Centre for Eye Health

ATLAS
LITERATURE REVIEW
Issue 11• Autumn 2024

Welcome to the eleventh issue of Centre for Eye Health's ATLAS Literature Review. Each quarter we'll be bringing you reviews from our pick of the latest literature as part of your ATLAS subscription.

Primary open angle glaucoma increases the risk of retinopathy in patients with diabetes

Prepared by Michele Clewett

Clinical applications: It has long been acknowledged, although somewhat controversially, that patients with diabetes mellitus (DM) are at higher risk of developing glaucoma and the two conditions share some common risk factors. In this study the authors investigate whether patients with DM and primary open angle glaucoma (POAG) are more likely to develop diabetic retinopathy (DR) than their non-glaucomatous counterparts. The results of such a study may impact the review period recommended for patients with POAG and DM.

Summary: This large-cohort, global, retrospective study reviewed the records of 44,359 DM patients with POAG and 4,393,300 DM patients (18+ years old) with DM and no glaucoma. The study authors calculated the relative risk of developing DR in patients with glaucoma and T1DM and compared them with a similar cohort with T1DM only. A similar comparison was made for patients with T2DM.

Key findings: The risk at 10 years of DR being detected in all DM patients (T1DM and T2DM combined) was found to be significantly higher among POAG patients (5.45%) compared to those without glaucoma.
The risk of any type of DR being detected for the first time was significantly higher in patients with T1DM and POAG than in the cohort with T1DM and no glaucoma at 1,5 and 10 years, after adjusting for other factors and co-morbidities. This elevated risk was most apparent in when looking at mild or unspecified DR, with a minimal to absent difference in risk for moderate and severe DR, however low patient numbers in this last group should be noted. In the T2DM group, the risk of DR was elevated across all stages of DR and all timepoints.
The risk of PDR was notably greater in both the T1DM and T2DM patients within the POAG group compared to those without - across all time points. On the basis of this evidence, the authors concluded that vigilant screening for DR in patients with POAG is necessary to mitigate risk.

Reference: Chauhan MZ, Elhusseiny AM, Kishor KS, Sanvicente CT, et al. Association of Primary Open-Angle Glaucoma with Diabetic Retinopathy Among Patients with Type 1 and Type 2 Diabetes: A Large Global Database Study, Ophthalmology (2024)

[Click here for abstract](#)

In this issue:

This special issue of the Atlas Literature Review will present the latest literature around prognostic signs of impending disease progression, and disease risk.

- Primary open angle glaucoma increases the risk of retinopathy in patients wtih diabetes

- Detecting AMD progression earlier with OCT: The latest evidence on what to look for

- Identifying retinal signs associated with increased cardiovascular risk

- PAMM: An indicator of possible systemic vascular disease

Guide Dogs.

Detecting AMD progression earlier with OCT: The latest evidence on what to look for

Prepared by Michele Clewett

Clinical applications: Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people aged 55 and over in developed countries such as Australia. Existing and emerging treatments for late AMD (neovascular AMD and geographic atrophy) may be more effective if impending vision loss is detected earlier. Thus, being able to identify measurable signs or structural changes (biomarkers) that precede or indeed predict the onset of late AMD is developing as a valuable skill in the quest to prevent vision loss from AMD.

Summary: One hundred and fourteen OCT prognostic biomarkers for AMD have been identified in the literature. This review sought to analyse each of these to determine which were most significant in determining or predicting the risk of progression to late AMD, and to quantify that risk. Those biomarkers with the greatest magnitudes of prediction to late AMD based on available evidence were identified. Identifying these biomarkers in clinical practice may be a highly valuable skill that optometrists caring for patients with AMD can develop, and utilise to ensure timely interventions are undertaken as appropriate.

