FEATURED ARTICLE

Association of lipid-lowering drugs and antidiabetic drugs with age-related macular degeneration: a meta-analysis in Europeans

British Journal Ophthalmology. Nov 2022

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Background/aims: To investigate the association of commonly used systemic medications with prevalent age-related macular degeneration (AMD) in the general population.

Methods: We included 38 694 adults from 14 population-based and hospital-based studies from the European Eye Epidemiology consortium. We examined associations between the use of systemic medications and any prevalent AMD as well as any late AMD using multivariable logistic regression modelling per study and pooled results using random effects meta-analysis.

Results: Between studies, mean age ranged from 61.5±7.1 to 82.6±3.8 years and prevalence ranged from 12.1% to 64.5% and from 0.5% to 35.5% for any and late AMD, respectively. In the meta-analysis of fully adjusted multivariable models, lipid-lowering drugs (LLD) and antidiabetic drugs were associated with lower prevalent any AMD (OR 0.85, 95% CI=0.79 to 0.91 and OR 0.78, 95% CI=0.66 to 0.91). We found no association with late AMD or with any other medication.

Conclusion: Our study indicates a potential beneficial effect of LLD and antidiabetic drug use on prevalence of AMD across multiple European cohorts. Our findings support the importance of metabolic processes in the multifactorial aetiology of AMD.

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BIOMARKERS

Relationship Between Drusen Height and OCT Biomarkers of Atrophy in Non-Neovascular AMD.

Investigative Ophthalmology & Visual Science. 2022 Oct 3

Au A, Santina A, Abraham N, Levin MF, Corradetti G, Sadda S, Sarraf D.

Purpose: To determine if increasing drusen height correlates with predictive optical coherence tomography (OCT) biomarkers of atrophy.

Methods: Retrospective cross-sectional study that enrolled patients with drusen associated with intermediate AMD. Macular drusen were classified as small, intermediate, large, or very large based on OCT quartile measurement of height. Drusen diameter was also tabulated. The presence and localization of the OCT biomarkers of atrophy were assessed: disruption of the external limiting membrane and ellipsoid zone, intraretinal hyper-reflective foci, RPE disruption, choroidal

hypertransmission, and presence of hyporeflective cores. Predictive OCT biomarkers of atrophy were correlated with drusen height.

Results: A total of 155 eyes from 104 patients met the inclusion and exclusion criteria. The mean age was 75.7 ± 8.7 years, and patients were predominantly female (74.0%). The mean visual acuity was logMAR 0.2 ± 0.2 (Snellen equivalent 20/32). The average drusen height was 134.6 ± 107.5 µm and the greatest horizontal diameter was 970.7 ± 867.4 µm. Disruption of the external limiting membrane and ellipsoid zone, RPE thickening or thinning, intraretinal hyper-reflective foci, choroidal hypertransmission, and presence of hyporeflective cores ($P < 0.05$) were more common in eyes with large drusen and very large drusen versus small or intermediate drusen. All biomarkers were positively correlated with drusen height. OCT biomarkers of atrophy were predominantly located at the apex of the drusen.

Conclusions: Predictive OCT biomarkers of atrophy, specifically signs of RPE breakdown and disruption, occur more commonly in large or very large drusen, especially in drusen with greater height and separation of the RPE from the underlying choroid.

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DIAGNOSIS AND IMAGING

Impact of Reticular Pseudodrusen on Choriocapillaris Flow Deficits and Choroidal Structure on Optical Coherence Tomography Angiography.

Investigative Ophthalmology & Visual Science. 2022 Nov 1

Wu Z, Zhou X, Chu Z, Gregori G, Wang RK, Rosenfeld PJ, Guymer RH.

Purpose: To examine the impact of reticular pseudodrusen (RPD) on choriocapillaris blood flow and choroidal structure in individuals with intermediate age-related macular degeneration (AMD).

Methods: Individuals with bilateral large drusen underwent optical coherence tomography (OCT), color fundus photography, near-infrared reflectance, and fundus autofluorescence imaging to determine the presence of RPD. These participants also underwent swept-source OCT angiography (SS-OCTA) imaging to determine (1) choriocapillaris flow deficit (FD) parameters, including the percentage, mean size, and number of FDs present; and (2) choroidal structural parameters, including mean choroidal thickness and choroidal vascularity index. Differences in these parameters between eyes with and without coexistent RPD were examined with and without adjustment for potential key confounders such as drusen volume from the SS-OCTA scans and age.

Results: This study included 102 eyes from 51 individuals with bilateral large drusen, and the analyses showed that there were no significant differences in the choriocapillaris FD parameters ($P \geq 0.062$ for all) and choroidal structural parameters ($P \geq 0.059$ for all), with or without adjustment for potential confounders in this cohort. However, the percentage of FDs and the mean FD size were both significantly greater with increasing drusen volume ($P \leq 0.038$ for both).

