Drug Treatment


Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis.

Virgili G1, Parravano M, Evans JR, et al.

**Background:** Diabetic macular oedema (DMO) is a common complication of diabetic retinopathy. Antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) can reduce oedema, improve vision and prevent further visual loss. These drugs have replaced laser photocoagulation as the standard of care for people with DMO.

**Objectives:** The 2014 update of this review found high-quality evidence of benefit with anti-VEGF modalities, compared to laser photocoagulation, for the treatment of DMO. The objective of this updated review is to compare the effectiveness and safety of the different anti-VEGF drugs using network meta-analysis methods.

**Search Methods:** We searched various electronic databases on 26 April 2017.

**Selection Criteria:** We included randomised controlled trials (RCTs) that compared any anti-angiogenic drug with an anti-VEGF mechanism of action versus another anti-VEGF drug, another treatment, sham or no treatment in people with DMO.

**Data Collection & Analysis:** We used standard Cochrane methods for pair-wise meta-analysis and we augmented this evidence using network meta-analysis methods. We focused on the relative efficacy and safety of the three most commonly used drugs as interventions of direct interest for practice: aflibercept and ranibizumab, used on-label; and off-label bevacizumab. We collected data on three efficacy outcomes (gain of 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters; mean change in best-corrected visual acuity (BCVA); mean change in central retinal thickness (CRT)), three safety outcomes (all severe systemic adverse events (SSAEs); all-cause death; arterial thromboembolic events) and quality of life. We used Stata ‘network’ meta-analysis package for all analyses. We investigated the risk of bias of mixed comparisons based on the variance contribution of each study, having assigned an overall risk of bias to each study.
Main Results: Twenty-four studies included 6007 participants with DMO and moderate vision loss, of which two studies randomised 265 eyes of 230 participants and one was a cross-over study on 56 participants (62 eyes) that was treated as a parallel-arm trial. Data were collected on drugs of direct interest from three studies on aflibercept (975 eyes), eight studies on bevacizumab (515 eyes), and 14 studies on ranibizumab (1518 eyes). As treatments of indirect interest or legacy treatment we included three studies on pegaptanib (541 eyes), five studies on ranibizumab plus prompt laser (557 eyes), one study on ranibizumab plus deferred laser (188 eyes), 13 studies on laser photocoagulation (936 eyes) and six studies on sham treatment (793 eyes). Aflibercept, bevacizumab and ranibizumab were all more effective than laser for improving vision by 3 or more lines after one year (high-certainty evidence). Approximately one in 10 people improve vision with laser, and about three in 10 people improve with anti-VEGF treatment: risk ratio (RR) versus laser 3.66 (95% confidence interval (CI) 2.79 to 4.79) for aflibercept; RR 2.47 (95% CI 1.81 to 3.37) for bevacizumab; RR 2.76 (95% CI 2.12 to 3.59) for ranibizumab. On average there was no change in visual acuity (VA) with laser after one year, compared with a gain of 1 or 2 lines with anti-VEGF treatment: laser versus aflibercept mean difference (MD) -0.20 (95% CI -0.22 to -0.17) logMAR; versus bevacizumab MD -0.12 (95% CI -0.15 to -0.09) logMAR; versus ranibizumab MD -0.12 (95% CI -0.14 to -0.10) logMAR. The certainty of the evidence was high for the comparison of aflibercept and ranibizumab with laser and moderate for bevacizumab comparison with laser due to inconsistency between the indirect and direct evidence. People receiving ranibizumab were less likely to gain 3 or more lines of VA at one year compared with aflibercept: RR 0.75 (95% CI 0.60 to 0.94), moderate-certainty evidence. For every 1000 people treated with aflibercept, 92 fewer would gain 3 or more lines of VA at one year if treated with ranibizumab (22 to 148 fewer). On average people receiving ranibizumab had worse VA at one year (MD 0.08 logMAR units, 95% CI 0.05 to 0.11), moderate-certainty evidence; and higher CRT (MD 39 µm, 95% CI 2 µm to 76 µm; low-certainty evidence). Ranibizumab and bevacizumab were comparable with respect to aflibercept and did not differ in terms of VA: RR of gain of 3 or more lines of VA at one year 1.11 (95% CI 0.87 to 1.43), moderate-certainty evidence, and difference in change in VA was 0.00 (95% CI -0.02 to 0.03) logMAR, moderate-certainty evidence. CRT reduction favoured ranibizumab by -29 µm (95% CI -58 µm to -1 µm, low-certainty evidence). There was no evidence of overall statistical inconsistency in our analyses. The previous version of this review found moderate-certainty evidence of good safety of antiangiogenic drugs versus control. This update used data at the longest available follow-up (one or two years) and found that aflibercept, ranibizumab and bevacizumab do not differ regarding systemic serious adverse events (SSAEs) (moderate- or high-certainty evidence). However, risk of bias was variable, loop inconsistency could be found and estimates were not precise enough on relative safety regarding less frequent events such as arterial thromboembolic events or death (low- or very low-certainty evidence). Two-year data were available and reported in only four RCTs in this review. Most industry-sponsored studies were open-label after one year. One large publicly-funded study compared the three drugs at two years and found no difference.

