EXTENT OF DIABETIC MACULAR EDEMA BY SCANNING LASER OPHTHALMOSCOPE IN THE RETROMODE AND ITS FUNCTIONAL CORRELATIONS

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Background: To determine whether scanning laser ophthalmoscope in the retromode (RM-SLO) is useful to evaluate the extent of diabetic macular edema (DME) and its functional characteristics.

Methods: Comparative case series of 37 eyes (27 patients with diabetes). Inclusion criteria were: center involving DME determined by optical coherence tomography; RM-SLO, optical coherence tomography, fluorescein angiography (FA), and microperimetry performed on the same day; no significant media opacities. Two masked retinal specialists independently graded all images. The full extent of DME areas and two grades (small and large) DME areas were separately evaluated. The relationship between the DME extent obtained by RM-SLO and FA was assessed by Pearson correlation coefficient, intraclass correlation coefficient, and Bland–Altman plot. T-test was used to compare DME extent to central retinal thickness and macular sensitivity.

Results: The values of RM-SLO from the right and left prospective were highly correlated in the evaluation of the extent of DME (rho = 0.99, $P < 0.0001$). Mean DME area on RM-SLO was 5.7 + 5.6 mm^2 (range, 0.3–18.2 mm^2); mean DME area on FA was 6.4 + 5.9 mm^2 (range, 0.3–19.7 mm^2). The correlation between RM-SLO and FA in the evaluation of DME extent was highly significant (rho = 0.97, $P < 0.0001$), even when DME extent was divided in 2 major areas (intraclass correlation coefficient >0.8, $P < 0.0001$). The correlation between retinal sensitivity and DME area (RM-SLO) was significant (rho = –0.61, $P = 0.0003$).

Conclusion: The extent has become an important parameter for monitoring DME, with or without treatment. The extent of DME well correlates with functional data, mainly retinal sensitivity. Retromode SLO can be reliably and easily used in the evaluation of DME extent, avoiding the use of invasive FA.

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Diabetic macular edema (DME), a major cause of visual loss in the working-age population, is usually assessed by slit-lamp biomicroscopy, fluorescein angiography (FA), optical coherence tomography (OCT), and more recently by fundus autofluorescence.[1–7] Although OCT has become the gold standard in the evaluation of DME (mainly to quantify retinal thickness and volume and to determine the pattern of macular edema), the evaluation of the extent of DME is still quite unpredictable.[3,8] En-face OCT cannot exactly determine the extent of cystoid DME because of the different layer location of the cysts.[8] However, FA, which can be used to quantify the extent of DME and to evaluate different cystic patterns

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(honeycomb and petaloid), is an invasive technique and its use in clinical practice is decreasing.[4] Recently, a scanning laser ophthalmoscope in the retromode (RM-SLO), a noninvasive imaging technique, was used for the evaluation of cystoid macular edema of different origin.[8–10] Retromode SLO represents a modification and advancement of the indirect mode SLO because it provides a repeatable and reliable higher contrast images as consequence of its fully modified confocal aperture (the opening is positioned laterally from the confocal light path).[11,12] Retromode SLO has shown to easily visualize cystoid spaces in DME, regardless of the layer of retina in which they occur, because scattered light gives a shadow to the silhouetted cystoid space.[13] Retromode SLO showed a good agreement in evaluating both honeycomb and petaloid patterns of DME, as cysts of different dimensions, compared with FA.[13] Moreover, RM-SLO can easily visualize subfoveal neuroretinal detachment in DME.[13]

The main purpose of this study was to evaluate whether RM-SLO can also be used to quantify the extent of DME. The secondary aim was to correlate DME extent to retinal thickness and functional data obtained with microperimetry, which exactly quantifies retinal sensitivity.