Conclusions: The coexistence of RPD in eyes of individuals with intermediate AMD was not associated with significant impairments in choriocapillaris blood flow and choroidal vascular structural changes, with or without adjustment for key confounders. These findings suggest that macular changes in these vascular parameters may not be associated with the presence of RPD.

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Optical coherence tomography angiography analysis of microvascular abnormalities and vessel density in treatment-naïve eyes with diabetic macular edema.

BMC Ophthalmology. 2022 Nov 3

Braham IZ, Kaouel H, Boukari M, Ammous I, Errais K, Boussen IM, Zhioua R.

Background: The aim of this study was to evaluate the structural retinal vascular integrity using optical coherence tomography angiography (OCTA) in treatment-naïve eyes with diabetic macular edema (DME) and to compare it with findings in diabetic eyes without DME.

Methods: In this prospective study, 70 eyes with diabetic retinopathy were included (37 eyes with DME and 33 eyes without DME). The medical records, including swept-source optical coherence tomography and 9 × 9 mm swept-source OCTA images were reviewed and compared between DME and non-DME groups. Microaneurysms, intraretinal microvascular abnormalities (IRMA), areas of capillary non perfusion, foveal avascular zone (FAZ), and capillary vascular density (CVD) were analyzed in the superficial capillary plexus (SCP) and the deep capillary plexus (DCP).

Results: Compared to the non-DME eyes, DME eyes had more microaneurysms in the SCP and the DCP (p = 0,039 and p = 0,024 respectively), more IRMA in the SCP (p = 0,005), larger areas of capillary non perfusion in the SCP and the DCP (p = 0,026 and p = 0,02 respectively) and larger FAZ in both plexuses (p = 0,048 in the SCP and p = 0,012 in the DCP). The CVD in the DCP was lower in DME eyes compared to non-DME eyes (p = 0,007). The severity of DME was significantly correlated to the number of microaneurysms and to the FAZ surface. Central macular thickness was significantly correlated with the number of microaneurysms in the DCP, the surface of capillary non perfusion areas and the FAZ area in both plexuses.

Conclusions: OCTA with a 9 × 9 mm field of view showed that the retinal vascular integrity regarding the number of microaneurysms, the number of IRMA, the surface of capillary non perfusion areas, the FAZ area and the CVD, was significantly more impaired in DME eyes compared to diabetic eyes without DME. The DCP seemed to be more affected in diabetic eyes with and without DME than the SCP.

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DRUG TREATMENT

Two-year outcomes of the APOLLON observational study of intravitreal aflibercept monotherapy in France in patients with diabetic macular edema.

Scientific Reports. 2022 Oct 29

Korobelnik JF, Daien V, Faure C, Tadayoni R, Giocanti-Aurégan A, Dot C, Kodjikian L, Massin P; APOLLON study investigators.

APOLLON (NCT02924311) was a prospective observational study to evaluate the effectiveness of intravitreal aflibercept (IVT-AFL) treatment of diabetic macular edema (DME) over 24 months in

routine clinical practice in France. The primary endpoint was mean change from baseline in best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study letters) by 12 months, and safety was monitored throughout the study. Of 402 patients enrolled across 61 participating clinics and hospitals in France, 168 patients were followed for at least 24 months and included in the effectiveness analyses (79 treatment-naïve and 89 previously treated). After 24 months of IVT-AFL treatment, the mean (± standard deviation [SD]) change in BCVA from baseline was + 6.5 (± 10.7) letters in treatment-naïve patients ($p < 0.001$) and + 1.6 (± 17.0) letters in previously treated patients ($p = 0.415$) from a baseline of 63.8 (± 13.6) and 60.5 (± 16.5) letters. The mean number of IVT-AFL treatments over 24 months was 11.3 (± 4.9) and 11.9 (± 4.7) for treatment-naïve and previously treated patients. This final analysis of the APOLLON study indicated that following 24 months of IVT-AFL treatment in routine clinical practice in France, treatment-naïve patients with DME achieved significant gains in visual acuity and previously treated patients maintained prior visual acuity gains.Trial registration number: NCT02924311.

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The effect of vitreomacular interface in neovascular age-related macular degeneration treated with intravitreal injection of anti-VEGF.

BMC Ophthalmology. 2022 Nov 3

Han F, Chen X, Zhao R, Jin X, Tan W, Zhang Y.

Background: The purpose of this study is to study the effect of repeated intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs on vitreomacular interface.