Authors’ Conclusion: Anti-VEGF drugs are effective at improving vision in people with DMO with three to four in every 10 people likely to experience an improvement of 3 or more lines VA at one year. Aflibercept may confer some advantage over ranibizumab and bevacizumab in people with DMO at one year in visual and anatomic terms but it is unclear whether this applies to the long-term. There is a need for more evidence on the long-term (greater than two years) comparative effects of these anti-VEGF agents. Evidence from RCTs may not apply to real-world practice, where people in need of antiangiogenic treatment are often under-treated and under-monitored. We found no signals of differences in overall safety between the three antiangiogenic drugs that are currently available to treat DMO, but our estimates are imprecise for cardiovascular events and death.

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Other treatment & diagnosis


Dexamethasone for unresponsive diabetic macular oedema: optical coherence tomography biomarkers.


**PURPOSE:** To analyse the effects of intravitreal dexamethasone implant (DEX) in patients with diabetic macular oedema (DME) unresponsive to ranibizumab treatment, in relation to the inflammatory optical coherence tomography (OCT) retinal features, subfoveal neuroretinal detachment (SND) and hyperreflective retinal spots (HRS).

**METHODS:** Patients with DME poorly responsive to three injections of ranibizumab were treated with DEX. Best-corrected visual acuity (BCVA) and central macula thickness (CMT, measured by Spectralis SD-OCT) were assessed at baseline and at 1, 3, and 6 months.

**RESULTS:** Overall, 44 eyes were included in the study. In the whole group, mean BCVA (baseline 51.5 ± 8.3 letters) increased significantly at 1 month (to 56.9 ± 8.8 letters; Tukey HSD p = 0.017) and was 55.5 ± 8.8 letters at 3 months (Tukey HSD p = 0.128). Central macula thickness (CMT) reduced significantly at 1 and 3 months (417 ± 149 μm and 469 ± 128 μm, respectively, both Tukey HSD p < 0.001 versus baseline). Subgroup analysis showed a significant BCVA increase at 1 month in eyes with SND + HRS (from 51.2 ± 9.2 to 58.2 ± 9.0, p = 0.029), and a trend to BCVA increase in eyes with HRS (from 52.3 ± 6.4 to 56.8 ± 7.9, p = 0.080), with a significant CMT decrease in both groups (p < 0.001). No changes of either parameter were found in eyes without SND and HRS.

**CONCLUSION:** Spectral domain OCT is useful in identifying some inflammatory features in DME. Among DME eyes ‘poorly responsive’ to ranibizumab, those with SND and HRS responded better to DEX implants than those without these features.

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Cell-based therapy for retinal disease: the new frontier.

Zarbin M.