Materials and Methods

A total of 37 eyes of 27 consecutive patients with diabetes were included in this study. All patients were recruited from the Diabetic Retinopathy clinics from March to August 2009. Inclusion criteria were men or women with Type 1 or 2 diabetes mellitus, center involving DME determined by OCT, no significant media opacities, and patients having RM-SLO, OCT, FA, and microperimetry performed on the same day. Best-corrected visual acuity was determined and recorded in decimals. All patients underwent slit-lamp fundus examination of the macula using 60-diopter lens. A written consent form was obtained from all patients and the approval from our institutional review board. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Scanning Laser Ophthalmoscope in the Retromode

Retromode SLO images were obtained with F-10 SLO (Nidek Co, Gamagori, Japan). The principal technical characteristics of this imaging modality and its difference from the so-called "dark-field" mode have already been described in detail.[13,14] Briefly, F-10 is a scanning laser ophthalmoscope that uses 4 different wavelengths, among them the infrared laser set at 790 nm is used for RM-SLO. To obtain a RM-SLO image, a central stop and a laterally oriented oval-shaped opening is used, from both the right (RM-SLO right) and left side (RM-SLO left). Therefore, each eye has two RM-SLO acquired images. In this way, scattered light from just one direction is collected for each picture, and shadows to highlight objects are obtained by blocking the reflected light from the other direction.[8] Retromode SLO differs from the previously reported dark-field mode SLO. The SLO in the indirect mode (dark-field) used both a central stop and a full-ring aperture. Using SLO dark field, a relatively large amount of multiply scattered light passing through a ring aperture is collected.[12,15] In contrast, RM-SLO uses a modified central stop. The opening of the ring aperture is further restricted and is laterally deviated from the confocal light path. When the scattered light from one side meets an abnormal retinal profile (retinal elevation or depression), the shadow of this abnormal profile is highlighted in the final image. Therefore, although a confocal system allows one focal plane to reflect light, the RM-SLO imaging mode allows all retinal layers to create shadows through the laterally deviated light, which results in a pseudo 3-dimensional image of retinal structure with high contrast (Figure 1).[10,13,14] Retromode SLO images were evaluated for the presence and extent of macular edema, which is visible as an elevated area.

Fluorescein Angiography

Fluorescein angiography of Early Treatment Diabetic Retinopathy Study Field 2 was taken in all studied eyes after an adequate dilatation by a trained photographer using Topcon TRC 50IA 35° fundus camera (Topcon, Tokyo, Japan) and saved in JPEG format. Late-phase FA images of the macula were graded for the extent of fluorescein leakage.

Optical Coherence Tomography

Optical coherence tomography was performed using the Stratus OCT TM scanner (Zeiss Humphrey Instruments; Carl Zeiss Meditec GmbH, Oberkochen, Germany) with the 4.1 (0052) version software. The scanning protocol used for this study was "fast macular thickness" program that creates a retinal map algorithm consisting in 6 radiating cross-sectional scans, each one 6 mm in length produces a circular plot in which the foveal zone is the central circular zone, 1 mm in diameter. For the purpose of this study, retinal thickness in the central 1 mm was used as the OCT measurement of central macular thickness. Macular edema was assigned if central retinal thickness

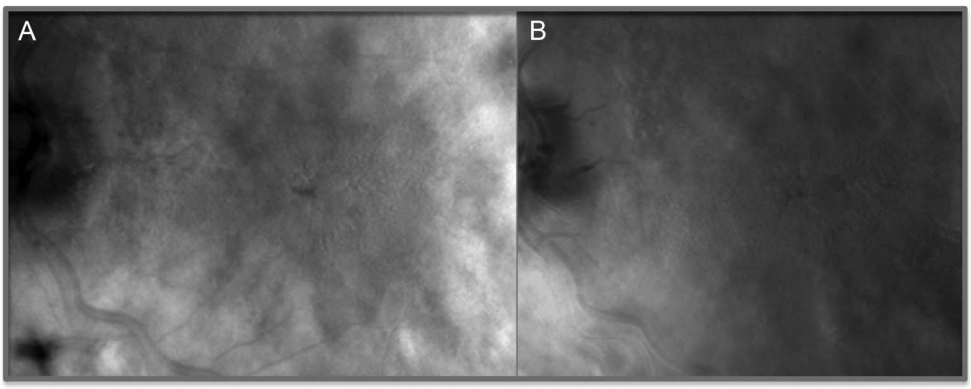

Fig. 1. Retromode SLO images of a patient with cystoid DME. **A.** Retromode SLO image obtained from a right prospective (RM-SLO right). **B.** Retromode SLO image of the same patient obtained from a left prospective (RM-SLO left). Both images easily visualize cysts of different dimensions, location, and the extent of macular edema and can be interchangeable used.