Methods: Neovascular age-related macular degeneration patients who received intravitreal injections of anti-VEGF drugs were included. Eyes with severe vitreous opacity, uveitis, complicated cataract surgery and previous vitrectomy were excluded. Vitreomacular interface, best corrected visual acuity (BCVA) and central retinal thickness (CRT) assessment were performed once a month for at least 3 months. The nature and time of the change event are recorded. Groups were divided according to whether vitreomacular interface change events occurred. To analyse the risk factors of vitreomacular interface changes and their influence on treatment effect.

Results: A total of 87 eyes were evaluated. Vitreomacular interface change event occurred in 9 eyes. Pre-existing vitreomacular interface abnormality (VMIA) was a risk factor for the VMI change ($P = 0.033$, OR = 16.518, 95% CI: 1.258 to 216.939). 60% of interface events occurred in the first 3 months of treatment. The final BCVA of eyes with vitreomacular interface unchanged was significantly higher than that at baseline ($P = 0.001$), and the final CRT was also significantly lower than that at baseline ($P < 0.001$). The final CRT of eyes vitreomacular interface changed was significantly lower than that at baseline ($P = 0.015$), however, there was no statistical significance in BCVA ($P = 0.468$).

Conclusion: Intravitreal injection of anti-VEGF drugs has a certain probability to cause changes in the vitreomacular interface, and the risk is higher in eyes with pre-existing vitreomacular interface abnormality. The effect of intravitreal injections on the vitreomacular interface was concentrated in the first three injections, and subsequent increases in the number of injections did not significantly increase the risk of vitreomacular interface abnormality. Ophthalmologists should increase attention to the vitreomacular interface in the early stages of anti-VEGF therapy and counsel patients accordingly.

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PATHOGENSIS

Characteristics of intermediate age-related macular degeneration with hyperreflective foci.

Scientific Reports. 2022 Nov 1

Kikushima W, Sakurada Y, Sugiyama A, Yoneyama S, Matsubara M, Fukuda Y, Shijo T, Kotoda Y, Fragiotta S, Kashiwagi K.

Hyperreflective foci (HRF) are the findings observed in optical coherence tomography (OCT) in several retinal diseases and are believed to be associated with the increased risk of atrophy in eyes with age-related macular degeneration (AMD). In this study, we investigated the clinical and genetic characteristics of intermediate AMD with HRF. We reviewed the medical charts for 155 patients with intermediate AMD, in whom macular neovascularization (MNV) was observed in the contralateral eye. The presence or absence of an HRF was evaluated using a spectral-domain OCT volume scan spanning the macular region. Patients were followed longitudinally for at least 12 months, and the maximum follow-up period was 60 months. Genotyping of ARMS2 A69S and CFH I62V was performed in all participants. Of the 155 patients (mean age: 77.8 ± 7.6 years, male/female: 103/52), HRF was observed in 53 eyes (34.2%) and was significantly associated with type-3 MNV ($p = 1.0 \times 10-5$) in the contralateral eye, pseudodrusen ($p = 5.0 \times 10-4$), thinner subfoveal choroidal thickness ($p = 0.013$), and risk of ARMS2 A69S ($p = 0.023$). During follow-up (40.8 ± 17.5), 38 eyes (24.5%) developed advanced AMD. The mean time to the onset of advanced AMD was 29.8 ± 12.9 months in eyes with intermediate AMD. HRF was associated with MNV ($p = 1.0 \times 10-3$), but not with atrophy.

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EPIDEMIOLOGY

UK Biobank retinal imaging grading: methodology, baseline characteristics and findings for common ocular diseases.

Eye (London, England). 2022 Nov 3

Warwick AN, Curran K, Hamill B, Stuart K, Khawaja AP, Foster PJ, Lotery AJ, Quinn M, Madhusudhan S, Balaskas K, Peto T; UKBB Eye and Vision Consortium.

Background/objectives: This study aims to describe the grading methods and baseline characteristics for UK Biobank (UKBB) participants who underwent retinal imaging in 2009-2010, and to characterise individuals with retinal features suggestive of age-related macular degeneration (AMD), glaucoma and retinopathy.

Methods: Non-mydriatic colour fundus photographs and macular optical coherence tomography (OCT) scans were manually graded by Central Administrative Research Facility certified graders and quality assured by clinicians of the Network of Ophthalmic Reading Centres UK. Captured retinal features included those associated with AMD (≥1 drusen, pigmentary changes, geographic atrophy or exudative AMD; either imaging modality), glaucoma (≥0.7 cup-disc ratio, ≥0.2 cup-disc ratio difference between eyes, other abnormal disc features; photographs only) and retinopathy

(characteristic features of diabetic retinopathy with or without microaneurysms; either imaging modality). Suspected cases of these conditions were characterised with reference to diagnostic records, physical and biochemical measurements.

