4 July 2022

FEATURED ARTICLE

Improving the screening of risk factors in diabetic retinopathy.

Expert Review Endocrinology and Metabolism. 2022 May.

Scanlon PH.

Introduction: In 2002, Diabetic Retinopathy was reported as the leading cause of blindness in the working age group. The introduction of systematic screening programs in the UK has reduced visual loss and blindness due to diabetic retinopathy, but it does still occur with catastrophic consequences for the individual.

Areas Covered: The author conducted an ongoing search for articles relating to diabetic retinopathy since 2000 utilizing Zetoc Alert with keywords and contents page lists from relevant journals. This review covers the risk factors for loss of vision due to diabetic retinopathy and discusses ways in which the awareness of these risk factors can be used to further reduce visual loss. Some risk factors such as glycemic and B/P control are well known from landmark trials. This review has included these factors but concentrated more on the evidence behind those risk factors that are not so clearly defined or so well known.

Expert Opinion: The major risk factors are well known, but one continues to find that people with diabetes lose vision in situations in which a better awareness of the risks by both the individual with diabetes and the health workers involved may have prevented the visual loss.
DOI: 10.1080/17446651.2022.2078305

BIOMARKERS

Subretinal drusenoid deposits as a biomarker of age-related macular degeneration progression via reduction of the choroidal vascularity index.

Eye (London). 2022 Jun 23.

Abdolrahimzadeh S, Di Pippo M, Sordi E, Cusato M, Lotery AJ.

Background/Objectives: This study aimed to analyse the role of the choroid in early age-related

macular degeneration (AMD) by analysing choroidal vascularity index (CVI) in pure cohorts of patients with subretinal drusenoid deposits (SDD) or conventional drusen (CD).

Subjects/Methods: This was an observational cross-sectional study. Comprehensive ophthalmologic examination and multimodal imaging including fundus photography, autofluorescence, near infrared reflectance, and spectral domain optical coherence tomography (SDOCT) was performed. CVI processing was performed on a foveal horizontal SDOCT scan with binarization using Image J Image software and calculated as the ratio between luminal area (LA) and total area (TA).

Results: Sixty-nine eyes of 69 participants were included; 23 eyes with SDD alone, 22 eyes with CD alone, and 24 control eyes of healthy age-matched subjects. CVI was significantly reduced in the SDD and CD group compared to controls ($p = 0.0001$). Post-hoc analysis revealed a significant reduction of CVI in the SDD versus the control group ($p = 0.0002$), in the CD versus the control group ($p = 0.001$), and in the SDD versus the CD group ($p = 0.006$). Covariance analysis showed a significant difference of LA ($p = 0.033$) but no significant difference of TA ($p = 0.106$) between the three groups. Direct comparison between CD and SDD showed a significant reduction of LA and TA in the SDD group. **Conclusions**: CVI may have prognostic implications in early AMD. SDD is a biomarker of AMD progression and the mechanism for this could be via reduction of the CVI.
DOI: 10.1038/s41433-022-02134-y

Impact of Persistent Retinal Fluid in Patients with Neovascular Age-Related Macular Degeneration in Routine Clinical Practice.

Ophthalmic Surgery Lasers and Imaging Retina. 2022 Jun.

Iyer AI, Muste JC, Kalur A, Talcott KE, Singh RP.

Background and Objective: To determine whether quantification of intraretinal fluid (IRF) and subretinal fluid (SRF) can be used as a biomarker for predicting visual prognosis in routine clinical practice.

Patients and Methods: Retrospective, nonrandomized cohort study review of patients with neovascular age-related macular degeneration from January 1, 2012, to March 1, 2018.

Results: In the 286-patient cohort, the mean baseline, 6-month, and 12-month best-corrected visual acuity (BCVA) was 60.24 ± 18.63, 65.57 ± 16.56, and 65.61 ± 17.37 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, respectively ($P < .001$). The regression coefficient in the linear mixed effects regression model quantifying the association between eyes in the fourth and first quartile of IRF and 12-month BCVA was -4.14 (95% CI, -6.65 to -1.63) ($P = .001$) ETDRS letters. The regression coefficient quantifying the association between eyes in the fourth and first quartile of SRF and 12-month BCVA was -0.7 (95% CI, -3.07 to 1.27) ($P = .56$) ETDRS letters.