(CRT) was >230 μm.[3] Macular volume was also recorded. All images were saved on hard disk and graded for CRT and volume data.

Microperimetry

Microperimetry was performed on all studied eyes using MP1 Microperimeter (Nidek Co). This technique is described in detail elsewhere.[16] Briefly, for the purpose of this study, the following parameters were used: a fixation target consisting of red ring, 1° in diameter; white monochromatic background at 4 asb, stimulus size Goldman III with 200-ms projection time; and a customized radial grid of 45 stimuli covering the central 12° (centered on the fovea), 1° apart for the inner stimuli and 2° apart for the outer stimuli. The starting stimulus light attenuation was set at 10 dB. A 4-2-1 double staircase strategy was used with an automatic eye tracker that compensates for eye movements.[16,17] Five minutes of mesopic visual adaptation are planned before the test. All subjects underwent microperimetry with dilated pupils. Mean retinal sensitivity was evaluated within the central 12°.

Two retinal specialists trained in image grading independently graded in a masked fashion, all images on a 17-inch monitor (S.V. and E.P.). Each grader delineated the area of DME on both FA and RM-SLO, and the values of the measurements were averaged (Figures 2 and 3). The extent of DME areas was then automatically calculated. The delineated DME areas were further divided in 2 subgroups, which were separately evaluated: small DME areas (≤7 mm^2) and large DME areas (>7 mm^2). In case of disagreement, adjudication was given by the third party (E.M.).

Statistical Analyses

The relationship between measures of the extent of DME area obtained by means of RM-SLO and FA was assessed by Pearson correlation coefficient (rho), intraclass correlation coefficient (3,1), and Bland–Altman plot.[18,19] To thoroughly describe the interchangeable usage of the 2 instruments, stratified analysis was performed; the cutoff of 7 mm^2 of macula area extent measured by FA was used in this analysis. Comparison of the 2 subsets of data (≤7 mm^2 or >7 mm^2) was made with respect to OCT 1-mm central macular thickness and macular sensitivity using *t*-test. Wilcoxon two-sample test was used to evaluate the difference in mean best-corrected visual acuity. SAS (version 9.3) for personal computer was used for all analyses. Statistical test were considered significant when $P < 0.05$.

Results

Of 27 patients (37 eyes), 21 were men and 6 women. Mean age ± SD of patients was 61.6 ± 12.8 years (range, 31–79 years). Mean central macular thickness ± SD was 438.5 ± 128.8 μm (range, 262.0–717.0 μm). Mean macular sensitivity ± SD was 14.8 ± 3.8 dB (range, 5.3–19.6 dB). Mean macular volume ± SD was 9.7 ± 2.1 mm^3 (range, 7.1–14.9 mm^3). All eyes had cystoid pattern of DME on FA. Retromode SLO from the right and left prospective were highly correlated between them in the evaluation of the area of DME extent (rho = 0.99, $P < 0.0001$). Therefore, only the results of RM-SLO taken from the right field are reported (RM-SLO left data are fully available). Mean DME area on RM-SLO ± SD was 5.7 ± 5.6 mm^2 (range, 0.3–18.2 mm^2); mean DME area on FA ± SD was 6.4 ± 5.9 mm^2 (range, 0.3–19.7 mm^2). Mean difference between RM-SLO and FA was −0.6 ± 1.4. The correlation between RM-SLO and FA in the evaluation of DME extent was highly significant (rho = 0.97, $P < 0.0001$) (Figure 4).

