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Diagnosing and monitoring diabetic macular edema: structural and functional tests

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Abstract Diabetic macular edema remains a major cause of visual impairment in adults despite the use of intensive glycemic control, photocoagulation therapy and new intravitreal drugs in the treatment of this disease. Although early diagnosis and treatment lead to better results, we still have patients who become legally blind. Therefore, better structural and functional characterization of this disease is necessary in order to customize treatment.

Keywords Diabetic macular edema · Microperimetry · OCT · Fundus autofluorescence · Fluorescein angiography

Introduction

Diabetic macular edema (DME) is the leading cause of legal blindness in diabetic patients [1]. DME can occur at any stage of diabetic retinopathy (DR), although it is more likely to occur as the disease progresses [2]. The pathophysiological mechanisms leading to DME are still poorly understood due to its complex and multifactorial origin. It is generally believed that vascular microangiopathy, with endothelial cell damage, pericyte loss and consecutive break-down of the inner blood–retinal barrier, is involved in the pathogenesis of DME [3, 4]. Moreover, other factors such as hypoxia, altered blood flow, retinal ischemia, and inflammation are also associated with the progression of DME [5]. However, recently an increasing body of evidence suggests that neurodegeneration precedes the earliest clinical manifestation of diabetic retinal vasculopathy [6, 7]. In fact, early clinical changes in visual function have been found by means of colour contrast sensitivity, dark adaptation (nyctometry), electroretinography, and more recently by microperimetry, confirming the precocious occurrence of neurovisual abnormalities in diabetic patients [8–11].

DME is currently evaluated with biomicroscopy, color fundus photography, optical coherence tomography (OCT), fluorescein angiography (FA) as morphologic tests and visual acuity (VA) as a functional test. FA has been used for more than 50 years in the evaluation of external and internal blood–retinal barriers. In DME, it has been mostly used for the evaluation of unexplained visual loss and for guiding treatment of clinically significant macular edema (CSME) [12]. El Asrar et al. [13] showed that FA may be particularly useful in detecting refractory areas in previously treated DME cases with laser photocoagulation. However, FA is an invasive test and its use in the management of DME is more limited than in the past, even though it is mandatory before deciding any therapeutic intervention [14].

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Recently, OCT has been proposed as a new standard diagnostic technique to quantify and monitor DME [15]. Browning et al. [16] demonstrated that foveal and macular OCT thickness appear to be more sensitive than slit lamp biomicroscopy in evaluating CSME. Virgili et al. [17] reported high sensitivity and specificity of OCT versus slit lamp biomicroscopy and stereoscopic fundus photography in evaluating CSME, especially in the initial stages. OCT allows for both quantitative and qualitative evaluation of DME. Otani et al. [18] described different OCT patterns of DME: cystoid, sponge-like and subfoveal neuoretinal detachment (SND). Several studies have shown a high correlation between OCT findings and FA patterns in DME [14, 19, 20]. These correlations address the changes in intraretinal structure. In fact, large foveal cysts, located in the outer nuclear layer and/or Henle's layer found on OCT correspond quite well to petaloid cystoid leakage pattern on FA [19, 20]. Whereas FA does not allow for SND visualization, OCT nicely shows the extent and height of SND. Since OCT introduction into clinical practice, prevalence and prognosis of SND in diabetics have been more studied and understood [21].

OCT also offers a repeatable and objective way to evaluate retinal thickness and volume in DME, which is the most used parameter in clinical trials when evaluating the effect of any treatment [22]. With the advent of spectral domain OCT (SD-OCT), fine intraretinal structure can be analyzed in more detail. In particular, the integrity of single retinal layers and cyst localization within retinal layers can be precisely determined. Moreover, the reflectivity of retinal cysts was proposed as an indicator of exudative origin (high internal reflectivity) versus degenerative origin (low internal reflectivity) [23]. This parameter might be important in treatment evaluation [23]. When evaluating DME, we should bear in mind that the same OCT machine should be used for the follow-up of any individual eye in order to compare retinal thickness values; otherwise a conversion factor for different instruments needs to be applied (but this is still under investigation) [24].

