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FEATURED ARTICLE

Reticular Pseudodrusen: the Third Macular Risk Feature for Progression to Late Age-related Macular Degeneration.

Ophthalmology. 2022 May 31.

Agrón E, Domalpally A, Cukras CA, Clemons TE, Chew EY, Keenan TDL; AREDS and AREDS2 Research Groups.

Purpose: To analyze reticular pseudodrusen (RPD) as an independent risk factor for progression to late age-related macular degeneration (AMD), alongside traditional macular risk factors (soft drusen and pigmentary abnormalities) considered simultaneously.

Design: Post hoc analysis of two clinical trial cohorts: Age-Related Eye Disease Study (AREDS) and AREDS2.

Participants: Eyes with no late AMD at baseline in AREDS (n=6959 eyes, 3780 participants; mean age 69.4y) and AREDS2 (n=3355 eyes, 2056 participants; mean age 72.3y).

Methods: Color fundus photographs (CFP) from annual study visits were graded for soft drusen, pigmentary abnormalities, and late AMD. RPD presence was determined by grading of fundus autofluorescence images (AREDS2) and deep learning grading of CFP (AREDS). Proportional hazards regression analyses were performed, considering AREDS AMD severity scales (modified simplified severity scale (person) and 9-step scale (eye)) and RPD presence simultaneously.

Main Outcome Measures: Progression to late AMD, geographic atrophy (GA), and neovascular AMD (NV).

Results: In AREDS, for late AMD analyses by person, in a model considering the modified simplified severity scale simultaneously, RPD presence was associated with higher risk of progression: hazard ratio (HR) 2.15 (95% CI 1.75-2.64). However, the risk associated with RPD presence differed significantly at different simplified severity scale levels: HR 3.23 (1.60-6.51), 3.81 (2.38-6.10), 2.28 (1.59-3.27), and 1.64 (1.20-2.24), at levels 0-1/2/3/4, respectively. Considering the 9-step scale (by eye), RPD presence was also associated with

higher risk: HR 2.54 (2.07-3.13). The HRs were 5.11 (3.93-6.66) at levels 1-6 and 1.78 (1.43-2.22) at 7-8. In AREDS2, by person, RPD presence was not associated with higher risk: HR 1.18 (0.90-1.56); by eye, it was: HR 1.57 (1.31-1.89). No significant differences in risk were observed at different severity levels, for the limited spectrum in AREDS2. In both cohorts, RPD presence carried higher risk for GA than NV.

Conclusions: RPD represent an important anatomical risk factor for progression to late AMD, particularly GA. However, the added risk associated with RPD varies markedly by severity level. It carries highly increased risk at lower/moderate levels and less increased risk at higher levels. RPD status should be included in updated AMD classification systems, risk calculators, and clinical trials.

DOI: 10.1016/j.ophtha.2022.05.021

GENETICS

Correlation between genetic and environmental risk factors for age-related macular degeneration in Brazilian patients.

PLoS One. 2022 Jun 3.

Rim PHH, de Vasconcellos JPC, de Melo MB, Medina FMC, Sacconi DPD, Lana TP, Hirata FE, Magna LA, Marques-de-Faria AP.

Purpose: To analyze the correlations between age-related macular degeneration (AMD) and genetic and environmental risk factors for in a Brazilian population. DESIGN: Cross-sectional study with a control group.

Methods: We collected data on 236 participants 50 years of age or older (141 with AMD and 95 controls without the disease). Data was obtained using a questionnaire and included information on demographics, ocular and medical history, family history of AMD, lifestyle, and smoking and drinking habits. Genetic evaluations included direct sequencing for the LOC387715 (rs10490924) variant, as well as PCR and enzymatic digestion for the CFH Y402H (rs1061170) and HTRA1 (rs11200638) variants. We performed a risk assessment of environmental risk factors and genetic variants associated with AMD and determined correlations between AMD and the data collected using multiple linear regression analysis.

Results: Of the 141 AMD cases, 99 (70%) had advanced AMD in at least one eye (57% neovascular AMD and 13% geographic atrophy), and 42 (30%) had not-advanced AMD. Family history of AMD (OR: 6.58; 95% CI: 1.94-22.31), presence of cardiovascular disease (CVD) (OR: 2.39; 95% CI: 1.08-5.28), low physical activity level (OR: 1.39; 95% CI: 0.82-2.37), and high serum cholesterol (OR: 1.49; 95% CI: 0.84-2.65) were associated with an increased risk for AMD. There was a significant association between CVD and incidence of advanced AMD (OR: 2.29; 95% CI 0.81-6.44). The OR for the risk allele of the LOC387715 gene, the CFH gene and the HTRA1 gene were 2.21 (95% CI: 1.47-3.35), 2.27 (95% CI: 1.52-3.37), and 2.76 (95% CI: 1.89-4.03), respectively. In the stepwise multiple linear regression analyses, the HTRA1 and CFH risk alleles, family history of AMD, the LOC387715 risk allele, and CVD were associated with an increased risk of AMD for a total of 25.6% contribution to the AMD phenotype.