Figure 4 shows the agreement between RM-SLO versus FA for both small (≤7 mm^2) and large DME (>7 mm^2) areas. The agreement was good for all

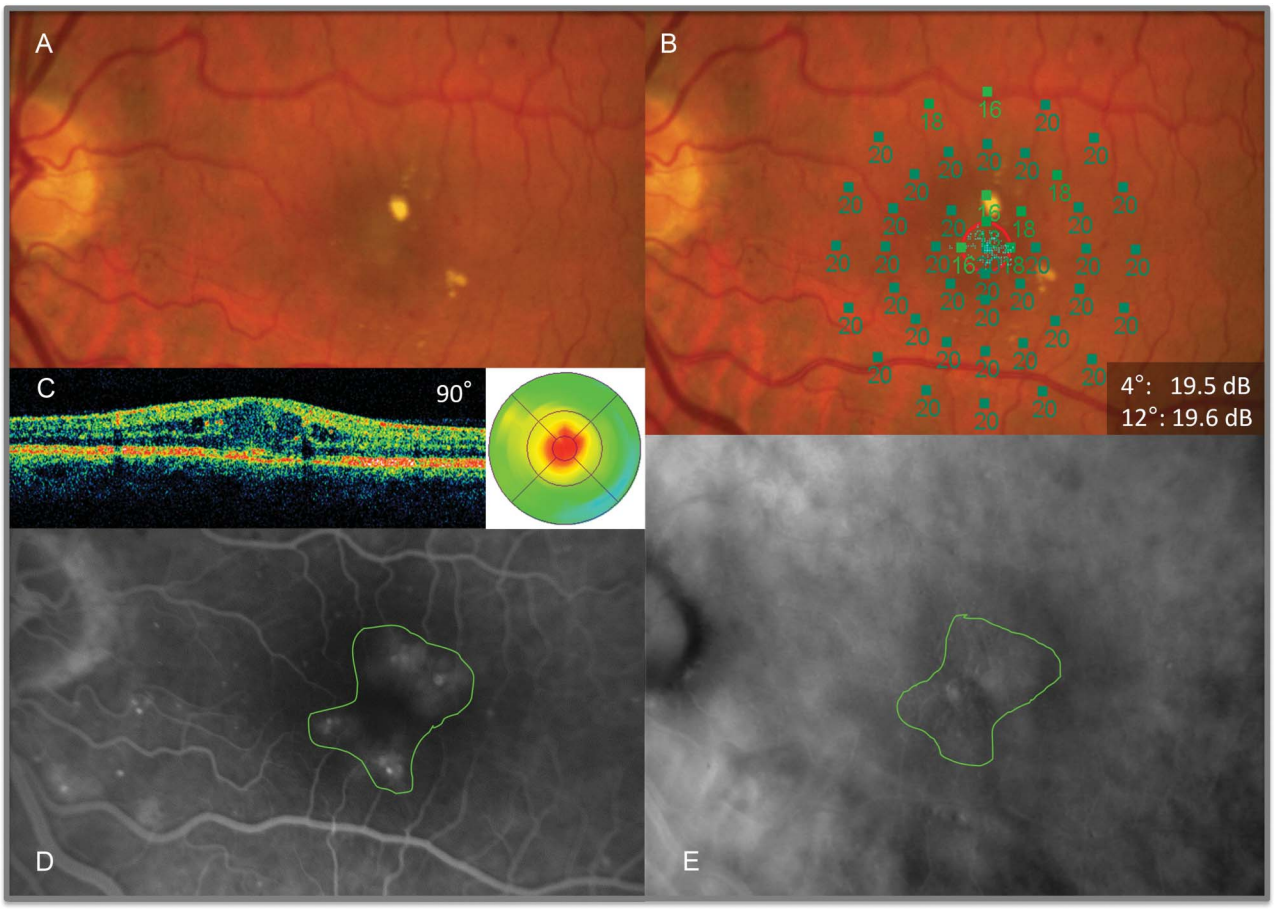

Fig. 2. Fundus color photograph (**A**), Microperimetry (**B**), OCT line scan (at 90°) and OCT map (**C**), FA (**D**), RM-SLO (**E**) of the left eye of a patient with exudative cystoid DME. The extent of macular edema (small area, ≤7 mm^2) is delineated on FA and RM-SLO images.

evaluations, although slightly inferior for large areas (Figure 4).

The agreement between RM-SLO versus FA in the evaluation of DME extent was highly significant; intraclass correlation coefficient (3,1) equals 0.97 for all areas, 0.84 for small areas, and 0.90 for large areas ($P < 0.0001$ for all).