The most common functional test used in everyday clinical practice in diabetic patients is VA determination. VA is still considered the gold standard in clinical practice of vision testing, but it does not adequately reflect functional vision. Functional vision describes the impact of sight on quality of life. This parameter better represents the patient's point of view [10]. The most widely adopted test for VA assessment is the Snellen chart, although it has well-documented limits and does not allow for direct comparison of data obtained from different studies [25]. Therefore, new and more standardized charts with logMAR progression have been designed and introduced into clinical practice (and adopted for the Early Treatment Diabetic Retinopathy Study (ETDRS chart) in order to create more reliable and universal language in clinical trials, when measuring VA [26].

Recently, the Diabetic Retinopathy Clinical Research Network reported only modest correlation between VA and OCT-measured center point thickness in diabetic patients. They also found a modest correlation between changes in retinal thickening and VA after focal laser treatment for DME, suggesting that OCT measurement alone may not be a good surrogate for VA as a primary outcome in studies of DME [22]. Therefore other functional tests need to be evaluated and compared with OCT in order to better understand DME evolution and treatment outcomes. Besides VA, other functional tests have been used to evaluate functional alterations in diabetic patients. These include both psychophysical tests [such as: color vision, contrast sensitivity, dark adaptation (nyctometry), perimetry, and more recently microperimetry] or electrophysiological tests (multifocal electroretinography, visual-evoked potentials). Among these tests, just microperimetry provides exact, point-by-point correlation between morphology and function. Recently, microperimetry has gained increasing importance in evaluation of functional impairment in diabetic patients. Microperimetry, or fundus perimetry, is a functional technique which quantifies macular sensitivity, exactly correlating it to fundus characteristics, and determines retinal fixation characteristics [10]. It also allows for automatic and precise examination of the same retinal points during follow-up, irrespective of fixation changes [10]. In DME, a significant inverse correlation between macular thickness and macular sensitivity has been documented using microperimetry (Fig. 1) [27–30]. Vujosevic et al. [27] reported a significant inverse relationship between retinal sensitivity and normalized thicknesses, with a decay of 0.83 dB ($p < 0.0001$) for every 10 % of deviation of retinal thickness from the normal measurements obtained with OCT. Therefore, microperimetry seems to represent a better functional test than best corrected