Key findings: This review found the highest risk of AMD progression in treatment-naïve early/intermediate AMD was an external limiting membrane (ELM) abnormality, followed by abnormalities of the ellipsoid zone (EZ) and the interdigitation zone. The presence of reticular pseudodrusen concurrent with large drusen, hypo-reflective drusen cores and intra-retinal hyper-reflective foci (IHRF) all out-performed a traditionally used biomarker – the presence of large drusen. A drusen volume ≥ 0.03mm3 and total retinal volume of drusen also had a high certainty of evidence. Other OCT biomarkers such as drusenoid pigment epithelium detachment, shallow irregular retinal pigment epithelium elevations, and nascent geographic atrophy had a moderate certainty of evidence, and require more studies for validation.

The authors further stratified these risk factors by progression to neovascular and geographic atrophy specifically. Those biomarkers with the greater risk for geographic atrophy were IHRF and hypo-reflective drusen cores with the biomarker conferring greatest risk of nAMD being ellipsoid zone abnormality.

Reference: Trinh M, Cheung R, Duong A, Nivison-Smith L, Ly A (2024) OCT prognostic biomarkers for progression to late age-related macular degeneration: A systematic review and meta-analysis. Ophthalmology Retina. doi: https://doi.org/10.1016/j.oret.2023.12.006. Pub online ahead of print, December 2023.
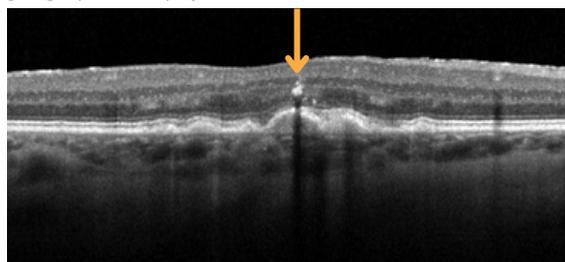
[Click here for abstract](#)
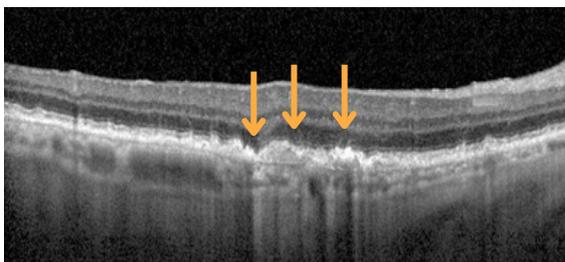
The arrows show areas of ELM, EZ and interdigitation zone disruption. This CFEH patient progressed to geographic atrophy within 18 months.
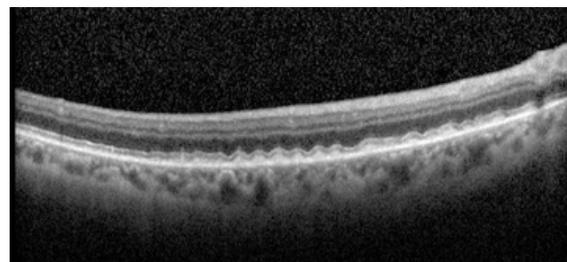
Reticular pseudodrusen (RPD) concurrent with large drusen - RPD are discrete hyper reflective material above the RPE in the subretinal space.

Hyper-reflective foci appear as a dot-like intraretinal hyper-reflective lesion at the apex of drusen.
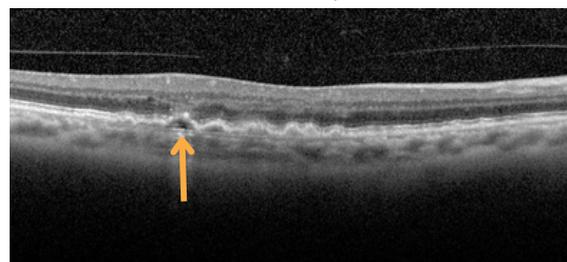
Drusen substructures show a heterogenous internal reflectivity within the drusen

Identifying retinal signs associated with increased cardiovascular risk

Prepared by Michele Clewett

Clinical applications: It has long been known that the vascular effects of systemic hypertension and diabetes may be visible in a retinal examination. In more recent times, particularly since the advent of advanced imaging technologies such as Optical coherence tomography (OCT) and OCT angiography (OCTA), extensive research has been undertaken into retinal biomarkers, the presence of which may herald a higher risk of cardiovascular disease (CVD) including stroke and myocardial infarction. Identifying these biomarkers during retinal examination can help facilitate a preventative medicine approach when these findings and their significance is communicated to the patient's healthcare providers.