Mean best-corrected visual acuity (decimals ± SD) was 0.44 ± 0.26 (range, 0.06–0.9). Best-corrected visual acuity was significantly higher in eyes with small DME areas (0.56 ± 0.25; range, 0.06–0.9) versus eyes with large DME areas (0.24 + 0.14; range, 0.06–0.5) ($P = 0.0004$).

Mean CRT (533.6 ± 113.0 μm) was significantly higher in the large DME areas versus small DME areas (378.0 ± 99.3 μm) ($P = 0.0001$) (Figure 5). Correlation between DME area determined on RM-SLO and OCT determined CRT was rho = 0.52 ($P = 0.0013$). Mean macular sensitivity was significantly higher over the small DME areas (16.4 ± 2.8 dB) versus large DME areas (12.0 ± 3.8 dB) ($P = 0.001$) (Figure 5). Correlation between retinal sensitivity and DME area determined on RM-SLO was statistically significant (rho = –0.61, Pearson correlation coefficient, $P = 0.0003$).

Discussion

In this study, we found that RM-SLO is a reliable technique for noninvasive evaluation of DME extent. Retromode SLO images taken from both the right and left prospective for each eye are fully superimposable in the evaluation of DME extent compared with FA. Therefore, one-side RM-SLO image is enough to quantify DME extent in each eye. Diabetic macular edema extent determined with RM-SLO was slightly smaller than that determined with FA. This confirms previous data, which demonstrated that FA leakage is not always equivalent to retinal edema.[4] Early changes of the blood–retinal barrier, seen on FA as intraretinal dye leakage, are not always accompanied by increased retinal thickness. Therefore, FA may not be an ideal examination to detect and evaluate early retinal edema.

