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DIABETIC RETINOPATHY UPDATE

Microperimetry in diabetic retinopathy

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Abstract Diabetic retinopathy has an enormous impact on visual function, even before permanent visual acuity loss. Moreover, adequate functional tests are mandatory to diagnose and follow diabetic patients treated for diabetic macular edema (DME). More precisely, the visual function safety profile of any therapy for DME should be accurately investigated. Microperimetry offers the possibility to obtain an exact fundus-related quantification of retinal sensitivity, and it is changing the current approach to the functional investigation of diabetic retinopathy.

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Contents

1. Introduction

Diabetic retinopathy is one of the major causes of permanent visual (acuity) loss in the working population. Moreover, the prevalence of diabetes mellitus is dramatically increasing worldwide. Visual loss is commonly quantified by a full contrast visual acuity test (by Snellen or ETDRS charts). Unfortunately, this full-contrast visual acuity test doesn't reflect the real visual functional abnormalities due to the retinal involvement secondary to diabetes mellitus. Moreover, subtle and precocious neurosensory visual abnormalities have been quantified in diabetic patients in order to detect early visual dysfunction, even before the onset of clinically detectable

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retinopathy. The aim of these investigations is to try to identify among diabetic subjects a population at higher risk of developing vision threatening retinopathy (Bresnick, 1986; Midena et al., 1990). Psychophysical visual function testing may reflect the neural activity of the whole visual pathway, but it is known that psychophysical tests are valuable clinical indicators of retinal function derangements induced by the metabolic changes secondary to diabetes mellitus. In fact, in diabetic patients impaired vision in dim light and difficulties in recognizing the contour of objects in low contrast conditions are common complaints even with good visual acuity and full visual fields (Hyvärinen et al., 1983). Visual acuity is still considered the gold standard in clinical practice of vision testing, but it does not entirely reflect functional vision. Functional vision describes the impact of sight on the quality of life that represents *the patient's point of view* (Sharma et al., 2005; Owsley and Sloane, 1987; Midena, 2006). This approach is better quantified using all available psychophysical tests, mainly analyzing fundus-related retinal sensitivity threshold. This paper reviews the current application of fundus-related perimetry, better known as microperimetry, in the diagnosis and follow-up of diabetic retinopathy.

2. Microperimetry (fundus-related perimetry)

Perimetry encompasses the assessment of differential light threshold of retinal locations from the fovea to the preplanned periphery. Static perimetry is particularly useful for detailed probing in carefully selected areas and represents the current cornerstone of visual field testing. Standard threshold static automated perimetry quantifies the differential light threshold required to detect a static white light stimulus in the visual field. Since standard threshold perimetry uses a static achromatic stimulus, it is thought to non-selectively evoke both major groups of retinal ganglion cells. Newer technologies are aimed at earlier detection of subtle deficits and enhancing diagnostic accuracy. In diabetic macular edema (DME), visual acuity loss is quite relevant and irreversible when long lasting edema involves the center of the macula; in these cases the outcome of laser treatment is poor. But, before the loss of visual acuity is reported by patients, they may suffer from other disturbances of visual function such as: waviness, blurring, relative scotoma and decrease of contrast sensitivity which are not assessed and quantified in routine examination. Therefore, a visual function test aimed at identifying vision threatening retinopathy before visual acuity is affected would be of great value. One possible approach may be to identify decreased sensitivity in central and paracentral areas using microperimetry (Midena, 2006). As elegantly stated by Sunnes et al., conventional visual field examination is inadequate for the accurate functional evaluation of macular diseases and detection of small scotoma, particularly when foveal function is compromised and the patient may have unstable and extrafoveal fixation (Sunness et al., 1995). Accuracy of the conventional visual field rests on the assumption that fixation is foveal and stable. Moreover, the detection of the site and stability of retinal fixation (foveal or extrafoveal) and the quantification of retinal threshold over small and discrete retinal lesions are beyond the possibilities of conventional, automatic and non automatic perimetry (Midena and Radin, 2006). The integration of retinal details with function has been achieved by fundus-related perimetry, more widely known as microperimetry. Microperimetry allows for the exact topographic correlation between fundus abnormalities and corresponding functional alterations by integration, with different methods, of differential light threshold (more commonly known as retinal sensitivity) and fundus imaging. It also allows to quantify fixation characteristics, by exactly defining location and stability of any foveal or extrafoveal (PRL: preferred retinal locus) fixation site, as well as determination of size, site and shape of scotoma. Moreover, the possibility of an automatic follow-up examination (using the microperimeter MP1, Nidek Co, Japan) which allows the evaluation of exactly the same retinal points tested at the baseline, regardless any change in fixation characteristics is a valuable tool of this technique, mainly in the evaluation of treatment outcome. Microperimetry offers several advantages versus standard perimetry in the quantification of macular sensitivity, such as: direct real time fundus control; direct correlation between sensitivity and fundus details; detection of central microscotomata; continuos monitoring of fixation. The original Scanning Laser Ophthalmoscope (SLO, Rodenstock, Germany) was the first instrument combining static perimetric testing and simultaneous observation of the fundus. SLO allowed a real-time examination by an infrared (IR) source of the retina and allowed the manual projection of visual stimuli of different shapes, sizes and intensities over selected retinal areas. The sensitivity map, obtained according to the stimulation pattern (in dB or pseudocolors), was available at the end of the examination. This map contained the fixation area, the fixation target, and the threshold data. This instrument is no more commercially available.

