FEATURED ARTICLE

Progressive peripapillary choroid thinning and retinal neurodegeneration in patients with diabetes: A 3-Year Cohort Study.

Retina (Philadelphia, Pa). 2022 Dec 1

Zhang S, Zhu Z, Bulloch G, Guo X, Shang X, Chen Y, Liao H, Li Y, Huang W, Wang W.

Purpose: To investigate longitudinal changes in peripapillary choroidal thickness (pCT) and retinal nerve fiber thickness (pRNFLT) in patients with Type 2 diabetes mellitus.

Methods: This was a prospective observational cohort study. Patients with Type 2 diabetes mellitus without diabetic retinopathy (DR) at baseline were recruited, followed up for three years, and further divided into an incident DR group and a non-DR group according to the outcome. The pCT and pRNFLT were measured through swept-source optical coherence tomography at 1-year interval, and the mean rates of pCT and pRNFLT thinning were compared between the DR groups.

Results: A total of 682 patients (682 eyes) were included in the final analysis. After 3-years follow-up, 122 (17.89%) developed DR. Both pCT and pRNFLT progressively thinned (-2.37 [-2.80 to -1.95] μm/year; -0.40 [-0.55 to -0.25] μm/year, respectively, $P < 0.05$) and accelerated thinning was observed in the incident DR group. The rates of pCT thinning (-3.92 [-4.96 to -2.88] μm/year, -2.03 [-2.49 to -1.57] μm/year, respectively) and pRNFLT loss (-1.03 [-1.31 to -0.76] μm/year, -0.26 [-0.43 to -0.09] μm/year, respectively) in the incident DR group were 1.93 and 3.96 times faster than those in the non-DR group, respectively. In addition, pCT and pRNFLT thinning were negatively related in Type 2 diabetes mellitus population, and faster pCT thinning indicated slower pRNFLT loss.

Conclusion: Patients with Type 2 diabetes mellitus were at a higher risk of developing DR when accelerated pCT and pRNFLT thinning were present, indicating that heavier choroidal damage and retinal neurodegeneration precede clinical DR. The pCT and pRNFLT have the potential to serve as novel sensitive biomarkers of preclinical and early DR.

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DRUG TREATMANT

Long-term treatment outcomes after bevacizumab therapy for macular neovascularization in Caucasian patients with high myopia.

Retina (Philadelphia, Pa). 2022 Nov 16

Ravenstijn M, Klaver CCW, Yzer S

Purpose: To report long-term treatment outcomes of intravitreal bevacizumab (IVB) in myopic macular neovascularization (MNV).

Methods: Retrospective analysis of longitudinal, clinical data of high myopic MNV patients treated with IVB. One-hundred-seventeen eyes of 106 patients were followed from first injection up to 12 years. Outcome measures were best-corrected visual acuity (BCVA) change during follow-up and myopic MNV recurrence.

Results: Mean (±SD) baseline BCVA (0.56±0.46 LogMar, 20/80) significantly improved after first treatment (0.33±0.33, 20/50, P<0.001). At 4 years (n= 86) BCVA was no longer significantly better than at baseline (0.55±0.57, P = 0.30) and continued to deteriorate to 0.83±0.76 (20/125) at 10 years (n=27). Of the 27 eyes (23%) who reached 10 years of follow-up, 53% developed MNV-related chorioretinal atrophy (CRA). The cumulative incidence of recurrent myopic MNV was 34% at 2 years and 59% at 5 years. BCVA decrease in eyes with or without recurrent MNV was similar (P=0.58). Patchy CRA (HR 3.0, P=0.02) and subfoveal MNVs (HR 2.5, P=0.048) were significantly associated with recurrent MNV.

Conclusion: This retrospective myopic MNV study revealed that visual improvement after IVB injections was not maintained over time. MNV recurrences occurred frequently but did not alter the already poor visual prognosis.

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RISK OF DISEASE

Early choroidal changes detected by swept-source OCT in type 2 diabetes and their association with diabetic kidney disease.

BMJ Open Diabetes Research & Care. 2022 Nov

Da Silva MO, Chaves AECDC, Gobbato GC, Lavinsky F, Schaan BD, Lavinsky D.

Introduction: Microvascular changes in eye and kidney shares some common factors in diabetes mellitus (DM). The purpose was to evaluate choroidal thickness (CT) and choriocapillaris (CC) density in patients with type 2 diabetes (T2D) and their association with diabetic kidney disease (DKD) using swept-source optical coherence tomography (SS-OCT).

Research design and methods: A cross-sectional study was conducted with patients with T2D with mild or no diabetic retinopathy (DR) and non-diabetic controls. CT was measured with SS-OCT, and CC vascular density was measured with OCT angiography. These parameters were compared with inner retinal layers thickness in patients with and without DKD and non-diabetic controls.