**ABSTRACT:** The availability of noninvasive high-resolution imaging technology, the immune-suppressive nature of the subretinal space, and the existence of surgical techniques that permit transplantation surgery to be a safe procedure all render the eye an ideal organ in which to begin cell-based therapy in the central nervous system. A number of early stage clinical trials are underway to assess the safety and feasibility of cell-based therapy for retinal blindness. Cell-based therapy using embryonic stem cell-derived differentiated cells (e.g., retinal pigment epithelium (RPE)), neural progenitor cells, photoreceptor precursors, and bone marrow-derived hematopoietic stem/progenitor cells has demonstrated successful rescue and/or replacement in preclinical models of human retinal degenerative disease. Additional research is needed to identify the mechanisms that control synapse formation/disjunction (to improve photoreceptor transplant efficacy), to identify factors that limit RPE survival in areas of geographic atrophy (to improve RPE transplant efficacy in eyes with age-related macular degeneration), and to identify factors that regulate immune surveillance of the subretinal space (to improve long-term photoreceptor and RPE transplant survival).

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**Quantitative fundus autofluorescence in non-neovascular age-related macular degeneration.**

Orellana-Rios J, Yokoyama S, Agee JM, et al.

**BACKGROUND AND OBJECTIVE:** To use quantitative fundus autofluorescence (qAF) to analyze different stages of non-neovascular age-related macular degeneration (AMD).

**PATIENTS AND METHODS:** In this cohort study, 38 pseudophakic patients and 36 age-matched controls participated. We performed near-infrared, spectral-domain optical coherence tomography and qAF imaging on 31 pseudophakic eyes and controls of participants older than 60 years with non-neovascular AMD phenotypes using the Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany).

**RESULTS:** The patients included in this study had a mean age of 83.9 years, and 35.7% patients were men. Mean qAF was higher in control participants than in all patients with AMD (P < .001). According to non-neovascular AMD phenotype, mean qAF levels were significantly lower in eyes with subretinal drusenoid deposits than in control eyes (P < .05). The lowest mean qAF was in patients with geographic atrophy.

**CONCLUSION:** Quantitative fundus autofluorescence of non-neovascular AMD decreases from normal to early to late AMD, suggesting that loss of lipofuscin fluorophores, not increase, signifies AMD progression.

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**Intraretinal fluid identification via enhanced maps using optical coherence tomography images.**

Vidal PL, de Moura J, Novo J, et al.

**ABSTRACT:** Nowadays, among the main causes of blindness in developed countries are age-related macular degeneration (AMD) and the diabetic macular edema (DME). Both diseases present, as a common symptom, the appearance of cystoid fluid regions inside the retinal layers. Optical coherence tomography (OCT) image modality was one of the main medical imaging techniques for the early diagnosis and monitoring of AMD and DME via this intraretinal fluid detection and characterization. We present a novel methodology to identify these fluid accumulations by means of generating binary maps (offering a direct representation of these areas) and heat maps (containing the region confidence). To achieve this, a set of 312 intensity and texture-based features were studied. The most relevant features were selected using the sequential forward selection (SFS) strategy and tested with three archetypal classifiers: LDC, SVM and Parzen window. Finally, the most proficient classifier is used to create the proposed maps. All of the tested classifiers returned satisfactory results, the best classifier achieving a mean test accuracy higher than 94% in all of the experiments. The suitability of the maps was evaluated in a context of a screening issue with three different datasets obtained with two different devices, testing the capabilities of the system to work independently of the used OCT device. The experiments with the map creation were performed using 323 OCT images. Using only the binary maps, more than 91.33% of the images were correctly classified. With only the heat maps, the proposed methodology correctly separated 93.50% of the images.

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Epidemiology


Association of dietary nitrate intake with the 15-Year incidence of age-related macular degeneration.


**BACKGROUND:** Dietary nitrate, found predominantly in green leafy vegetables and beetroot, is a precursor of nitric oxide. Under- or overproduction of nitric oxide is implicated in the etiology of several eye diseases. However, the potential influence of dietary nitrate intake on age-related macular degeneration (AMD) risk has not been assessed.