Summary: This review article examines evidence from the published literature, selected for their strength, clarity and comprehensiveness, and presents an illustrated summary of retinal changes that confer an increased cardiovascular risk, also dismissing those for which the evidence is inconclusive. It examines OCT and OCTA markers that may be prognostic of increased cardiovascular risk in a similar way.

Key findings: Retinal conditions for which there is <u>substantial evidence</u> for increased cardiovascular risk include:

- Central retinal artery occlusion (CRAO). In the first year after an event of CRAO, a patient has over a 25% chance of suffering an acute stroke, MI, or dying.
- Central retinal vein occlusion (CRVO). Associated with an increased risk of incident CVD of over 10% compared to an age-matched cohort.
- Cotton wool spots (CWS). CWS and other signs of hypertensive retinopathy are associated with a 2 to 4-fold increased risk of stroke within 3 years, with intracerebral haemorrhagic stroke the most common. After adjusting for co-morbidities, the presence of CWS are also associated with an increased risk of congestive heart failure.
- Reticular pseudodrusen (or subretinal drusenoid deposits) in AMD. There is strong evidence to suggest that patients with AMD and RPD are at much higher risk of CVD (heart pump compromise, valvular dysfunction, or carotid disease) and lower high-density lipoprotein. On the strength of the evidence, the authors recommend prompt referral for a systemic cardiovascular workup for patients with SDD and AMD.

The authors also identified biomarkers that may <u>potentially have cardiovascular significance</u>, including:

- Paracentral Acute Middle Maculopathy (PAMM) which is discussed separately in the next paper review.
- Retinal ischemic perivascular lesions (RIPLs). This refers to focal atrophy of the inner nuclear layer (INL) as seen on OCT, accompanied by expansion of the outer nuclear layer giving the middle retinal layers an undulating appearance. The presence of RIPLs is associated with an increased risk of CVD, with that risk increasing with the number of lesions present.

The final part of this review looks at <u>multimodal imaging results and potential correlations with CVD</u>.

- Fundus photography and artificial intelligence (AI). This is an evolving area showing some promise for potential CVD risk stratification using retinal photographs and machine learning. A recent AI model developed could predict the myocardial infarction risk of over 11,000 patients with greater than 70% sensitivity and specificity.
- OCT – Retinal and choroidal thickness. RNFL thinning is associated with an increased risk of CVD, with Chen et al. (2023) showing that every 5 μm decrease in RNFL thickness increases CVD risk by 8% (in non-glaucoma subjects). Choroidal thinning has been shown by multiple studies to be associated with increased risk of CVD, although this has limited utility due to significant variations in normal choroidal thickness due to age and refractive status.
- OCTA. Ongoing research and machine learning indicates that various OCTA biomarkers (such as vessel density in the different capillary plexuses of the retina) have potential to predict risk of cardiometabolic conditions including hyperlipidemia, diabetes mellitus, hypertension, and congestive heart failure. The challenge however is that many of these biomarkers are non-specific and present across multiple conditions, so further research is needed before the clinical application of this knowledge becomes clear.

Reference: Colcombe J, Mundae R, Kaiser A, Bijon J, Modi Y. Retinal Findings and Cardiovascular Risk: Prognostic Conditions, Novel Biomarkers, and Emerging Image Analysis Techniques. Journal of Personalized Medicine. 2023; 13(11):1564. https://doi.org/10.3390/jpm13111564

<u>Click here for full paper</u>

PAMM: An indicator of possible systemic vascular disease

Prepared by Michele Clewett

Clinical applications: Paracentral Acute Middle Maculopathy (PAMM) characterised by the presence of a hyper-reflective band within the inner nuclear layer (INL) of the retina on OCT which, over time, results in thinning of the INL without involvement of the outer retina. Paracentral visual field defect and a hypo-reflective paracentral lesion on infra-red imaging are typically associated.