Conclusions: The analysis correlating environmental and genetic risk factors such as family history of AMD, and CVD and the variants of HTRA1, CFH, and LOC387715 genes showed an expressive contribution for the development of AMD among this admixed population.

DOI: 10.1371/journal.pone.0268795

Vitronectin and Its Interaction with PAI-1 Suggests a Functional Link to Vascular Changes in AMD Pathobiology.

Cells. 2022 May 27.

Biasella F, Strunz T, Kiel C, On Behalf Of The International AMD Genomics Consortium (IAMDGC) Weber BHF, Friedrich U.

The pathogenesis of age-related macular degeneration (AMD), a frequent disorder of the central retina, is incompletely understood. Genome-wide association studies (GWAS) suggest a strong contribution of genomic variation in AMD susceptibility. Nevertheless, little is known about biological mechanisms of the disease. We reported previously that the AMD-associated polymorphism rs704C > T in the vitronectin (VTN) gene influences protein expression and functional aspects of encoded vitronectin, a human blood and extracellular matrix (ECM) protein. Here, we refined the association of rs704 with AMD in 16,144 cases and 17,832 controls and noted that rs704 is carried exclusively by the neovascular AMD subtype. Interaction studies demonstrate that rs704 affects the ability of vitronectin to bind the angiogenic regulator plasminogen activator inhibitor 1 (PAI-1) but has no influence on stabilizing its active state. Western blot analysis and confocal imaging reveal a strong enrichment of PAI-1 in the ECM of cultured endothelial cells and RPE cell line ARPE-19 exposed to vitronectin. Large-scale gene expression of VTN and PAI-1 showed positive correlations and a statistically significant increase in human retinal and blood tissues aged 60 years and older. Our results suggest a mechanism by which the AMD-associated rs704 variant in combination with ageing may contribute to the vascular complications in AMD.

DOI: 10.3390/cells11111766

DRUG TREATMENTS

The effect of pegcetacoplan treatment on photoreceptor maintenance in geographic atrophy monitored by AI-based OCT analysis.

Ophthalmology Retina. 2022 Jun 3.

Riedl S, Vogl WD, Mai J, Reiter GS, Lachinov D, Grechenig C, McKeown A, Scheibler L, Bogunović H, Schmidt-Erfurth U.

Purpose: To investigate the therapeutic effect of intravitreal pegcetacoplan on the inhibition of photoreceptor (PR) loss and thinning in geographic atrophy (GA) on conventional spectral domain-optical coherence tomography (SD-OCT) imaging by deep learning-based automated PR quantification.

Design: Post-hoc analysis of a prospective, multicenter, randomized, sham-controlled, masked phase II trial investigating the safety and efficacy of pegcetacoplan for the treatment of GA due to age-related macular degeneration.

Participants: Study eyes of 246 patients, randomized 1:1:1 to monthly (AM), bimonthly (AEOM) and sham (SM) treatment.

Methods: We performed fully automated, deep learning-based segmentation of retinal pigment epithelium (RPE) loss and PR thickness on SD-OCT volumes acquired at baseline, month 2, 6 and 12. The difference in the change of PR loss area was compared between treatment arms. Change in PR thickness adjacent to the GA borders and in the whole 20 degrees scanning area was compared between treatment arms.

Main Outcome Measures: Square root transformed PR loss area in µm or mm, PR thickness in µm, PR loss/RPE loss ratio.

Results: A total of 31,556 B-Scans of 644 SD-OCT volumes of 161 study eyes (AM: 52, AEOM: 54, SM: 56) were evaluated from baseline to month 12. Comparison of mean change in PR loss area revealed statistically significantly less growth in the AM group at month 2, 6 and 12 compared to SM (-41µm ± 219 vs. 77µm ± 126, p=0.0004; -5µm ± 221 vs. 156µm ± 139, p<0.0001; 106µm ± 400 vs. 283µm ± 226 p=0.0014). PR thinning was significantly reduced under monthly treatment compared to sham within the GA junctional zone as well as throughout the 20 degrees area. A trend towards greater inhibition of PR loss compared to RPE loss was observed under therapy.

Conclusions: Distinct and reliable quantification of PR loss using deep learning-based algorithms offers an essential tool to evaluate therapeutic efficacy in slowing disease progression. PR loss and thinning are reduced by intravitreal complement C3 inhibition. Automated quantification of PR loss/maintenance based on OCT images is an ideal approach to reliably monitor disease activity and therapeutic efficacy in GA management in clinical routine and regulatory trials.