Results: Ninety-three eyes from patients with T2D and 34 eyes from controls volunteers were included. Within the T2D group, 56 eyes with DKD and 37 eyes from patients with no diabetic kidney disease were examined. A statistically significant reduction of CT was observed in patients with DKD compared with controls, with no difference in CC density. There was an association between ganglion cell layer and central choroidal thickness reduction in the DKD group.

Conclusions: Patients with T2D with DKD showed a decrease in CT with no difference in CC density compared with non-diabetic controls. This thinning might be related to vascular changes of choroidal layers such as Haller's and Sattler's with preservation of CC density, which is crucial for outer retina

and retinal pigment epithelium health. Longitudinal studies are warranted to determine the association of choroidal changes with the pathogenesis of diabetes, and its association with early DKD and progression to more severe DR.

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GENETICS

GWAS of age-related macular degeneration reveals two new loci implying shared genetic components with central serous chorioretinopathy.

Ophthalmology. 2022 Nov 21

Akiyama M, Miyake M, Momozawa Y, Arakawa S, Maruyama-Inoue M, Endo M, Iwasaki Y, Ishigaki K, Matoba N, Okada Y, Yasuda M, Oshima Y, Yoshida S, Nakao SY, Morino K, Mori Y, Kido A, Kato A, Yasukawa T, Obata R, Nagai Y, Takahashi K, Fujisawa K, Miki A, Nakamura M, Honda S, Ushida H, Yasuma T, Nishiguchi KM, Mori R, Tanaka K, Wakatsuki Y, Yamashiro K, Kadonosono K, Terao C, Ishibashi T, Tsujikawa A, Sonoda KH, Kubo M, Kamatani Y.

Purpose: To investigate the genetic architecture of age-related macular degeneration (AMD) in a Japanese population. DESIGN: Genome-wide association study (GWAS).

Subjects: A total of 3,772 AMD cases and 16,770 controls in the Japanese population were enrolled in the association analyses. METHODS: We conducted a meta-analysis of two independent GWASs that included a total of 2,663 AMD cases and 9,471 controls using the imputation reference panel for genotype imputation specified for the Japanese population (N = 3,541). A replication study was performed employing an independent set of 1,109 AMD cases and 7,299 controls.

Main outcome measure: Associations of genetic variants with AMD. RESULTS: A meta-analysis of the two GWASs identified six loci significantly associated with AMD ($P < 5.0 \times 10^{-8}$). Of these loci, four were known to be associated with AMD (CFH, C2/FB, TNFRSF10A, and ARMS2); two were novel (rs4147157 near WBP1L and rs76228488 near GATA5). The newly identified associations were confirmed in a replication study ($P < 0.01$). After the meta-analysis of all data sets, we observed strong associations in these loci ($P_{meta} = 1.88 \times 10^{-12}$ and 1.35×10^{-9}, for rs4147157 and rs76228488, respectively). When we looked up the associations in the reported central serous chorioretinopathy (CSC) GWAS conducted in the Japanese population, both loci were significantly associated with CSC ($P = 4.86 \times 10^{-3}$ and 4.28×10^{-3}, for rs4147157 and rs76228488, respectively). We performed a genetic colocalization analysis for these loci, and estimated that the posterior probabilities of shared causal variants between AMD and CSC were 0.39 and 0.60 for WBP1L and GATA5, respectively. Genetic correlation analysis focusing on the epidemiologically suggested clinical risk factors implicated shared polygenic architecture between AMD and smoking cessation ($r_g = -0.33$, $P = 0.01$, false discovery rate = 0.099).

Conclusion: Our findings imply shared genetic components conferring the risk of both AMD and CSC.

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Associations of Alzheimer Disease-Protective APOE Variants With Age-Related Macular Degeneration.

JAMA Ophthalmology 2022 Nov 17

Rasmussen KL, Tybjærg-Hansen A, Nordestgaard BG, Frikke-Schmidt R.

Importance: The association of major lipid genes with and their potential as drug targets for age-related macular degeneration (AMD) is unknown. These associations are important to study because AMD is the leading cause of irreversible late-onset blindness in high-income countries.

Objective: To determine whether the full range of structural genetic variation in apolipoprotein E (APOE), a master gene in peripheral and cerebral lipid metabolism, is associated with risk of AMD.

Design, setting, and participants: This cohort study used data from the Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study (CGPS) cohorts. Participants were followed from study inclusion at the time of blood sampling to occurrence of event, death, emigration, or December 7, 2018, whichever came first. For participants in CCHS, the APOE gene was sequenced, and 9 variants with a heterozygote frequency of at least 0.0002 were genotyped in the CGPS. Observers were masked to patient groupings. Data were analyzed from March to September 2021.

Exposures: The exposure was APOE status, and the direct gene product in plasma, apoE levels, was measured in all participants.

