Editorial

Is Central Retina Thickness the Most Relevant Parameter in the Management of Diabetic Macular Edema?

Diabetic macular edema (DME) is a major cause of visual impairment in patients with diabetes mellitus. A recent meta-analysis on prevalence of DME diagnosed using optical coherence tomography (OCT) reported that the pooled overall prevalence of DME was 5.47% (95% confidence interval [CI] 3.66%–7.62%), with 5.81% (95% CI 0.07%–18.51%) in low-to-middle income countries and slightly lower in high-income countries (5.14%; 95% CI 3.44%–7.15%), although this difference was not statistically significant.[1] A significant increase in vascular endothelial growth factor (VEGF) and numerous inflammatory cytokines in the vitreous and aqueous humor has been reported in patients/eyes with DME, thus confirming its complex, multifactorial pathogenesis.[2] Currently, the treatment of DME is mainly based on baseline visual acuity and foveal involvement and/or central retinal thickness (CRT) value, as recommended by the major ophthalmology societies and organizations involved in developing guidance and advice for health and social care practitioners.[3–5] Many clinicians tend to rely on CRT to monitor treatment response and to drive treatment decisions, in part because OCT provides a more reliable and objective measure than visual acuity testing as performed in many clinical settings (without refraction, using Snellen charts). However, DRCR network has proposed that patients with good visual acuity (≥20/25) and center-involved DME could be managed with observation without treatment unless visual acuity worsens, as no significant difference in visual acuity loss at 2 years in protocol V, was found whether eyes were initially managed with aflibercept or with laser photocoagulation or observation.[6] It needs to be acknowledged that proportion of eyes with final visual acuity 20/20 or better was significantly greater with aflibercept treatment (77%) than observation (66%), $P = 0.03$, whereas proportion of eyes with final visual acuity 20/25 or better was similar in each group (∼85%) in the protocol V.[6] Both the American Academy of Ophthalmology and the EURETINA recommend anti-VEGF drugs as the first-line treatment and corticosteroids largely as the second-line treatment in center-involved (CI)-DME. Retinal laser is recommended only in cases of non–CI-DME. The National Institute for Health and Care Excellence considers CRT thickness cut-off 400 μm, besides CI-DME as cause of visual impairment, from which to start the intravitreal injections. Optimal treatment regimen includes continuous injections at appropriately fixed retreatment intervals or treat and extend, until visual acuity and/or OCT stability is reached. Thereafter, monitoring and retreatment intervals should be determined by the physician and based on detection of disease activity, as assessed by changes in best-corrected visual acuity and/or anatomical parameters.[7]

Despite the ubiquitous use of central retinal thickness to make treatment decisions and monitor response to treatment, data from randomized clinical trials including anti-VEGF treatments and macular laser, from the DRCR-network reported only weak to moderate correlation between the CRT and visual acuity in eyes with DME.[8,9] In fact, a recent post hoc analysis of Protocol T found only a weak correlation between visual acuity and central subfield thickness (CST) at baseline (Pearson correlation coefficient 0.36; 95% CI, 0.30–0.43) that was similar among the three treatment groups (aflibercept, bevacizumab, and ranibizumab).[8] The changes in CST accounted for only a small proportion of the total variation in changes in visual acuity during the study and up to 104-week follow-up. Thus, the findings from the study do not support using changes in CST measured on OCT as a surrogate for changes in visual acuity in phase three clinical trials evaluating anti-VEGF for DME, neither in clinical practice as a guide to inform the physician or patient about changes in visual acuity after anti-VEGF treatment.[8] This has major impact when the treatment of DME aims to improve vision and would be expected to parallel CRT decrease. It becomes challenging to manage cases where CRT decrease after

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treatment does not reflect the gain in visual acuity. In cases where the treatment of DME aims to preserve already good vision, changes in visual acuity can be minimal, but could be expected due to the ceiling effect, whereas changes in CRT could be much larger, thus again leading to poor correlation between visual acuity and CRT. In fact, in protocol V, the patients were treated if visual acuity decreased until the resolution of macular edema based on the assumption that no treatment would have led to visual acuity decrease over time.[6]