Conclusion: IRF and SRF are valuable biomarkers for BCVA outcomes in treatment-naïve neovascular age-related macular degeneration in routine clinical practice.
DOI: 10.3928/23258160-20220602-02

DRUG TREATMENT

Is there a Dose-Response Relationship? Real-World Outcomes of Anti-Vascular Endothelial Growth Factor Treatment in Neovascular Age-Related Macular Degeneration.

Ophthalmologica. 2022 Jun 22.

Shor R, Barak A, Loewenstein A, Shahar-Gonen M, Goldstein M, Gamzu R, Zur D.

Purpose: To explore the dose-response relationship of anti-vascular endothelial growth factor (VEGF) agents, with bevacizumab as 1st line treatment, on visual acuity (VA) outcome during the first year of treatment in neovascular AMD (nAMD) patients in real-life conditions.

Methods: A retrospective, observational, single center study at the Ophthalmology Division, Tel Aviv Medical Center. Inclusion criteria was naive AMD patients treated with anti VEGF injections between the years 2017-2020. Electronical medical records (EMRs) were scanned using the MD-Clone software, data from time of diagnosis, containing baseline VA, final VA, number of injections and the injected agent was gathered. Subjects were divided to three groups based on their baseline VA ('good, 'middle' and 'bad').

Results: A total of 672 patients were included. The cohort demonstrated a statistically non-significant correlation with a positive trend between the log transform of the number of annual injections and the change in VA (P=0.145). However, a significant correlation was established within the 'low VA' group, (P = 0.015). The 'good' and 'middle' VA groups did not reach statistical significance. Baseline VA was the single significant predictor for VA gain within patients with baseline VA of 6/12 or less.

Conclusions: A dose-response relationship between anti-VEGF injections and VA outcome was found only for patients with low baseline VA. Individual patient characteristics might need to be included to precise individualized treatment regimen and improve visual outcome.

DOI: 10.1159/000525653

DIAGNOSIS AND IMAGING

A Screening Tool for Self-Evaluation of Risk for Age-Related Macular Degeneration: Validation in a Spanish Population.

Translational Vision Science and Technology. 2022 Jun.

García-Layana A, López-Gálvez M, García-Arumí J, Arias L, Gea-Sánchez A, Marín-Méndez JJ, Sayar-Beristain O, Sedano-Gil G, Aslam TM, Minnella AM, Ibáñez IL, de Dios Hernández JM, Seddon JM.

Purpose: The objectives of this study were the creation and validation of a screening tool for age-related macular degeneration (AMD) for routine assessment by primary care physicians, ophthalmologists, other healthcare professionals, and the general population.

Methods: A simple, self-administered questionnaire (Simplified Théa AMD Risk-Assessment Scale [STARS] version 4.0) which included well-established risk factors for AMD, such as family history, smoking, and dietary factors, was administered to patients during ophthalmology visits. A fundus examination was performed to determine presence of large soft drusen, pigmentary abnormalities, or late AMD. Based on data from the questionnaire and the clinical examination, predictive models were developed to estimate probability of the Age-Related Eye Disease Study (AREDS) score (categorized as low risk/high risk). The models were evaluated by area under the receiving operating characteristic curve analysis.

Results: A total of 3854 subjects completed the questionnaire and underwent a fundus examination. Early/intermediate and late AMD were detected in 15.9% and 23.8% of the patients, respectively. A predictive model was developed with training, validation, and test datasets. The model in the test set had an area under the curve of 0.745 (95% confidence interval [CI] = 0.705-0.784), a positive predictive value of 0.500 (95% CI = 0.449-0.557), and a negative predictive value of 0.810 (95% CI = 0.770-0.844).

Conclusions: The STARS questionnaire version 4.0 and the model identify patients at high risk of developing late AMD.

Translational Relevance: The screening instrument described could be useful to evaluate the risk of late AMD in patients >55 years without having an eye examination, which could lead to more timely referrals and encourage lifestyle changes.

DOI: 10.1167/tvst.11.6.23

A common finding in foveal-sparing extensive macular atrophy with pseudodrusen implicates basal laminar deposits.

Retina. 2022 Jul 1.

Fragiotta S, Parravano M, Sacconi R, Costanzo E, Viggiano P, Prascina F, Capuano V, Souied EH, Querques G.