Main outcomes and measures: Cox regression was applied to estimate risk of AMD associated with APOE genotype. RESULTS: A total of 105 546 participants (mean [SD] age, 57.7 [13.4] years; 58 140 [55%] female participants) were included. Compared with participants with the common ε33 genotype, risk of AMD was lower in participants with ε44 (multifactorially adjusted hazard ratio [aHR], 0.66; 95% CI, 0.45-0.96) and ε43 (aHR, 0.80; 95% CI, 0.71-0.90) genotypes and higher in the ε32 (aHR, 1.15; 95% CI, 1.00-1.31) genotype. Compared with noncarriers, risk of AMD was higher for participants with Gly145Asp (aHR, 3.53; 95% CI, 1.14-10.96) and Arg154Cys (aHR, 4.52; 95% CI, 1-13-18.13) heterozygotes. Results were similar after further adjustment for lipid traits and after adjustment for the APOE ε2/ε3/ε4 variant. Combining all common and rare structural variants in a weighted allele score, risk of AMD per 1-mg/dL genetically higher plasma apoE was increased in the adjusted model (aHR, 1.12; 95% CI, 1.05-1.19), the adjusted model plus APOE ε2/ε3/ε4 status (aHR, 1.82; 95% CI, 1.20-2.76), and the adjusted model in individuals with the ε33 genotype only (aHR, 1.77; 95% CI, 1.14-2.75).

Conclusions and relevance: These findings highlight that structural variation in APOE beyond the ε2/ε3/ε4 variants may be important for risk of AMD in a population of European ancestry. Rare functional ε2-like variants in APOE have previously been reported to have protective associations for Alzheimer disease but the present findings suggest a simultaneous high risk of AMD. This would limit the drug target potential of mechanisms resembling these variants.

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PATIENT OUTCOMES

Central retinal vein occlusion 36-month outcomes with anti-vascular endothelial growth factors: the Fight Retinal Blindness! registry.

Ophthalmology, Retina. 2022 Nov 9

Hunt A, Nguyen V, Bhandari S, Ponsioen T, McAllister IL, Arnold J, Young S, Gabrielle PH, Mehta H, Toole LO, Alforja S, Zarranz-Ventura J, Barthelmes D, Gillies M.

Purpose: To analyze the 3-year outcomes in a broad population of patients starting vascular endothelial growth factor (VEGF) inhibitors for central retinal vein occlusion (CRVO) in routine clinical practice. DESIGN: Observational database study

Participants: 527 treatment-naïve CRVO eyes that commenced VEGF inhibitors between December 1, 2010-2018 tracked in the Fight Retinal Blindness! registry.

Methods: Longitudinal models were used to plot changes in visual acuity (VA) and central subfield thickness (CST).

Main outcome measures: Mean change in VA from baseline to 36 months, injections, visits, completion, switching and suspensions of therapy >180 days at final review.

Results: Overall (527 eyes) mean VA change (95% CI) was +10 (7, 12) letters, 37% had final VA ≥70 and 30% ≤35 letters, mean CST changed -306µm. Completers (257/527, 49%) had mean 36-month changes in VA and CST of +12 letters and -324µm with a median of 18 injections at 26 visits. The adjusted mean VA change was similar with each VEGF inhibitor (mean, +11.4 letters) despite a greater reduction in CST with aflibercept (-310µm) vs. ranibizumab (-258µm) vs. bevacizumab (-216µm; P < 0.001). Eyes with baseline VA that was trial-eligible (19-73 letters, 356/527, 68%) gained 7 letters, very-poor (<19 letters, 129/527, 24%) gained 22 letters, or very-good (>73 letters, 42/527, 8%) lost 7 letters. Switching (160/527, 30%) was most often to aflibercept (79 eyes). Using suspensions and discontinuation reasons we identified similar proportions had ceased therapy (154/527, 29%) as were still receiving it at 36 months (165/527, 31%). Only 62/527 eyes (12%) had resolution of macular edema without treatment for over 6 months.

Conclusions: Patients with CRVO that commenced VEGF inhibitors in routine care for whom follow-up was available had VA improvements of around 12 letters at three years, but with more than 50% lost to follow the VA outcome for the entire group is likely worse. The choice of VEGF inhibitor influenced CST but not VA outcomes. We estimate that around half of eyes were still receiving injections after 36 months.

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DIAGNOSIS AND IMAGING

Growth of nonexudative macular neovascularization in age-related macular degeneration: an indicator of biological lesion activity.

Eye (London, England). 2022 Nov 25

Wang Y, Sun J, Wu J, Jia H, Feng J, Chen J, Yan Q, Huang P, Wang F, Bo Q, Sun X.

Purpose: To investigate the growth of nonexudative macular neovascularization (MNV) in age-

related macular degeneration (AMD) using swept-source optical coherence tomography angiography (SS-OCTA).