Recently, with the use of automatic softwares, macula fluid volume was proposed to be better parameter than CST to diagnose DME and to assess anatomical change during therapy.[10,11] Post hoc analysis of Protocol T data, in which intraretinal and subretinal fluid was quantified using a deep learning algorithm, found that the presence of subretinal fluid (SRF) at baseline was associated with a significantly worse baseline best-corrected visual acuity of 63.2 (95% CI 66.1–60.2) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score versus 66.9 (95% CI 65.7–68.1) ETDRS letter score without SRF ($P < 0.001$) and a greater gain in ETDRS letter score (0.5 [95% CI 0.3–0.8] every 4 weeks in eyes with SRF vs. 0.4 [95% CI 0.3–0.5] in eyes without SRF at baseline; $P = 0.02$) when adjusted for baseline best-corrected visual acuity.[11] For every 10 nL reduction of intraretinal fluid (IRF) and SRF in the central 1 mm, best-corrected visual acuity improved by a mean of 0.15 (95% CI 0.10–0.20) and 0.34 (95% CI 0.18–0.52) in ETDRS letter score.[11] Thus, artificial intelligence may be used to automatically measure fluid volumes facilitating a comparison of the differential efficacy of anti-VEGF agents.[11]

However, the assessment of DME is by far more complex than pure evaluation of CRT/CST and macular volume due to the complex interplay of microvascular modifications and neuronal injury leading to neurovascular uncoupling, retinal inflammation, and finally impaired outflow, which may all ultimately impact the visual function.[12] The use of OCT has enabled to evaluate different structural parameters within the retinal tissue in DME that could be related to visual acuity or treatment response. The most commonly evaluated structural parameters include hyperreflective retinal spots/dots/foci (HRS, HRD, and HRF), subfoveal neuroretinal detachment (SND), disorganization of inner retinal layers (DRIL), and integrity of the outer retinal layers (external limiting membrane/photoreceptors' integrity).[13–19]

Hyperreflective retinal spots have been proposed as OCT sign of activated microglial cells, thus indicating an inflammatory condition within the retina tissue.[13–16] The HRS have been evaluated by several groups and not only in DME but also in age-related macular degeneration and retina vein occlusion.[16,20,21] As different retina lesions can be detected as HRS on OCT, those indicating activated microglia cells (and not hard exudates, retinal vessels/microaneurysms, anteriorly migrated RPE cells, and degenerated photoreceptors or macrophages engulfing them) have specific characteristics: small dimension (<30 μm), reflectivity similar to nerve fiber layer, no back shadowing, and can be located in the inner and the outer retina layers.[13] HRS decrease after both anti-VEGF[22] and steroid treatment.[23] In eyes with DME nonresponsive to anti-VEGF treatment, a higher number of HRS[24] and presence of SND were associated with significant increase in visual acuity and decrease in CRT after steroid treatment.[25]

It was suggested that DME eyes with abundant HRS, moderate-to-severe hard exudates, or severe intraretinal cysts at baseline were more likely to exhibit anatomical improvements after treatment with the steroid implant.[26] The clinical evidence from different groups worldwide seems to indicate that when a high number of HRS in the retina are detected on OCT, this may indicate a significant inflammatory condition that could guide treatment choice. However, most articles evaluating the impact of HRS on DME treatment outcome are retrospective; thus, it would need to be further evaluated within the large prospective studies if HRS could potentially become a valid predictive biomarkers of treatment response and could guide more personalized treatment.