With the introduction of a new microperimeter, a liquid crystal display (LCD) microperimeter (MP1) with a coupled color fundus camera, visualization of color fundus details allows to directly report functional data onto clinical fundus image and automatic tests are also obtained. MP-1 microperimeter has both an infrared and a color fundus camera, as well as an automatic real-time tracking system that allows for a full automatic retinal fixation and threshold determination as well as automatic follow-up and differential maps determination, independently from fixation characteristics. The main technical characteristics of this instrument have been previously described in detail (Vujosevic et al., 2006; Midena et al., 2004; Midena et al., 2007). Roschneider et al. compared MP-1 and SLO microperimeters and found that both instruments analyzed retinal sensitivity and fixation characteristics, and the results obtained from both instruments were directly comparable. However, MP-1 is superior to SLO due to the automatic real-time alignment system, a larger field of (fundus) view ($44° \times 36°$ MP1 versus $33° \times 21°$ SLO) and color image (Rohrschneider et al., 2005).

The most relevant characteristics of advanced microperimetry performed with the MP-1 microperimeter may be briefly summarized as follows:

- Exact fundus-related stimulation
- Automatic eye-tracking system
- Automatic static and kinetic stimulation (with standardized or customized grids and centration)
- Normative age-related database (Midena et al., 2010)
- Age-related differential maps (local defect determination, shallow defects determination, etc...)
- Automatic follow-up and differential maps

- Screening tests (short test duration: < 5 min)
- Morpho/functional relationship investigation (overlapping of sensitivity maps over different types of fundus images)

MP-1 microperimetry is a mesopic test that requires a 5–10 min dark light adaptation before starting the examination.

In the last 15 years, microperimetry has been successfully used in the diagnosis and follow-up of different macular disorders, including: age-related macular degeneration, myopic maculopathy, macular dystrophies and diabetic macular edema (DME) (Midena et al., 2004; Mori et al., 2001; Rohrschneider et al., 2000; Mori et al., 2002; Rohrschneider et al., 1997; Sunness et al., 1996; Kube et al., 2005; Loewenstein et al., 1998; Midena, 2005; Varano et al., 2005). In DME microperimetry has been used for: the quantification of macular sensitivity; the correlation of macular sensitivity to macular thickness, visual acuity and fundus autofluorescence data; and the fixation patterns determination in different stages and types of edema.

Different studies report the correlation between retinal sensitivity, determined with microperimetry, and VA in patients with CSME (Vujosevic et al., 2006; Rohrschneider et al., 2000; Okada et al., 2006). Moreover, reduced retinal sensitivity is related to increasing retinal thickness (Vujosevic et al., 2006; Kube et al., 2005; Okada et al., 2006). In a study published by Vujosevic et al. a significant inverse relationship was found, in patients with CSME, between retinal sensitivity and normalized retinal thickness values obtained with OCT, with a decay of 0.83 dB ($p < 0.0001$) for every 10% of deviation of retinal thickness from the normal values (Vujosevic et al., 2006). (Fig. 1). This means that normalized macular thickness better copes with macular function, than any absolute value (Vujosevic et al., 2006). Microperimetry seems to represent a better functional testing than BCVA for quantifying visual function in diabetic patients, because it incorporates a functional measure that may potentially supplement the predictive value of OCT and visual acuity (Vujosevic et al., 2006; Okada et al., 2006; Vujosevic et al., 2008).

Besides retinal sensitivity, microperimetry allows to quantify retinal fixation characteristics. Fixation characteristics (location and stability) are relevant parameters for understanding patient's quality of vision, especially reading ability, and its knowledge may be important in planning laser treatment (Rohrschneider et al., 2000; Vujosevic et al., 2008; Møller and Bek, 2003; Møller et al., 2005). Reading ability better correlates with subjective quality of vision rather than distant visual acuity (Rohrschneider et al., 2000). Whereas different studies agree that macular sensitivity deteriorates in patients with DME, data about fixation characteristics are quite contrasting (Vujosevic et al., 2006; Mori et al., 2001; Rohrschneider et al., 2000; Kube et al., 2005; Okada et al., 2006; Carpineto et al., 2007). Kube et al. found decreased fixation stability in patients with DME using SLO-microperimetry (Kube et al., 2005). Carpineto et al. found that all eyes with eccentric or unstable fixation had cystoid DME (Carpineto et al., 2007). Vujosevic et al. found that fixation patterns are not significantly influenced by either topographical extension of edema (focal or diffuse) or by the OCT classification of edema (Vujosevic et al., 2008). Moreover, fixation pattern was not significantly influenced by the presence of subfoveal serous neuroretinal detachment, showing a different fixation behavior compared to age related macular degeneration (Midena et al., 2004; Vujosevic et al., 2008). The only parameter influencing fixation was the presence of subfoveal hard exudates. In these cases, the knowledge of fixation location and stability is fundamental in order to avoid complications due to the photocoagulation of newly developed fixation area (Fig. 2).