Purpose: To characterize structural and clinical alterations preceding the diffuse macular atrophy in extensive macular atrophy with pseudodrusen (EMAP) and their evolution toward atrophic changes. METHODS: A retrospective chart review was performed of patients with early-onset reticular pseudodrusen (i.e., pre-EMAP) younger than 55 years and EMAP with foveal sparing. Patients were included if they had complete medical records and multimodal imaging.

Results: A total of 12 patients were reviewed, of whom 4 of 12 patients (7 eyes) presented a pre-EMAP stage, characterized by the presence of pseudodrusen-like deposits without atrophic changes, while the remaining 8 of 12 patients (10 eyes) exhibited EMAP with foveal sparing (60.1 ± 6.4 years). Subretinal deposits of various stages tended to fade, leaving subretinal pigment epithelium accumulation of hyperreflective material with a physical separation between the retinal pigment epithelium-basal lamina and the Bruch membrane, along with the persistence of hyperreflective material after retinal pigment epithelium loss. These findings preceded atrophy development in a pre-EMAP stage and the EMAP stage with foveal sparing.

Conclusion: Our findings presented distinct multimodal imaging features in eyes with reticular pseudodrusen depicting a peculiar phenotype of rapidly progressing atrophy in midlife. The disease spectrum may include other forms of geographic atrophy allied by thickened basal laminar deposits.

DOI: 10.1097/IAE.0000000000003463

Assessment of retinal microvascular alterations in individuals with amnestic and nonamnestic mild cognitive impairment using optical coherence tomography angiography.

Retina. 2022 Jul 1.

Robbins CB, Akrobetu D, Ma JP, Stinnett SS, Soundararajan S, Liu AJ, Johnson KG, Grewal DS, Fekrat S.

Purpose: To assess retinal microvascular alterations in individuals with amnestic mild cognitive impairment (MCI) and nonamnestic MCI.

Methods: One hundred twelve eyes of 59 amnestic MCI participants, 32 eyes of 17 nonamnestic MCI participants, and 111 eyes of 56 controls with normal cognition were included. Optical coherence tomography angiography vessel density and perfusion density in the Early Treatment Diabetic Retinopathy Study 3-mm circle and ring were assessed. Retinal thickness parameters including retinal nerve fiber layer thickness, ganglion cell-inner plexiform layer thickness, central subfield thickness, and subfoveal choroidal thickness were also analyzed. Multivariable generalized estimating equations were used for statistical analysis.

Results: Perfusion density in the 3-mm inner ring was significantly lower in amnestic MCI patients when compared with nonamnestic MCI participants (0.29 ± 0.03 vs. 0.34 ± 0.09, P = 0.025) and controls with normal cognition (0.29 ± 0.03 vs. 0.39 ± 0.02, P < 0.001), after adjustment for age and sex as covariates. Vessel density, retinal nerve fiber layer thickness, ganglion cell-inner plexiform layer thickness, central subfield thickness, and subfoveal choroidal thickness did not differ among or between diagnostic groups.

Conclusion: Perfusion density was significantly reduced in individuals with amnestic MCI, compared with those with nonamnestic MCI and controls with normal cognition.

DOI: 10.1097/IAE.0000000000003458

REVIEW

Human pluripotent stem cells for the modelling of retinal pigment epithelium homeostasis and disease: A review.

Clinical and Experimental Ophthalmology. 2022 Jun 23.

Hall J, Paull D, Pébay A, Lidgerwood GE.

Human pluripotent stem cells (hPSCs), which include induced pluripotent stem cells and embryonic stem cells, are powerful tools for studying human development, physiology and disease, including those affecting the retina. Cells from selected individuals, or specific genetic backgrounds, can be differentiated into distinct cell types allowing the modelling of diseases in a dish for therapeutic development. hPSC-derived retinal cultures have already been used to successfully model retinal pigment epithelium (RPE) degeneration for various retinal diseases including monogenic conditions and complex disease such as age-related macular degeneration. Here, we will review the current knowledge gained in understanding the molecular events involved in retinal disease using hPSC-derived retinal models, in particular RPE models. We will provide examples of various conditions to illustrate the scope of applications associated with the use of hPSC-derived RPE models.

DOI: 10.1111/ceo.14128

Current and Novel Therapeutic Approaches for Treatment of Diabetic Macular Edema.

Cells. 2022 Jun 17.

Chauhan MZ, Rather PA, Samarah SM, Elhusseiny AM, Sallam AB.

