthy subjects during a 40 m obstacle walk. All subjects had to perform the gait trial with and without macular degeneration simulation glasses. The order of starting with or without glasses alternated between each subject in order to test for training effects. Multiple 3D spatio-temporal gait parameters were calculated for the normal vision as well as the impaired vision groups. The parameters trial time, stride time, stride time coefficient of variation (CV), stance time, stance time CV, stride length, cadence, gait velocity and angle at toe off showed statistically significant differences between the two groups. Training effects were visible for the trials which started without vision impairment. Inter-group differences in the gait pattern occurred due to an increased sense of insecurity related with the loss of visual acuity from the simulation glasses. In summary, we showed that 3D spatio-temporal gait parameters derived from inertial sensor data are viable to detect differences in the gait pattern of subjects with and without a macular degeneration simulation. We believe that this study provides the basis for an in-depth analysis regarding the impact of macular degeneration on gait.

PMID: 28227629

Conf Proc IEEE Eng Med Biol Soc. 2016 Aug;2016:1348-1351.

Determining the difference in eyegaze measurements in individuals with age related macular degeneration.

Liu H, Wong D, Yow AP, Xu Y, Yin F, Laude A, Lim TH, Huiying Liu, Wong D, Ai Ping Yow, Yanwu Xu, Fengshou Yin, Laude A, Tock Han Lim, Laude A, Liu H, Lim TH, Yin F, Xu Y, Wong D, Yow AP.

Abstract: Age-related Macular Degeneration (AMD) is one of the leading causes of blindness in the elderly. Visual loss associated with AMD often results in a central scotoma which is an alteration in the central vision, leading to distortion or loss of vision. Current methods of detecting AMD are typically manual, require holding fixation and an external response trigger. In this paper, we propose the use of eyegaze tracking to detect for the presence of AMD, using a simple set of test patterns. Experimental results show that the derived eyegaze measurements can help to identify individuals with AMD from healthy individuals. This could lead to the detection of AMD using eye tracking data, and could result in a potential system device for screening.

PMID: 28226753

PLoS One. 2017 Feb 22;12(2):e0169816. eCollection 2017.

SF-6D utility values for the better- and worse-seeing eye for health states based on the Snellen equivalent in patients with age-related macular degeneration.

Visser MS, Amarakoon S, Missotten T, Timman R, Busschbach JJ.

OBJECTIVE: Economic evaluations in wet age-related macular degeneration (ARMD) is hampered as often utility values for solely one eye are used, mostly the better-seeing eye (BSE). Moreover, frequently chosen methods rely on patient values and/or disease specific measures, while economic evaluations prefer generic quality of life (QoL) measures based on societal preferences. The generic QoL utility instrument EQ-5D has shown to be insensitive for differences in visual acuity. The aim of this study was therefore to provide societal utility values, using the generic SF-6D, for health states acknowledging both BSE and worse-seeing eye (WSE).

METHODS: SF-6D utility values of 191 ARMD patients (≥ 65 years) with 153 follow-up measures at 1 year were used to fill health states defined by the combination of BSE and WSE using Snellen equivalents; no visual loss ($\geq 20/40$), mild-moderate ($< 20/40 \rightarrow 20/200$) and severe ($\leq 20/200$).

RESULTS: QoL utilities were estimated for the SF-6D, ranging from 0.740 for ARMD patients without visual loss to 0.684 for patients with a combination of mild-moderate visual loss in their BSE and severe visual loss in their WSE.

CONCLUSION: Societal utility values are provided for ARMD patients using the generic QoL instrument SF-6D for visual acuity health states based on both BSE and WSE. The range of the values is smaller than previous elicited utilities with the disease-specific VisQoL. Besides, the utility values are placed on a more realistic position on the utility scale, and SF-6D utility values avoid the problem associated with the interpretation of disease-specific utility values.

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Measurement of Perceived Stress in Age-Related Macular Degeneration.

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PURPOSE: To validate the Perceived Stress Scale (PSS) in patients with age-related macular degeneration (AMD) using Rasch analysis.

METHODS: Study participants with AMD were recruited from the retina service of the Department of Ophthalmology at the Ohio State University during clinical visits for treatment or observation. Visual acuity with habitual distance correction was assessed. A 10-item version of the PSS was administered in large print or by reading the items to the patient. Rasch analysis was used to investigate the measurement properties of the PSS, including fit to the model, ability to separate between people with different levels of perceived stress, category response structure performance, and unidimensionality.

RESULTS: A total of 137 patients with a diagnosis of AMD were enrolled. The mean ($\pm$ SD) age of participants was 82 ± 9 years. Fifty-four percent were female. Median Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity of the better eye was 65 letters (Snellen 20/50), with a range of approximately 20/800 to 20/15. Forty-seven percent of participants were receiving an anti-VEGF injection on the day of the study visit. The response category structure was appropriate. One item, "How often have you felt confident in your ability to handle your personal problems?" was removed due to poor fit statistics. The remaining nine items showed good fit to the model, acceptable measurement precision as assessed by the Rasch person separation statistic, and unidimensionality. There was some evidence of differential item functioning by age and visual acuity.

CONCLUSIONS: The Perceived Stress Scale demonstrated acceptable measurement properties and may be useful for the measurement of perceived stress in patients with AMD.

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Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: Health impacts and mechanisms of circadian disruption.

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Abstract: Exposure to Artificial Light At Night (ALAN) results in a disruption of the circadian system, which is deleterious to health. In industrialized countries, 75% of the total workforce is estimated to have been involved in shift work and night work. Epidemiologic studies, mainly of nurses, have revealed an association between sustained night work and a 50-100% higher incidence of breast cancer. The potential and multifactorial mechanisms of the effects include the suppression of melatonin secretion by ALAN, sleep deprivation, and circadian disruption. Shift and/or night work generally decreases the time spent sleeping, and it disrupts the circadian time structure. In the long run, this desynchronization is detrimental to health, as underscored by a large number of epidemiological studies that have uncovered elevated rates of several diseases, including cancer, diabetes, cardiovascular risks, obesity, mood disorders and age-related macular degeneration. It amounts to a public health issue in the light of the very substantial number of individuals involved. The IARC has classified shift work in group 2A of "probable carcinogens to humans" since "they involve a circadian disorganization". Countermeasures to the effects of ALAN, such as melatonin, bright light, or psychotropic drugs, have been proposed as a means to combat circadian clock disruption and improve adaptation to shift and night work. We review the evidence for the ALAN impacts on health. Furthermore, we highlight the importance of an in-depth mechanistic understanding to combat the detrimental properties of exposure to ALAN and develop strategies of prevention.

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