Diabetic macular edema with SND has been associated with higher concentration of IL-6 in the vitreous compared with DME without SND.[27] Diabetic macular edema with SND has been proposed as a specific pattern of DME with greater choroidal thickness, more reduced retinal sensitivity, and higher number of HRS thus indicating inflammatory pattern of DME.[14] In fact, DME with SND showed major reduction in HRS, DRIL extension, CRT and specific OCT-Angiography parameters of the foveal avascular zone, and perfusion density at the deep capillary plexus versus DME without SND after intravitreal steroids versus anti-VEGF treatment.[14,15]

The presence of DRIL has been proposed as the OCT sign of cells destruction within the inner retinal layers, possibly indicating a disruption of visual pathways from the photoreceptors to the ganglion cells, thus an important prognostic and predictive parameter of visual acuity response to treatment in CI-DME.[17,18] Recent studies using OCT-A and OCT reported on important interplay and impact on reduced visual function, the presence of diabetic macular

ischemia (DMI) alone or in combination with DRIL (neuronal injury), and DME (inflammation and impaired outflow).[12] Visual function can be affected by either the primary vasculopathy alone affecting different retinal plexuses and choriocapillaris with varying extent of ischemia (DMI) on OCT-A, especially when the deeper retinal layers and choriocapillaris are involved with consequent injury to the photoreceptors, or by combined neuronal injury (neurovascular uncoupling) thus loss of retinal ganglion cells and amacrine cells, visible on OCT as the DRIL sign (DMI + DRIL) or in addition, the association with the breakdown of blood–retinal barrier and tight junctions, and increased vascular permeability due to inflammation and impaired outflow of the retinal fluid exacerbated by the loss of the deep capillary plexus (DME + DMI + DRIL).[12]

As for the HRS, also for DRIL evaluation, most studies are retrospective, and the level of evidence would need to be strengthen with the prospective studies to better understand its potential prognostic value on visual acuity and how the change in DRIL extension/area may affect visual acuity after DME treatment.

The integrity of the outer retina layers is also considered an important parameter associated with visual acuity in DME.[19] In a post hoc analysis of the VISTA randomized clinical trial, the integrity of the ellipsoid zone (EZ) of the photoreceptors improved after aflibercept treatment and was found correlated with visual function.[28]

The combined evaluation of different OCT parameters documented that the presence of DRIL, HRS, and EZ disruption at baseline increases the risk of visual acuity loss in patients with DME and good baseline visual acuity managed by observation up to 1 year follow-up[29] (Figure 1).

Data from real-life retina clinic-based study on 196 eyes with CI-DME reported that a combined use of baseline SD-OCT biomarkers and their subsequent change can predict visual acuity and improvement in vision in DME eyes treated with anti-VEGF injections. More in detail, baseline DRIL, HRS, and disruption of ELM/EZ and COST were associated with worse baseline and subsequent visual acuity up to 24 months after anti-VEGF treatment. The resolution in DRIL (P = 0.048), ELM/EZ (P = 0.001), and COST disruption (P = 0.002) after treatment was associated with greater improvement in visual acuity at 12 months.[30] Using logistic regression analysis, only restoration of ELM/EZ integrity was significantly associated with a 3.53 higher likelihood of achieving functional success at 12 months (P = 0.008).

Optical coherence tomography can be integrated with OCT-A for the noninvasive evaluation of foveal avascular zone metrics and different perfusion parameters in specific capillary plexuses. OCT-A metrics mainly in the deep capillary plexus DCP can improve the evaluation of risk progression of DR and development of DME beyond traditional systemic risk factors.[31] Changes in deep capillary plexus have been associated with treatment response to anti-VEGF.[32] However, the presence of artifacts due to the intraretinal cysts may significantly affect the evaluation of areas of reduced/nonperfusion. This needs to be taken into account when using different methods of image analysis.[15]

However, in everyday clinical practice, we still rely only on the quantitative measurement of CRT when evaluating patients with DME and deciding the treatment, irrespective of other parameters that can be evaluated on OCT. It needs to be acknowledged that subjective evaluation of more detailed OCT parameters, for example, manual count of HRS, or evaluation of DRIL and integrity of the outer retinal layers, is time consuming and can lead to variable results, thus poorly practicable in a busy everyday clinical practice. Moreover, clinicians do not feel confident in the manual evaluation of these parameters and believe that a significant expertise would be