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Visual outcomes of observation, macular laser and anti-VEGF in diabetic macular edema in type 1 diabetes: a real-world study.

BMC Ophthalmology. 2022 Jun 9

Wirkkala J, Kubin AM, Ohtonen P, Yliselä J, Siik T, Hautala N.

Background: The treatment for diabetic macular edema (DME) has revolutionized during the last 15 years after the introduction of intravitreal anti-VEGF agents. The aim of the current study is to evaluate the real-world visual outcomes of diabetic macular edema (DME) treatment in patients with type 1 diabetes (T1D) in long-term follow-up.

Methods: A real-world, descriptive, population-based cohort and follow-up of all patients with T1D and DME in 2006-2020 in 34 communities of the Northern Ostrobothnia Hospital District. The main outcome measures included age, gender, duration of T1D at the onset of DME, stage of retinopathy, treatment of DME (observation, laser, intravitreal treatments, combination), and visual outcomes.

Results: A total of 304 eyes of 206 T1D patients with DME were included. 75% (n=155) had non-proliferative diabetic retinopathy during the onset of DME. 15% of the cases were observed, 33% had macular laser, 41% intravitreal anti-VEGF and 12% combination of laser and intravitreal injections. Patients in anti-VEGF and in combination groups gained 4.9 and 5.5 ETDRS letters after the initial DME episode (p<0.001 and p<0.001), and the long-term visual improvements were 4.1 and 5.1 ETDRS letters (p<0.001 and p<0.001), respectively. In observation and laser groups the initial gain of 0.1 (p>0.90) and loss of 0.4 ETDRS letter (p=0.61), respectively, was noted. After the follow-up, a 3.7 ETDRS letter decrease was documented in the observation group (p>0.90) and a 1.1 (p=0.14) ETDRS letter decline in the laser group of patients. At the beginning of treatment, eyes subjected to anti-VEGF alone or in combination with laser had lower visual acuity compared to eyes subjected to observation or macular laser. The average of a 6.1±4.8 anti-VEGF injections were needed to dry DME. Visual impairment due to DME decreased from 2.4% to 1.0% during the 15-year period.

Conclusions: Anti-VEGF alone or in combination with macular laser seems to be beneficial in terms of visual outcomes and treatment stability in T1D patients with central DME. Moreover, satisfying long-term visual outcomes were achieved with anti-VEGF treatment in a real-world setting.

DOI: 10.1186/s12886-022-02482-z

PATIENT EXPERIENCE

Are intravitreal injections essential during the COVID-19 pandemic? Global preferred practice patterns and practical recommendations.

International Journal Retina Vitreous. 2022 Jun 7.

Tan ACS, Schwartz R, Anaya D, Chatziralli I, Yuan M, Cicinelli MV, Faes L, Mustapha M, Phasukkijwatana N, Pohlmann D, Reynolds R, Rosenblatt A, Savastano A, Touhami S, Vaezi K, Ventura CV, Vogt D, Ambati J, de Smet MD, Loewenstein A; International Retina Collaborative.

Tertiary outpatient ophthalmology clinics are high-risk environments for COVID-19 transmission, especially retina clinics, where regular follow-up is needed for elderly patients with multiple comorbidities. Intravitreal injection therapy (IVT) for chronic macular diseases, is one of the most common procedures performed, associated with a significant burden of care because of the vigorous treatment regimen associated with multiple investigations. While minimizing the risk of COVID-19 infection transmission is a priority, this must be balanced against the continued provision of sight-saving ophthalmic care to patients at risk of permanent vision loss. This review aims to give evidence-based guidelines on managing IVT during the COVID-19 pandemic in common macular diseases such as age-related macular degeneration, diabetic macula edema and retinal vascular disease and to report on how the COVID-19 pandemic has affected IVT practices worldwide. To illustrate some real-world examples, 18 participants in the International Retina Collaborative, from 15 countries and across four continents, were surveyed regarding pre- and during- COVID-19 pandemic IVT practices in tertiary ophthalmic centers. The majority of centers reported a reduction in the number of appointments to reduce the risk of the spread of COVID-19 with varying changes to their IVT regimen to treat various macula diseases. Due to the constantly evolving nature of the COVID-19 pandemic, and the uncertainty about the normal resumption of health services, we suggest that new solutions for eye healthcare provision, like telemedicine, may be adopted in the future when we consider new long-term adaptations required to cope with the COVID-19 pandemic.

DOI: 10.1186/s40942-022-00380-6

Causes and Risk Factors of Repeated Hospitalization among Patients with Diabetic Retinopathy.

Journal of Diabetes Research. 2022 May 28.

Xiao Y, Liang Y, Lin Z, Kong H, Du Z, Hu Y, Ouyang S.