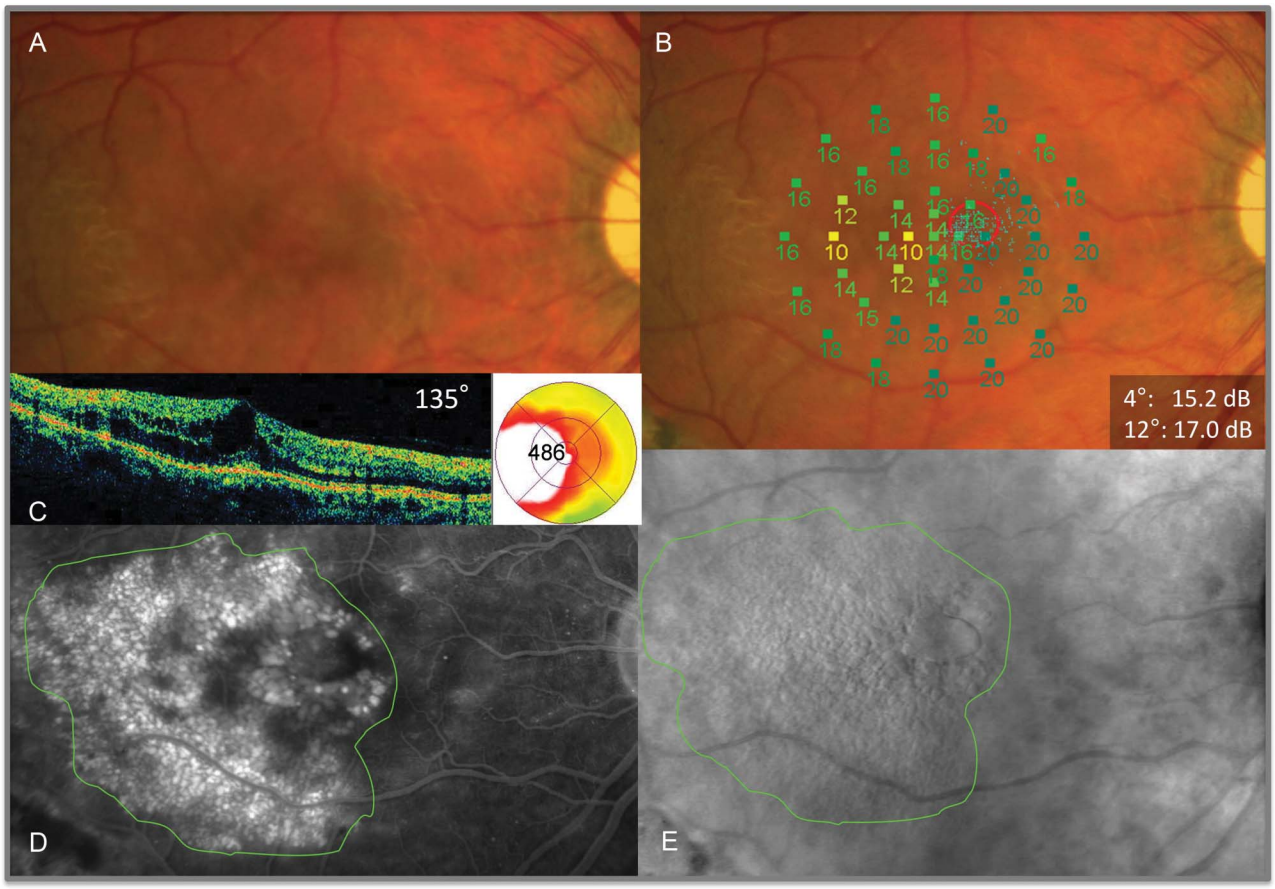

Fig. 3. Fundus color photograph (**A**), Microperimetry (**B**), OCT line scan (at 135°) and OCT map (**C**), FA (**D**), RM-SLO (**E**) of the right eye of a patient with cystoid DME. The extent of macular edema (large area, >7 mm^2) is delineated on FA and RM-SLO images.

Optical coherence tomography has become a gold standard for noninvasive detection of macular edema, even in early stages.[3] Recently, SLO in the retromode has been proposed for the evaluation of some DME characteristics.[13] In fact, RM-SLO showed 97% sensitivity (versus OCT) in detecting retinal thickening due to DME, with a cutoff value to define the presence of DME of 233 μm.[13] Moreover, RM-SLO showed high agreement in the evaluation of specific DME patterns, such as cystoid edema and subfoveal neuroretinal detachment.[13] Optical coherence tomography, even if used with the en-face mode (which is available in the most recent spectral domain OCT machines), can detect just a limited number of cystoid spaces in cystoid macular edema. This depends on the location of cystoid spaces, encompassing different retinal layers. Therefore, different en-face sections are needed to visualize all cystoid spaces and the full extent of cystoid macular edema.[10]

Katome et al[20] recently reported that the area of cystoid macular edema of different origin can be outlined by SLO in a mode these authors called "modified dark-field mode." The so-called "modified dark-field mode," as reported by Katome et al,[20] is identical to the RM-SLO, the term more commonly used in the literature. Moreover, the reduction of the area of cystoid edema after different treatments was significantly correlated to visual acuity, central visual field sensitivity, and OCT data.

Retromode SLO differs from the original indirect (dark-field) mode SLO, with an infrared laser, whose use was studied in the past in different retinal and subretinal disesease.[12,15,21] The original SLO indirect mode used both a central stop and a full-ring aperture. Using this system, a relatively large amount of multiply scattered light is collected.[10–12] In contrast, RM-SLO uses a modified central stop, in which the opening of the ring aperture is further restricted and is laterally deviated from the confocal light path. Retromode SLO represents a modification and advancement of the indirect mode SLO, providing a higher contrast images, well defined with a sort of three-dimensional rendering.

In this study, for the first time, an inverse correlation was found between the extent of DME and central macular sensitivity quantified by microperimetry.