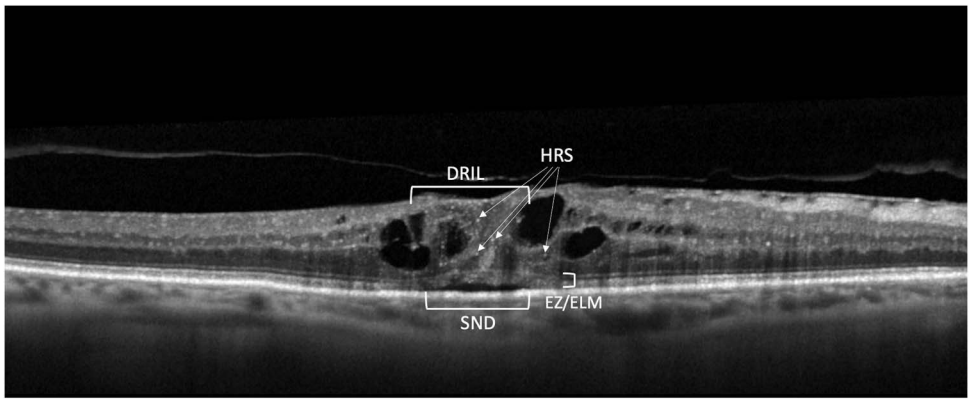

Fig. 1. Optical coherence tomography scan of cystoid diabetic macular edema with subfoveal neuroretinal detachment showing hyperreflective retinal spots, disorganization of the inner retinal layers and integrity of the outer retinal layers, ellipsoid zone of the photoreceptors, and external limiting membrane.

needed to implement it for reliable management of patients. For all these reasons, they remain mostly used in clinical research.

Automatic quantitative analysis of retinal fluid on standard OCT images that identifies and localizes separately intraretinal and subretinal fluid, and quantitative monitoring of fluid changes over time, has been proposed using deep learning (DL), and could lead to fast, objective, and precise management of patients with DME, saving the time in a busy clinical practice.[33]

In addition, a recent study proposed an automatic analysis for evaluation of integrity of ELM and ellipsoid zone and quantification of HRS besides the fluid volume in eyes with DME, reporting promising results.[34]

The advent of machine learning (ML) and DL enables the retinal physicians not only to segment, detect, or prognosticate using a single input variable but also using multimodal input variables that could involve both patients' demographics and ocular parameters. In fact, the use of DL has also unraveled numerous biomarkers in ocular imaging not only for predicting the systemic vascular health but also the information that was not known to many highly qualified retinal physicians such as the use of retinal imaging to predict sex[35] or the use of external eye photographs to predict DR and glycemic control (HbA1c levels).[36] As mentioned above, DME is a disease that could exhibit changes not limited to CRT and whether the use of ML or DL, combined with OCT scans and CRT, could be used as potential predictors to evaluate disease nature (VEGF driven, inflammatory driven, or others) to determine treatment options and also to prognosticate the functional or structural outcomes at specified time points (e.g., 3 months, 6 months, or 12 months) remain to be further explored.[37]

In conclusion, even if CRT is still used as a relevant parameter in the management of DME, the current body of scientific and clinical evidence may indicate the need to include other detailed structural parameters evaluated on OCT, which could help in better phenotyping DME and evaluating retinal integrity at different levels, all contributing to the final functional outcomes. As detailed evaluation of such parameters is time-consuming and may not be feasible to integrate in a busy everyday practice, an automatic tool with high sensitivity in detection of these OCT parameters would be useful to assist clinicians in the management of DME and could allow for more robust validation of these parameters. The eye care providers should continue working on increasing the strength of clinical data required for validation of novel surrogate or clinical end points that may lead to regulatory approval (with multicentric and prospective studies, including diverse cohorts) and engaging with regulatory bodies to include this type of analysis on new or existing OCT/OCT-A devices. This could have a clinical impact, as new treatments with different mechanisms of action are on the horizon. In this way, if proved reliable, the use of more detailed OCT parameters, and not just CRT, could help in monitoring/evaluating response to treatment and in delivering more personalized treatment in patients with DME right from the beginning.

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