**OBJECTIVE:** To investigate the temporal association between dietary nitrate intake (from both vegetable and nonvegetable sources) and the 15-year incidence of AMD, independent of potential confounders.


**PARTICIPANTS/SETTING:** The Blue Mountains Eye Study is a population-based study of adults aged 49+ at baseline, from a region west of Sydney, Australia. At baseline, 2,856 participants with complete dietary data and AMD information were examined, and of these, 2,037 participants were re-examined 15 years later and thus included in incidence analysis.

**MAIN OUTCOMES MEASURED:** Incidence of AMD (main outcome) was assessed from retinal photographs. Dietary intake was assessed using a semiquantitative food-frequency questionnaire. Nitrate intake from vegetables and nonvegetable sources was calculated by use of a validated comprehensive database.

**RESULTS:** After adjusting for age, sex, smoking, energy intake, fish consumption, and AMD risk alleles (complement factor H and age-related maculopathy susceptibility-2 single nucleotide polymorphisms), participants in the third quartile compared with those in the first quartile (reference group) of total nitrate and total vegetable nitrate intake had reduced risk of incident early AMD: odds ratio (OR) 0.61 (95% CI 0.41 to 0.90) and OR 0.65 (95% CI 0.44 to 0.96), respectively. Significant associations were not observed between the fourth vs first quartile of total nitrate and vegetable nitrate intake with incident early AMD: OR 0.74 (95% CI 0.51 to 1.08) and OR 0.69 (95% CI 0.47 to 1.00), respectively. Nonsignificant associations were also observed with 15-year incidence of late AMD and total nonvegetable nitrate intake.

**CONCLUSIONS:** These novel findings could have important implications, if the association between total nitrate intake and vegetable nitrate intake and 15-year incidence of early AMD is confirmed in other observational or intervention studies.

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Increased high density lipoprotein-levels associated with age-related macular degeneration. Evidence from the EYE-RISK and E3 Consortia.

Colijn JM, Hollander AID, Demirkan A, et al.

**PURPOSE:** Genetic and epidemiologic studies have shown that lipid genes and High Density Lipoproteins...
(HDL) are implicated in age-related macular degeneration (AMD). We studied circulating lipid levels in relation to AMD in a large European dataset, and investigated whether this relationship is driven by certain sub fractions.

**DESIGN:** (Pooled) analysis of cross-sectional data.

**PARTICIPANTS:** 30,953 individuals aged 50+ participating in the E3 consortium; and 1530 individuals from the Rotterdam Study with lipid sub fraction data.

**METHODS:** In E3, AMD features were graded per eye on fundus photographs using the Rotterdam Classification. Routine blood lipid measurements were available from each participant. Data on genetics, medication and confounders such as body mass index, were obtained from a common database. In a subgroup of the Rotterdam Study, lipid sub fractions were identified by the Nightingale biomarker platform. Random-intercepts mixed-effects models incorporating confounders and study site as a random-effect were used to estimate the associations.

**MAIN OUTCOME MEASURES:** early, late or any AMD, phenotypic features of early AMD, lipid measurements.

**RESULTS:** HDL was associated with an increased risk of AMD, corrected for potential confounders (Odds Ratio (OR) 1.21 per 1mmol/L increase (95% confidence interval[CI] 1.14-1.29); while triglycerides were associated with a decreased risk (OR 0.94 per 1mmol/L increase [95%CI 0.91-0.97]). Both were associated with drusen size, higher HDL raises the odds of larger drusen while higher triglycerides decreases the odds. LDL-cholesterol only reached statistical significance in the association with early AMD (p=0.045). Regarding lipid sub fractions: the concentration of extra-large HDL particles showed the most prominent association with AMD (OR 1.24 [95%CI 1.10-1.40]). The CETP risk variant (rs17231506) for AMD was in line with increased-HDL levels (p=7.7x10⁻⁷); but LIPC risk variants (rs2043085, rs2070895) were associated in an opposite way (p=1.0x10⁻⁶ and 1.6x10⁻⁴).