Methods: Patients with treatment-naïve nonexudative AMD in one eye and exudative AMD in the fellow eye who underwent SS-OCTA imaging for at least 12 months were retrospectively reviewed. The MNV area measurement was quantified in eyes with treatment-naïve nonexudative MNV using ImageJ for analysing the correlation between MNV growth and the onset of exudation, as well as evaluating the consistency of the MNV growth rate during the subclinical and exudative stages. Kaplan-Meier survival analysis and logistic regression analyses were used.

Results: In total, 45 eyes with treatment-naïve nonexudative AMD from 45 patients were enrolled. Treatment-naïve nonexudative MNV was identified in 21 eyes (46.67%) at baseline. The development of exudative findings was noted in eight eyes (17.78%), including six eyes with previously noted nonexudative MNV. Eyes with growing MNV (increase in area ≥50% within 12 months) had an increased risk of exudation and developed exudation earlier than eyes with stable MNV (13.60 [6.43-20.77] months versus 31.11 [26.61-35.62] months, $P < 0.0001$, Log-rank test). Consistent growth pattern of MNV lesions was further identified in eyes with growing MNV during anti-VEGF treatment.

Conclusion: SS-OCTA allows to qualitatively and quantitatively evaluate nonexudative MNV in AMD patients. Growing MNV involved higher probabilities and a faster onset of exudation compared to stable MNV. Identifying the growth of MNV on OCTA might be helpful for establishing treatment strategies and follow-up planning.

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Changes on optical coherence tomography angiography and fluorescein angiography in eyes with neovascular age-related macular degeneration.

International Journal of Ophthalmology. 2022 Nov 18

Ahn SM, Choi M, Yun C, Kim SW, Oh J.

Aim: To evaluate the changes on optical coherence tomography angiography (OCTA) and fluorescein angiography (FA) and their correlation in neovascular age-related macular degeneration (nAMD) before and after intravitreal aflibercept injections (IAIs).

Methods: In 43 treatment-naïve patients with nAMD, choroidal neovascularization (CNV) in OCTA were morphologically and quantitatively analyzed before and after IAIs to determine whether they are correlated with leakage on FA or not. By combining CNV in OCTA and leakage in FA, lesions were characterized as three types: L+C+ (with both CNV and leakage), L-C+ (with CNV but without leakage), or L+C- lesion (with leakage outside CNV).

Results: Before IAI, while 27 eyes had L+C+ lesion only, 16 eyes had both L+C+ and L-C+ lesions simultaneously. Tiny capillaries and anastomosis in CNV were more developed in L+C+ lesion, at 86.0% and 58.1%, respectively, relative to 9.3% and 9.3% in L-C+ lesions ($P<0.001$). After IAIs in 33 eyes, tiny capillaries and anastomosis were decreased in the lesions with cessation of leakage on FA ($P<0.001$ and $P=0.001$, respectively). In quantitative analysis, neovascularization length and numbers of junctions and endpoints were also significantly decreased.

Conclusion: Leakage on FA is associated with CNV morphology in OCTA and remained so after IAIs. Therefore, by carefully assessing the morphological and quantitative changes of CNV in OCTA before and after treatment, activity of nAMD is expected even though CNV on OCTA is not completely matched with fluorescein leakage.

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EARLY RESEARCH

Potential CRISPR Base Editing Therapeutic Options in a Sorsby Fundus Dystrophy Patient.

Genes (Basel). 2022 Nov 12

Elsayed MEAA, Kaukonen M, Kiraly P, Kapetanovic JC, MacLaren RE.

TIMP3 mutations are associated with early-onset macular choroidal neovascularisation for which no treatment currently exists. CRISPR base editing, with its ability to irreversibly correct point mutations by chemical modification of nucleobases at DNA level, may be a therapeutic option. We report a bioinformatic analysis of potential therapeutic options in a patient presenting with Sorsby fundus dystrophy. Genetic testing in a 35-year-old gentleman with bilateral macular choroidal neovascularisation revealed the patient to be heterozygous for a TIMP3 variant c.610A>T, p.(Ser204Cys). Using a glycosylase base editor (GBE), another DNA-edit could be introduced that would revert the variant back to wild-type on amino acid level. Alternatively, the mutated residue could be changed to another amino acid that would be better tolerated, and for that, an available 'NG'-PAM site was found to be available for the SpCas9-based adenine base editor (ABE) that would introduce p.(Ser204Arg). In silico analyses predicted this variant to be non-pathogenic; however, a bystander edit, p.Ile205Thr, would be introduced. This case report highlights the importance of considering genetic testing in young patients with choroidal neovascularisation, particularly within the context of a strong family history of presumed wet age-related macular degeneration, and describes potential therapeutic options.

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