Diabetic macular edema (DME) is a major ocular complication of diabetes mellitus (DM), leading to significant visual impairment. DME's pathogenesis is multifactorial. Focal edema tends to occur when primary metabolic abnormalities lead to a persistent hyperglycemic state, causing the development of microaneurysms, often with extravascular lipoprotein in a circinate pattern around the focal leakage. On the other hand, diffusion edema is due to a generalized breakdown of the inner blood-retinal barrier, leading to profuse early leakage from the entire capillary bed of the posterior pole with the subsequent extravasation of fluid into the extracellular space. The pathogenesis of DME occurs through the interaction of multiple molecular mediators, including the overexpression of several growth factors, including vascular endothelial growth factor (VEGF), insulin-like growth factor-1, angiopoietin-1, and -2, stromal-derived factor-1, fibroblast growth factor-2, and tumor necrosis factor. Synergistically, these growth factors mediate angiogenesis, protease production, endothelial cell proliferation, and migration. Treatment for DME generally involves primary management of DM, laser photocoagulation, and pharmacotherapeutics targeting mediators, namely, the anti-VEGF pathway. The emergence of anti-VEGF therapies has resulted in significant clinical improvements compared to laser therapy alone. However, multiple factors influencing the visual outcome after anti-VEGF treatment and the presence of anti-VEGF non-responders have necessitated the development of new pharmacotherapies. In this review, we explore the pathophysiology of DME and current management strategies. In addition, we provide a comprehensive analysis of emerging therapeutic approaches to the treatment of DME.

DOI: 10.3390/cells11121950

Oxidative Stress as a Main Contributor of Retinal Degenerative Diseases

Antioxidants (Basel). 2022 Jun 17.

Pinilla I, Maneu V.

Retinal degenerative diseases, including inherited retinal dystrophies (IRDs) and acquired multifactorial diseases, such as age-related macular degeneration (AMD), diabetic retinopathy (DR) or ganglion cell damage secondary to glaucoma or other pathologies, are the main causes of blindness in developed countries [...].

DOI: 10.3390/antiox11061190

RISK OF DISEASE

Circulating level of homocysteine contributes to diabetic retinopathy associated with dysregulated lipid profile and impaired kidney function in patients with type 2 diabetes mellitus.

Eye (London). 2022 Jun 23.

Chen X, Zhang X, Nie Y, Gong Z, Sivaprasad S, Fung AT, Wang Q, Qiu B, Xie R, Wang Y.

Background: To test the hypothesis that elevated plasma levels of homocysteine (Hcy) and lipoprotein (a) (LPA) contribute to diabetic retinopathy (DR) associated with dysregulated lipid profile, dyslipidaemia, and kidney function.

Methods: A total of 83 patients with type 2 diabetes mellitus (T2DM) were enrolled in this prospective case-control study. Patients were categorized into those with no DR (DM), non-proliferative DR (NPDR), and proliferative DR (PDR). Age and sex-matched individuals with no diabetes were included in the control group. Biochemical tests, including fasting blood glucose (FBG), glycated hemoglobin (HbA1c), Hcy, LPA, lipid profile, and urine microalbumin (UMA), were evaluated.

Results: Hcy was negatively correlated with high-density lipoprotein-cholesterol (HDL-C) ($p < 0.05$), but positively correlated with [total cholesterol (TC)-HDL-C)/HDL-C] ($p < 0.05$), low-density lipoprotein cholesterol (LDL-C)/HDL-C ($p < 0.05$), and UMA ($p < 0.05$). Traditional risk factors, Hcy, arteriosclerosis-associated plasma indices, and UMA, resulted as the independent risk factors for the occurrence of DM and DR. After controlling for age, sex, duration of DM, and FBG, a multiple ordinal logistic regression model showed that LPA [OR = 2.90, 95% confidence interval (95% CI) 1.16-7.23, $p = 0.023$)], LDL-C (OR = 4.28, 95% CI 1.24-14.79, $p = 0.021$), and (TC-HDL-C)/HDL-C (OR = 1.92, 95% CI 1.05-3.53, $p = 0.035$) were risk factors for DM and DR.

Conclusions: Hcy and LPA contributed to DM and DR. Hcy was positively correlated with kidney dysfunction and the ratios of lipid profiles, and negatively with HDL-C, LPA, LDL-C, and (TC-HDL-C)/HDL-C resulted as predictors of the occurrence of DM and severity of DR.

DOI: 10.1038/s41433-022-02144-w