Results: Among 68,514 UKBB participants who underwent retinal imaging, the mean age was 57.3 years (standard deviation 8.2), 45.7% were men and 90.6% were of White ethnicity. A total of 64,367 participants had gradable colour fundus photographs and 68,281 had gradable OCT scans in at least one eye. Retinal features suggestive of AMD and glaucoma were identified in 15,176 and 2184 participants, of whom 125 (0.8%) and 188 (8.6%), respectively, had a recorded diagnosis. Of 264 participants identified to have retinopathy with microaneurysms, 251 (95.1%) had either diabetes or hypertension.

Conclusions: This dataset represents a valuable addition to what is currently available in UKBB, providing important insights to both ocular and systemic health.

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RISK OF DISEASE

Hospital-based study of risk factors associated with development of myopic macular neovascularization in highly myopic eyes.

Ophthalmic Research. 2022 Oct 19.

Du R, Xie S, Lu H, Chen C, Xiong J, Uramoto K, Takahashi H, Onishi Y, Kamoi K, Nakao N, Fang Y, Ohno-Matsui K.

Introduction: Myopic macular neovascularization (MNV) is the most common cause of a reduction of central vision in eyes with pathologic myopia, and it can progress to macular atrophy in the long-term. The aim of this study was to determine the risk factors associated with the development of MNVs.

Methods: There were 17,198 follow-up records from 5,409 eyes of 2,784 highly myopic patients that were reviewed. The general information and ophthalmic information in the records were studied. The significance of the correlations of factors associated with the development and predicting the development of myopic MNV were determined.

Results: Being a woman (odds ratio [OR]: 0.727, P<0.001), having a longer axial length (OR = 0.948, P<0.001), a poorer baseline best-correct visual acuity (BCVA, OR = 2.098, P<0.001), having severe myopic maculopathy (overall: P<0.001), prior myopic MNV in the fellow eye (OR = 4.105, P<0.001), presence of patchy atrophy (overall P<0.001), lacquer cracks (OR = 1.718, P<0.001), prior foveal retinal detachment (RD, OR = 3.269, P<0.001), prior macular hole (MH, OR = 0.641, P <0.001), prior macular retinoschisis (OR = 1.533, P<0.001), and prior macular edema (OR = 1.508, P<0.001) were significantly correlated with the development of myopic MNV. Eyes with MNV and patchy atrophy would require an intensive follow-up examination for myopic patients as the fellow eye would have a risk of >70% for the development of myopic MNV in 3-years and nearly 80% in 5-years.

Conclusions: Clinicians need to pay special attention to eyes with severe grades of myopic maculopathy, prior myopic MNV in the fellow eye, presence of patchy atrophy, and prior foveal

retinal detachment to determine the onset of myopic MNV.

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CASE REPORTS

Temporary Vitelliform Regression After Intravitreal Ranibizumab Injection for Macular Neovascularization Complicating Best Disease.

International Medical Case Reports Journal. 2022 Oct 18

Fayed A.

Background: In this report, we present a case of a 12-year-old boy with Best vitelliform macular dystrophy (BVMD) complicated by macular neovascularization (MNV) and treated with two intravitreal ranibizumab injections. We document an unusual temporary regression of his vitelliform deposits and describe a 2-year follow-up course through multimodal imaging.

Case presentation: A 12-year-old boy complaining of metamorphopsia presented with bilateral yellowish subfoveal deposits, suggestive of BVMD, which was confirmed by fundus autofluorescence and electrooculography. The left eye showed an inferior juxtafoveal complicating MNV, for which the patient was treated with two intravitreal ranibizumab injections. In addition to demonstrating a remarkable response to injection, both clinically and through various multimodal imaging modalities, optical coherence tomography (OCT) showed a surprising temporary resolution of the subfoveal hypopreflective space denoting a regression in the lipofuscin deposits accumulating at the RPE and the subfoveal space. Within 2 months, there was a subsequent build-up of the subfoveal space and lipofuscin reaccumulation through serial imaging despite the clear regression of the MNV. The patient remained stable over a course of 2 years.

Conclusion: Our findings cast light on a rather unusual response to intravitreal anti-VEGF injections that has not been previously reported in literature in the form of a temporary disappearance of the subfoveal vitelliform deposits, which later began to reaccumulate. This process may reflect a temporary relief of the RPE dysfunction or decreased photoreceptor damage with regression of the complicating MNV, leading to decreased vitelliform deposition. Adding to other reports, our findings also provide a 2-year-long follow-up with serial multimodal documentation of the response to injection and suggest a favorable long-term prognosis for intravitreal anti-VEGF injections in eyes with BVMD presenting with early complicating MNVs.

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