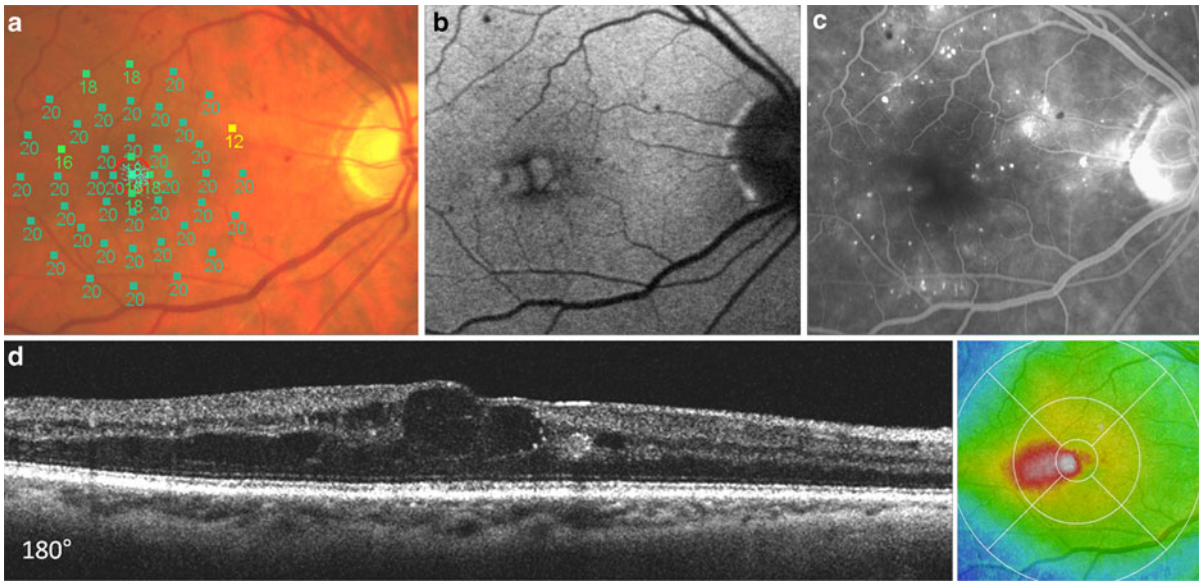

Fig. 1 **a** Microperimetry, **b** fundus autofluorescence, **c** fluorescein angiography and **d** OCT images (line scan and retinal thickness map) of a diabetic patient with central cystoid macular edema. Microperimetry shows initial decrease in central retinal sensitivity. Fundus autofluorescence shows spots of increased autofluorescence corresponding to intraretinal cysts on fluorescein angiography and OCT

VA in quantifying visual function in diabetics, potentially adding a functional measure that may supplement the predictive value of OCT and VA [27]. Moreover, microperimetry allows for determination of fixation location (central, relatively eccentric, and eccentric) and stability (stable, relatively unstable, and unstable). Published data about fixation characteristics in DME eyes is quite contrasting, mostly due to the differences in examined populations, especially differences in DME duration [29, 31, 32]. Kube et al. [29] found decreased fixation stability in patients with DME using SLO microperimetry. Carpineto et al. [32] found that all eyes with eccentric or unstable fixation had cystoid DME. Vujosevic et al. [31] reported, in a well-defined group of CSME eyes, that location and stability of fixation were normal, except when hard exudates were located in the fovea. DME pattern (focal or diffuse) or OCT type of edema (cystoid, sponge-like, SND) did not influence stability or location of fixation [31]. Therefore, the only parameter influencing fixation in DME patients is the presence of subfoveal hard exudates. In these cases, knowledge of fixation characteristics is fundamental in order to avoid complications due to the photocoagulation of a newly developed fixation area [31].

Recently a new non-invasive test, short wavelength fundus autofluorescence (FAF), has been proposed for the evaluation of DME (Fig. 2) [33–35].

FAF, which examines the metabolic activity of retinal pigment epithelium and photoreceptors, has been more extensively used in the evaluation of age-related macular degeneration and inherited macular dystrophies, but little is known about FAF alterations in DME and its functional correlations. Pece et al. [34] described different increased patterns of FAF (multicystic increased, single cyst increased, and combined single- and multicystic increased FAF) in patients with cystoid DME that correlated positively with FA and OCT findings. In a more detailed study, Vujosevic et al. [35] described three different patterns of foveal FAF in DME patients (normal FAF, single spot increased FAF, and multiple spot increased FAF) and correlated it with microperimetry and VA data. Vujosevic et al. [35] found that foveal FAF increases in a large proportion (76.8 %) of patients with CSME and that retinal sensitivity decreases over areas with increased FAF. Therefore, DME with an increased FAF pattern is, at least functionally, more severe than DME with a normal FAF pattern. Although the origin of increased FAF in DME patients is still not completely known, activation of microglial cells has been hypothesized [36].