**CONCLUSIONS:** Our study suggests that HDL-cholesterol is associated with increased risk of AMD and triglycerides negatively associated. Both show the strongest association with early AMD and drusen. Extra-large HDL sub fractions seem to be drivers in the relation with AMD, variants in lipid genes play a more ambiguous role in this association. Whether systemic lipids directly influence AMD or represent lipid metabolism in the retina remains a question to be answered.

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**Age-related macular degeneration in chronic kidney disease: a meta-analysis of observational studies.**

Chen YJ, Yeung L, Sun CC, et al.

**BACKGROUND:** Age-related macular degeneration (AMD) is an important cause of blindness in aged people. Chronic kidney disease (CKD) was reported to be associated with a higher risk of AMD. However, supporting evidence was inconsistent between studies. This work intends to examine whether a positive association exists between CKD and AMD by systematic review and meta-analysis.

**METHODS:** A systematic search of electronic databases (Medline, PubMed, Cochrane and EMBASE) and reference lists on June 2017. The key inclusion criteria were controlled trials that investigated the relationship between AMD and CKD. The outcome measures included risk ratios and/or occurrence rates of AMD in CKD vs. non-CKD population. Data were pooled according to the type of AMD by random effect model.

**RESULTS:** Twelve observational studies (3 cohorts, 2 case controls, and 7 cross-sectionals) with a total 335,601 participants were included. Eleven studies reported risk ratios and 9 reported occurrence rates. Pooled prevalence for early, advanced, and any AMD were all higher in the CKD population than in the non-CKD population. The pooled multivariate adjusted OR of CKD vs. non-CKD was 1.49 (95% CI 1.11-2.02)
for early, 1.55 (95% CI 1.05-2.27) for exudative, 1.58 (95% CI 1.12-2.23) for advanced, and 1.35 (95% CI 1.05-1.73) for any AMD. However, high statistical heterogeneity and methodological diversity existed. Moreover, results were inconsistent between different study designs.

**CONCLUSIONS:** The overall results support a positive association between CKD and AMD, although some limitations exist. Given the risk that AMD is increased in CKD, regular eye screenings for the CKD population is recommended for an early detection and intervention.

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**Pathogenesis**

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**Asian age-related macular degeneration: from basic science research perspective.**

Yanagi Y, Foo VHX, Yoshida A.

**ABSTRACT:** In Asian populations, polypoidal choroidal vasculopathy (PCV), a distinct phenotype of neovascular age-related macular degeneration (AMD), is more prevalent than Caucasians. Recently, there has been significant focus on how PCV differs from typical AMD. Although typical AMD and PCV share a variety of mechanisms by which abnormal angiogenic process occurs at the retinochoroidal interface, PCV has different clinical characteristics such as aneurysm-like dilation at the terminal of choroidal neovascular membranes, less frequent drusen and inner choroidal degeneration due to the thickened choroid. Recent studies support an important role for inflammation, angiogenesis molecules and lipid metabolism in the pathogenesis of neovascular AMD. Furthermore, although less attention has been paid to the role of the choroid in AMD, accumulating evidence suggests that the choriocapillaris and choroid also play a pivotal role in drusenogenesis, typical AMD and PCV. This review discusses the basic pathogenic mechanisms of AMD and explores the difference between typical AMD and PCV.

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**The carnitine shuttle pathway is altered in patients with neovascular age-related macular degeneration.**


**PURPOSE:** To identify metabolites and metabolic pathways altered in neovascular age-related macular degeneration (NVAMD).

**METHODS:** We performed metabolomics analysis using high-resolution C18 liquid chromatography-mass spectrometry on plasma samples from 100 NVAMD patients and 192 controls. Data for mass/charge ratio ranging from 85 to 850 were captured, and metabolic features were extracted using xMSanalyzer. Nested feature selection was used to identify metabolites that discriminated between NVAMD patients and controls. Pathway analysis was performed with Mummichog 2.0. Hierarchical clustering was used to
examine the relationship between the discriminating metabolites and NVAMD patients and controls.