The duration of diabetic macular edema, which cannot be exactly quantified in a cross sectional study, might have a relevant impact on the survival and/or functional reserve of macular cells undergoing mechanical and toxic stress induced by edema and this may explain the difference in fixation results described above. It seems that in patients with DME, the damage to photoreceptor occurs as a late phenomenon, and probably is not related to intraretinal cysts formation. In diabetic retinopathy, retinal neurodegeneration may precede photoreceptor loss, as previously reported (Vujosevic and Midena, 2006). Therefore, microperimetry may be of value in predicting the functional outcome of diabetic macular edema after interventions that seem equally effective in restoring normal foveal

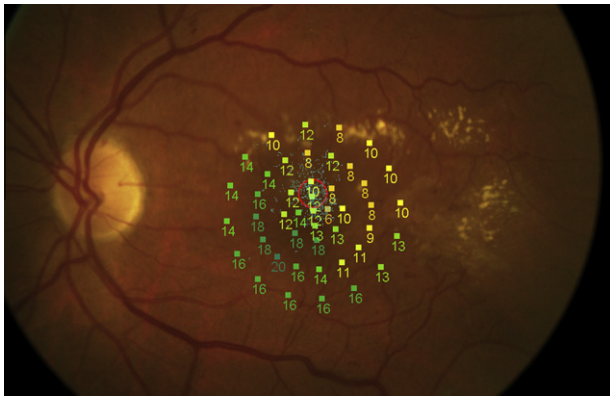

Figure 1 Microperimetry map (in decibels) superimposed onto the color fundus image in a case of clinically significant diabetic macular edema. Decrease of retinal sensitivity is shown on the temporal side of the macular region.

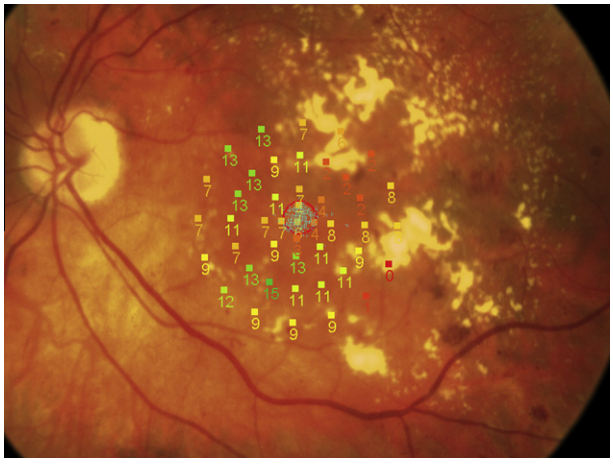

Figure 2 Microperimrtry map (in decibels) superimposed onto the color fundus image in a case of severe clinically significant diabetic macular edema with large hard exudates. Over hard exudates the retinal shows some dense scotomatous zones. Fixation (tiny light blue spots centered onto the fixation target, red circle) is still stable and central.

thickness. This hypothesis has been recently confirmed by a randomized and prospective study conducted by Vujosevic et al. These authors have demonstrated that subthreshold micropulse diode laser is as effective as modified ETDRS photocoagulation in reducing central retinal thickness. But with subthreshold treatment retinal macular retinal sensitivity stabilizes or improves, whereas with standard photocoagulation it significantly deteriorates, manifesting as progressive microscotomata (Vujosevic et al., 2010a).

That microperimetry is also useful in the understanding of pathophysiology of diabetic retinopathy, more precisely diabetic macular edema, has been very recently demonstrated by Vujosevic et al., who analyzed DME using both fundus autofluorescence and microperimetry, as functional correlates (Vujosevic et al., 2011). They have demonstrated that in DME fundus autofluorescence increases in 75% of affected eyes, and that these hyperfluorescent areas are characterized by reduced retinal sensitivity. Moreover they have hypothesized that increased fundus autofluorescence may depend on activated retinal glial cells, introducing the role of retinal glial cells in the pathophysiology of visual loss in diabetes.

3. Conclusion

Diabetes has a relevant impact on visual function, up to permanent visual acuity loss, when retinopathy is clinically evident. Visual acuity cannot represent the only functional way of quantifying visual function loss. Microperimetry has the major advantage of integrating the functional parameter (sensitivity threshold) to the morphologic status of the retina (biomicroscopy, fluorescein angiography, OCT and fundus autofluorescence). This approach has shown the peculiar characteristic of fixation changes in diabetes, compared to age-related macular degeneration, and the absolute safety of treating DME with a micropulse subthreshold diode laser versus conventional laser photocoagulation. Microperimetry may also contribute to the understanding of the pathophysiology of early phases of diabetic retinopathy.

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