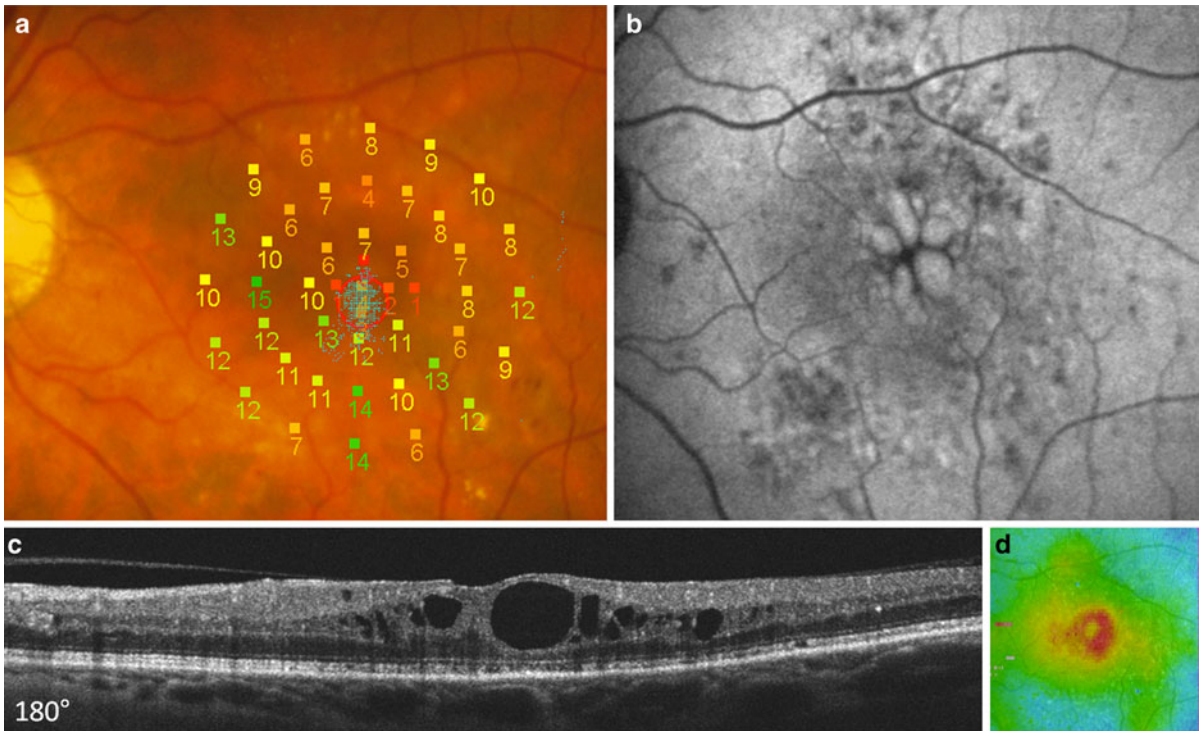

Fig. 2 **a** Microperimetry, **b** fundus autofluorescence, **c** OCT line scan and **d** OCT retinal thickness map of a diabetic patient with laser treated cystoid macular edema. Microperimetry shows decreased retinal sensitivity covering all central 12 degrees. Fundus autofluorescence shows multiple spots of increased autofluorescence in the fovea and decreased autofluorescence corresponding to laser spots, microaneurysms and hard exudates. OCT shows cystoid edema with incomplete posterior vitreous detachment

FAF and microperimetry have been recently evaluated after laser photocoagulation in DME [37]. Vujosevic et al. [37] evaluated micropulse diode laser treatment (MPDL) versus modified ETDRS laser photocoagulation in patients with center-involving DME. These authors found that macular sensitivity determined by microperimetry stabilizes or improves after MPDL tretament whereas macular sensitivity significantly decreases after modified ETDRS treatment. FAF showed no changes after MPDL treatment, whereas definite laser spots were easily seen on FAF images after modified ETDRS treatment [36]. Therefore less-invasive treatment options, with same efficacy as standard treatments should become more widespread, as recently reported [37, 38].

Although huge progress has been made in the evaluation and treatment of DME, we still face outcome pitfalls and we cannot differentiate, at baseline examination, responders from non-responders to any individual treatment. Therefore more analytical structural and functional evaluation, as reported in this paper, of diabetic patients is needed in order to obtain more precise DME phenotyping. Using this systematic and detailed diagnostic approach a more customized and selective management of diabetics affected by DME should be possible, allowing for better functional results and prevention of permanent visual loss.

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