**RESULTS:** Of the 10,917 metabolic features analyzed, a set of 159 was identified that distinguished NVAMD patients from controls (area under the curve of 0.83). Of these features, 39 were annotated with confidence and included multiple carnitine metabolites. Pathway analysis revealed that the carnitine shuttle pathway was significantly altered in NVAMD patients (P = 0.0001). Tandem mass spectrometry confirmed the molecular identity of five carnitine shuttle pathway acylcarnitine intermediates that were increased in NVAMD patients. Hierarchical cluster analysis revealed that 51% of the NVAMD patients had similar metabolic profiles, whereas the remaining 49% displayed greater variability in their metabolic profiles.

**CONCLUSIONS:** Multiple long-chain acylcarnitines that are part of the carnitine shuttle pathway were significantly increased in NVAMD patients compared to controls, suggesting that fatty acid metabolism may be involved in NVAMD pathophysiology. Cluster analysis suggested that clinically indistinguishable NVAMD patients can be separated into distinct subgroups based on metabolic profiles.

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**Genetics**


**Effects of antiangiogenic drugs on expression patterns of epigenetic pathway genes.**

Hamid MA, Moustafa MT, Cáceres-Del-Carpio J, et al.

**BACKGROUND AND OBJECTIVE:** To investigate the effects of antiangiogenic drugs on the transcription profile of acetylation genes in immortalized human retinal pigment epithelium cells (ARPE-19) in vitro.

**MATERIALS AND METHODS:** This in vitro study evaluated the effect of antiangiogenic drugs on the expression of histone acetylation genes on immortalized ARPE-19 cell cultures. ARPE-19 cells were cultured, plated, and treated for 24 hours with aflibercept (Eylea; Regeneron, Tarrytown, NY), ranibizumab (Lucentis; Genentech, South San Francisco, CA), or bevacizumab (Avastin; Genentech, South San Francisco, CA) at one (1×) or two times (2×) the concentrations of the clinical intravitreal dose. Untreated cells were used as controls. RNA was isolated, and real-time quantitative reverse transcription polymerase chain reaction analysis was performed on individual samples to quantify expression levels of genes associated with epigenetic acetylation pathways: histone acetyltransferase 1 (HAT1) and histone deacetylases 1, 6, and 11 (HDAC1, HDAC6, and HDAC11). Differences in cycle thresholds (ΔΔCts) were obtained, and folds were calculated using the formula 2^ΔΔCt. Main outcome measures were expression levels of candidate genes in treated versus untreated samples.

**RESULTS:** Compared with untreated cells, 1× ranibizumab-treated cells expressed higher levels of HDAC6, and 2× ranibizumab-treated cells expressed higher HDAC11 levels. Bevacizumab-treated (1×) cells had significant change in HDAC1, HDAC6, and HDAC11. In cultures treated with 2× bevacizumab, only HDAC11 expression levels were significantly affected compared with controls. Aflibercept-treated (1×) cells had changes in expression of HDAC1, HDAC6, and HDAC11. At 2× concentration, only HDAC11 was significantly changed.

**CONCLUSION:** Our results show that antiangiogenic drugs can affect the transcription profile of genes regulating the histone acetylation status in ARPE-19 cells in vitro. This finding may have an implication in differential patient response to anti-vascular endothelial growth factor therapy by means of possible interactions between treatment and patient's epigenomic profile.

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Low vision


Improving face identity perception in age-related macular degeneration via caricaturing.

Lane J, Rohan EMF, Sabeti F, et al.

