Retinopathy

A new biomarker to predict current and future visual acuity in diabetic macular oedema?

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What do people with diabetes fear most? Blindness. When they attend for screening, what do they want to know? Whether they will need treatment and whether they will lose their vision.

Currently, we know the population-level risk factors for the development and progression of diabetic retinopathy but not their relevance for individual patients. There have been a number of advances in the treatment of diabetic macular oedema (DMO) involving intravitreal injections of either steroids or anti-vascular endothelial growth factor agents. These treatments have shown a benefit over conventional laser treatment in that, for the first time, lost vision can be restored (Stewart, 2014). However, we are unable to predict which individuals will gain or lose vision.

The authors of the article under review state the importance of identifying reliable biomarkers of current and future vision. This will not only assist in counselling patients undergoing treatment but may also allow healthcare cost savings by identifying those people who will benefit from treatment. Perhaps more importantly, identification of the pathophysiological changes preceding visual loss will inform our understanding of the disease process and potential new treatments.

Whilst diabetic retinopathy has been regarded as a process largely involving damage to the various components of the retinal capillary bed secondary to hyperglycaemia, it has long been known that changes in the neuroretina may precede clinically visible features in the retina. This has led to current interest in the role of neuroprotective agents.

Optical coherence tomography (OCT) has revolutionised the management of DMO by allowing retinal thickness to be objectively quantified, rather than relying on a subjective clinical definition such as "clinically significant macular oedema". In particular, spectral-domain OCT has allowed high-resolution visualisation of the individual layers of the retina.

In the study summarised alongside, the authors identified a novel surrogate marker that was able to predict visual acuity (VA) in people with current or resolved DMO. They termed this marker "disorganisation of the retinal inner layers" (DRIL). Eighty eyes in 58 individuals were studied. DRIL appeared to be highly correlated with VA in people with current or resolved DMO and were more robustly and consistently associated with VA than any of the other recognised OCT features, including central retinal thickness, the current parameter used for treatment.

This was a small trial and the results need to be validated in larger longitudinal studies; however, the results are encouraging and pivotal in taking the science forward towards better-informed patient education and advice and patient-specific therapies. ■

Stewart MW (2014) Anti-VEGF therapy for diabetic macular edema. *Curr Diab Rep* **14**: 510

Diabetes

Neural retinal disorganisation is a robust marker of current and future visual acuity in DMO

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 In this single-site, cross-sectional study, the authors used spectral-domain optical coherence tomography to examine 80 eyes of 58 people with diabetes and either current or previously resolved diabetic macular oedema (DMO).

2 In each study eye, independent graders assessed seven B-scans of the foveal area for "disorganisation of the retinal inner layers" (DRIL). This was defined as the inability to distinguish between any two of the inner retinal layers (the outer plexiform layer, inner nuclear layer and the ganglion cell/inner plexiform layer complex) in >50% of the foveal zone.

3 Unadjusted bivariate analyses showed a significant association between better visual acuity (VA) and fewer foveal scans with DRIL; eyes with good VA had a mean of 1.7 out of 7 scans with DRIL, while eyes with poor VA had a mean of 5.8 scans with DRIL.

4 The association was significant both in eyes with current DMO and in those with previous DMO. DRIL was more robustly and consistently associated with VA than any other marker evaluated, including central retinal thickness, the presence of subretinal cysts, epiretinal membranes, microaneurysms, subretinal fluid, outer layer disruption/reflectivity and HbA_{1c}.

5 In a separate cohort of 96 people, early changes in DRIL over a 4-month period were associated with a worsening in VA over 1 year.

Sun JK, Radwan SH, Soliman AZ et al (2015) Neural retinal disorganization as a robust marker of visual acuity in current and resolved diabetic macular edema. *Diabetes* **64**: 2560–70

JAMA Ophthalmol

Prolonged monthly exposure to anti-VEGF agents and risk of death

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 A recent Cochrane review showed no significant overall increase in risk for death or cardiovascular (CV events) in people receiving anti-vascular endothelial growth factor (anti-VEGF) agents for diabetic macular oedema (DMO); however, the current meta-analysis shows that people with the highest level of exposure do in fact have an increased risk.

2 Four randomised controlled trials (two of ranibizumab and two of aflibercept) were reviewed. The analysis was limited to people with DMO who received monthly injections for 2 years (n=1328).