PAMM is thought to have an ischaemic aetiology, and current literature indicates an association with retinal vascular disease (RVD) as well as several systemic vascular co-morbidities. This paper explores the retinal and systemic comorbidities further to better understand the pathogenesis of what is often an isolated OCT finding. Findings of this study could help inform requests for further medical investigations.

Summary: This was a retrospective study of National Health Service (NHS) patients 18 or older diagnosed with PAMM between 2014 and 2021. 51.3% of the study cohort presented with PAMM but no RVD. 20.5% had associated RAO, 25.6% with RVO, and 2.6% with both RVO and RAO. PAMM was found to be more predominant in males (62.8% of study cohort), and Caucasian ethnicity. The authors explored the incidence of co-morbidities in these different study groups.

Key findings: The sub-group with PAMM but no RVD had a higher incidence of systemic co-morbidities, including previous stroke, myocardial infarction and pre-existing sickle cell disease (despite similar demographics to other sub-groups). This led the authors to suggest recommending a full systemic workup for patients with PAMM who have no RVD.

The study group cohort with PAMM and RVO tended to be younger, without significant systemic disease. By contrast, those with PAMM and RAO were found to have a higher prevalence of stroke or acute myocardial infarction, leading to the conclusion that patients with PAMM and RAO should also be recommended for a full systemic work-up.

Reference: Limoli C, Raja LD, Wagner SK, Ferraz D, Bolz M, Vujosevic S, Nucci P, Nicholson L, Keane PA, Khalid P, Huemer J. (2024) Exploring Patient Demographics and Presence of Retinal Vascular Disease in Paracentral Acute Middle Maculopathy, American Journal of Ophthalmology, Volume 260, pp182-189.

Click here for full paper link
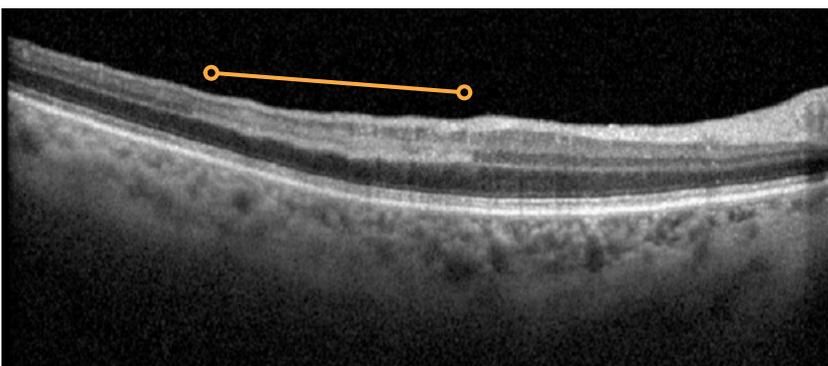
OCT line scan of a patient with PAMM. Note the hyper-reflective band within the inner nuclear layer (INL) of the retina, in the area indicated on the scan.
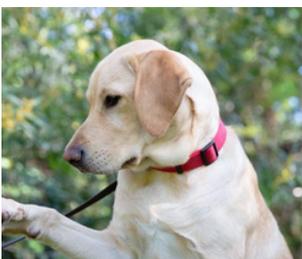
Guide Dogs.

Thank you for taking the time to read the CFEH Autumn 2024 ATLAS Literature Review.

We appreciate any feedback you may have about our educational resources, particularly the CFEH Atlas. This resource will undergo continuous review and improvement and more cases will be added over time. If you have any feedback or suggestions, we would love to hear them! Please send us an email: education@cfeh.com.au.