**ABSTRACT**: Patients with age-related macular degeneration (AMD) have difficulty recognising people's faces. We tested whether this could be improved using caricaturing: an image enhancement procedure derived from cortical coding in a perceptual 'face-space'. Caricaturing exaggerates the distinctive ways in which an individual's face shape differs from the average. We tested 19 AMD-affected eyes (from 12 patients; ages 66-93 years) monocularly, selected to cover the full range of vision loss. Patients rated how different in identity people's faces appeared when compared in pairs (e.g., two young men, both Caucasian), at four caricature strengths (0, 20, 40, 60% exaggeration). This task gives data reliable enough to analyse statistically at the individual-eye level. All 9 eyes with mild vision loss (acuity ≥ 6/18) showed significant improvement in identity discrimination (higher dissimilarity ratings) with caricaturing. The size of improvement matched that in normal-vision young adults. The caricature benefit became less stable as visual acuity further decreased, but caricaturing was still effective in half the eyes with moderate and severe vision loss (significant improvement in 5 of 10 eyes; at acuities from 6/24 to poorer than <6/360). We conclude caricaturing has the potential to help many AMD patients recognise faces.

PMID: 30315188 PMCID: PMC6185956 DOI: 10.1038/s41598-018-33543-3

Case Reports


Development of a full thickness macular hole after vitrectomy for rhegmatogenous retinal detachment: a sequential study via optical coherence tomography.

Yang HY, Yang CS.

**BACKGROUND**: To demonstrate a full thickness macular hole (MH) development after vitrectomy (VT) for rhegmatogenous retinal detachment (RRD) and to investigate the possible disease mechanism with optical coherence tomography (OCT).

**CASE PRESENTATION**: A 47-year-old female underwent 23G vitrectomy surgery to repair the macula-detached RRD successfully. However, intraretinal cysts initially developed two months after surgery. Cysts gradually increased in number and size, and cystoid macular edema was noted at the 5th month. Thereafter, inner retina dehiscence and a lamellar macular hole developed. The lamellar hole further dehisced and progressed into a full-thickness MH at the 10th month. The patient then received 23G vitrectomy and internal limiting membrane peeling surgery. OCT and fundus picture showed macular hole sealed 10 days afterward.

**CONCLUSIONS**: The mechanism of secondary MH included tangential traction, cystoid degeneration of macula, and glial migration. The sequential OCT studies provide evidence to support the disease mechanism of cystoid degeneration of the macula.

PMID: 30314435 PMCID: PMC6186112 DOI: 10.1186/s12886-018-0932-x
10-year follow-up of a subclinical choroidal neovascular membrane in a patient with age-related macular degeneration.

Chen KG, Christakis PG, Chew EY.

**Purpose:** To provide long-term, natural history data of a case of a subclinical choroidal neovascular membrane (CNVM) in the setting of age-related macular degeneration.

**Methods:** Retrospective review of the 10-year clinical course of a patient including multimodal imaging.

**Results:** A 75-year-old white female with macular degeneration presented with visual acuity of 20/25 in the right eye and 20/40 in the left eye. In the left eye, a retinal pigment epithelial detachment with associated subretinal and intraretinal fluid was found on spectral domain optical coherence tomography. Fluorescein angiography was consistent with a predominately classic CNVM, which was well-visualized on indocyanine green angiography. Treatment was initiated with bevacizumab for 10 months that reduced the amount of subretinal and intraretinal fluid, but progressive geographic atrophy developed over the subsequent 9 years reducing vision to 20/100. Interestingly, at initial presentation, a nonexudative fibrovascular pigment epithelial detachment was detected in the right (contralateral) eye. This was monitored with multimodal imaging twice yearly for 10 years without any signs of exudation, and vision remained 20/25. Optical coherence tomography angiography revealed a remarkably similar appearance of the subclinical CNVM compared with indocyanine green angiography 10 years prior, suggesting anatomical stability.

**Conclusion:** The advent of optical coherence tomography angiography has increased the detection of subclinical CNVMs. Recent evidence suggests that subclinical CNVMs have a high rate of progression to exudation over 1 year, which raises the question of whether early treatment is beneficial. This case provides 10-year follow-up with multimodal imaging (fluorescein angiography, indocyanine green angiography, optical coherence tomography, and optical coherence tomography angiography) of a subclinical CNVM, which remained stable and without exudation, suggesting that they may be closely observed.

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