Purpose: To identify the causes and risk factors of repeated hospitalization among patients with diabetic retinopathy (DR).

Methods: Our study retrospectively examined the data of DR patients who were readmitted for treatments to the Department of Ophthalmology, Guangdong Provincial People's Hospital between January 2012 and July 2021. We first analyzed the main causes of repeated admissions and then divided the patients into three groups according to the times of readmissions. Ordinal logistic regression was performed to determine the impact of patients' demographic and clinical characteristics. Moreover, comparisons of the length of stay and the hospitalization cost of DR patients with repeated admission causes were conducted.

Results: Among 2592 hospital discharges of 827 patients who experienced at least two hospitalizations, the major causes of repeated hospitalization were macular edema (30.83%), vitreous hemorrhage (29.09%), cataract (22.76%), proliferative membrane formation (6.91%), silicone oil removal (4.71%), retinal detachment (4.44%), and glaucoma

(4.17%). The results of ordinal logistic regression showed that younger patients with medical insurance and local residence have a higher risk of repeated hospitalization ($p < 0.05$). Furthermore, patients readmitted for vitreous hemorrhage, proliferative membrane formation, and retinal detachment experienced longer length of hospital stay and higher hospitalization cost ($p < 0.001$).

Conclusions: Multiple causes and risk factors contribute to repeated hospitalization, imposing a substantial physical and economic burden on DR patients. A better understanding of these causes and risk factors of readmission may lead to lowering such risks and alleviating patients' burden.

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REVIEW

Effects of circadian rhythm disruption on retinal physiopathology: Considerations from a consensus of experts.

European Journal of Ophthalmology. 2022 Jun 3.

Parravano M, Eandi CM, Figus M, Lupidi M, Menchini F, Nicolo' M, Parisi V(1), Toto L, Viola F, Vujosevic S, Querques G.

The circadian rhythms originate within the organism and synchronize with cyclic fluctuations in the external environment. It has been demonstrated that part of the human genome is under control of the circadian clock and that a synchronizer that helps to maintain daily rhythms is Melatonin, a neuro-hormone primarily synthesized by the pineal gland during the night. The chronic disruption of circadian rhythm has been linked to many conditions such as obesity, metabolic syndrome, type 2 diabetes, cancer, and neurodegenerative diseases. Studies in the mice showed that the disruption of the retinal circadian rhythm increases the decline during the aging of photoreceptors, accelerating age-related disruption of cone cell structure, function, and viability and that the melatonin receptor deletion seems to influence the health of retinal cells, speeding up their aging. In conclusion, preserving the circadian rhythms could be to add to the prevention and treatment of age-related degenerative retinal diseases, and although additional studies are needed, melatonin could be a valid support to favor this "chronoprotection action".

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DIAGNOSIS AND IMAGING

Morphology and fluorescein leakage in diabetic retinal microaneurysms: a study using multiple en face OCT angiography image averaging.

Graefes Archive of Clinical and Experimental Ophthalmology. 2022 Jun 4.

Fukuda Y, Nakao S, Kaizu Y, Arima M, Shimokawa S, Wada I, Yamaguchi M, Takeda A, Sonoda KH.

Purpose: To investigate the relevance of microaneurysm morphology in optical coherence tomography angiography (OCTA) image averaging and fluorescein leakage in diabetic retinopathy (DR).

Methods: In 38 consecutive patients with DR, ten consecutive 3- × 3-mm fovea-centered OCTA (HS100, Canon Inc., Tokyo, Japan) and fluorescein angiography (FA) were performed, and averaged OCTA images were created based on the 10 images. After detecting all microaneurysms in FA images, the morphology was classified into four types

(focal bulge, saccular/pedunculated, fusiform, and mixed) using averaged OCTA images. The correlation between microaneurysm leakage in FA, retinopathy stage, and microaneurysm morphology was estimated.

Results: Thirty-eight eyes (50.0%) of the 33 patients were available for analysis, and 370 (63.5%) of the 583 FA-detected microaneurysms were morphologically classifiable (focal bulge, 46; saccular/pedunculated, 143; fusiform, 29; and mixed, 152) in OCTA. There was a significant correlation between stage and percentage of microaneurysm morphology and between morphology and the presence of leakage ($P < 0.0001$ and $P < 0.01$, respectively). The proportion of focal bulges decreased with stage progression, while the other three types increased with stage progression. The percentage of FA leakage for focal bulge, saccular/pedunculated, fusiform, and mixed was 41.3%, 66.4%, 82.8%, and 66.4%, respectively, and the fusiform type showed significant FA leakage. **Conclusion**: Microaneurysm morphology is correlated with the DR stage and FA leakage. Microaneurysm morphology recognition using OCTA image averaging may be useful for the clinical evaluation of DR.

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