3 The estimated absolute risk per 1000 study population was higher in the anti-VEGF groups compared with sham or laser treatment in terms of all-cause death (38 vs 13), stroke (30 vs 13), CV-related death (28 vs 11), arteriothrombotic events (72 vs 47) and myocardial infarction (MI; 35 vs 32).

4 Compared with sham or laser treatment, the odds ratio with the anti-VEGF agents was 2.98 (95% confidence interval [CI], 1.44–6.14) for all-cause death, 2.33 (95% CI, 1.04–5.22) for stroke and 2.51 (95% CI, 1.08–5.82) for CV-related death.

5 The risk of MI or arteriothrombotic events was not significantly greater.

6 The authors note that their findings are unlikely to apply to people undergoing less intensive therapy, and that good results in DMO have been demonstrated with far fewer injections (e.g. two or three per year).

Avery RL, Gordon GM (2016) Systemic safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. *JAMA Ophthalmol* **134**: 21–9

JAMA Ophthalmol

Comparison of anti-VEGF agents for DMO

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 In this commentary, members of the American Society of Retina Specialists discuss the clinical implications of a study comparing the anti-vascular endothelial growth factor (anti-VEGF) agents aflibercept, bevacizumab and ranibizumab for diabetic macular oedema (DMO; *N Engl J Med* **372**: 1193–203).

2 Briefly, the study showed that visual acuity improved by 13.3 letters with aflibercept, compared with 9.7 letters with bevacizumab (P<0.001) and 11.2 letters with ranibizumab (P=0.03). Most of these differences were due to a greater effect of aflibercept in people with worse vision at baseline.

3 The authors point out that caution should be used when generalising the findings to other treatment regimens; however, they conclude that the cheaper bevacizumab may be a viable option in people with better visual acuity (20/32 to 20/40 Snellen), as they are unlikely to have significantly greater benefit from the other agents.

Heier JS, Bressler NM, Avery RL et al (2016) Comparison of aflibercept, bevacizumab, and ranibizumab for treatment of diabetic macular edema: extrapolation of data to clinical practice. *JAMA Ophthalmol* **134**: 95–9

Am J Ophthalmol

OCT angiography: A useful tool to evaluate DR?

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this prospective pilot study, the authors compared optical coherence tomography (OCT) angiography with fluorescein angiography (FA) in terms of ability to visualise pathological changes of diabetic retinopathy (DR).

2 In 42 eyes (25 participants), microaneurysms near the macula detected by FA appeared as focally dilated saccular or fusiform capillaries on OCT angiograms of the superficial and/or deep capillary plexus.

3 Non-perfused areas visible on FA appeared as lesions with no or sparse capillaries on OCT angiograms.

4 OCT angiography was also able to quantify the size of non-perfused areas, visualise the vascular structures of neovascularisation at the optic disc and quantify decreases and re-increases of flow in new vessels in an eye treated with anti-vascular endothelial growth factor agents.

5 The authors conclude that this is a useful tool to evaluate microvascular status and the effects of DR treatments.

Ishibazawa A, Nagaoka T, Takahashi A et al (2015) Optical coherence tomography angiography in diabetic retinopathy: a prospective pilot study. *Am J Ophthalmol* **160**: 35–44

> ***"The authors conclude that the cheaper bevacizumab may be a viable option in people with with better visual acuity (20/32 to 20/40 Snellen), as they are unlikely to have significantly greater benefit from the other agents."***

Ophthalmology

Ranibizumab's effects on DMO are independent of HbA_{1c}

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 In this *post hoc* analysis of two phase III trials of ranibizumab for diabetic macular oedema (DMO), the authors evaluated whether baseline or change in HbA_{1c} altered the effects of the agent over 3 years of treatment.

2 Overall, in 483 participants, best corrected visual acuity improved by a mean of 12 ETDRS (Early-Treatment Diabetic Retinopathy Study) letters in the two groups and central foveal thickness reduced by 269 µm.

3 The effects of ranibizumab were found to be independent of baseline or subsequent changes in HbA_{1c}.

Bansal AS, Khurana RN, Wieland MR et al (2015) Influence of glycosylated hemoglobin on the efficacy of ranibizumab for diabetic macular edema: a *post hoc* analysis of the RIDE/RISE trials. *Ophthalmology* **122**: 1573–9