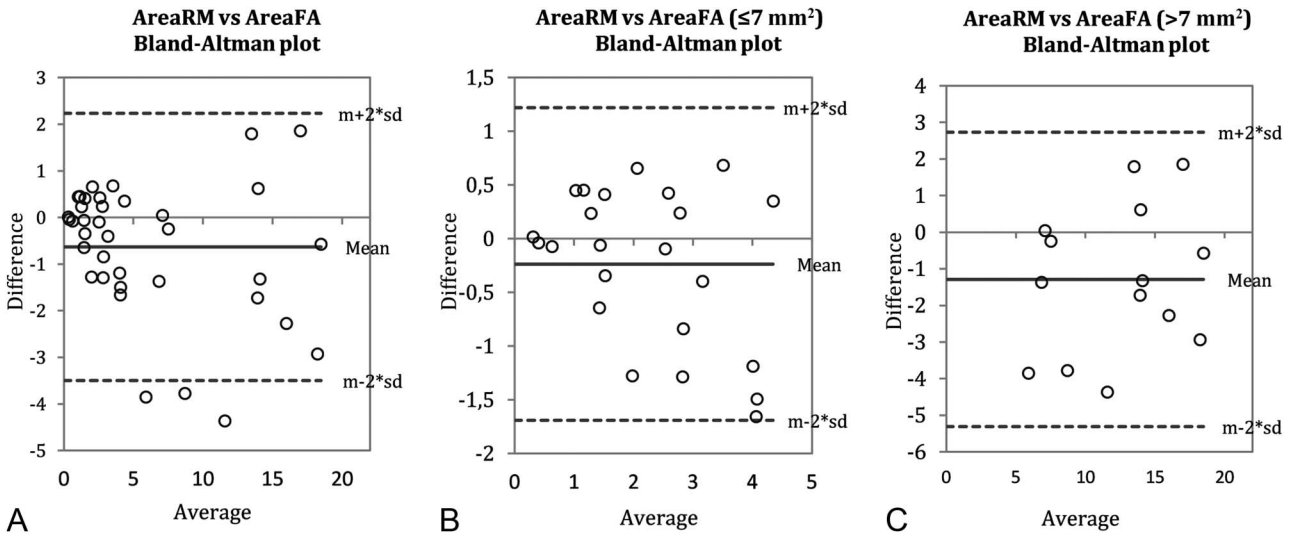

Fig. 4. Bland–Altman plots of the correlation between scanning laser ophthalmoscope in the retromode versus FA in the evaluation of DME extent. **A.** The agreement for all DME areas. **B.** The agreement for small DME areas (≤7 mm^2). **C.** The agreement for large DME areas (>7 mm^2). Intraclass correlations for interrater reliability (intraclass correlation coefficient [2,1] and their 95% confidence interval) between 2 graders in the evaluation of RM-SLO and FA images. Retromode SLO images: all, 0.989 (0.979–0.994); small DME areas, 0.930 (0.842–0.970); large DME areas, 0.930 (0.842–0.970). For FA images: all, 0.991 (0.960–0.996); small DME areas, 0.951 (0.703–0.985); large DME areas, 0.963 (0.771–0.990). AreaRM, DME area on scanning laser ophthalmoscope in the retromode; AreaFA, DME area on FA; m, mean; sd, standard deviation.

Katome et al[20] evaluated central visual field sensitivity with Humphrey Field Analyzer and correlated the increase of central visual field sensitivity to the decrease in extent of cystoid macular edema (of different vascular origin) 3 months after treatment. In a previous study, we reported the inverse correlation between the increased foveal fundus autofluorescence and retinal sensitivity over these areas (determined with microperimetry) in patients with DME.[7] The areas with increased foveal autofluorescence corresponded mainly to cystoid DME and had slightly increased retinal thickness when compared with areas with normal fundus autofluorescence (although statistically nonsignificant).[7] Therefore, combining noninvasive imaging modalities in the evaluation of pattern and extent of DME, such as RM-SLO and fundus autofluorescence, new data may be collected. This information cannot be obtained just by the evaluation of CRT by OCT.

The classification of DME as simply focal or diffuse is currently considered inadequate for the full evaluation of treatment outcomes and identification of possibly different DME phenotypes.[4] Even the OCT classification of different DME patterns (cystoid, diffuse, and subfoveal neuroretinal detachment) should be integrated with new parameters such as DME extent. This parameter, besides the site of location of DME (with or without foveal involvement), may enable the identification of new DME phenotypes, allowing for more tailored treatment to obtain better final visual results.

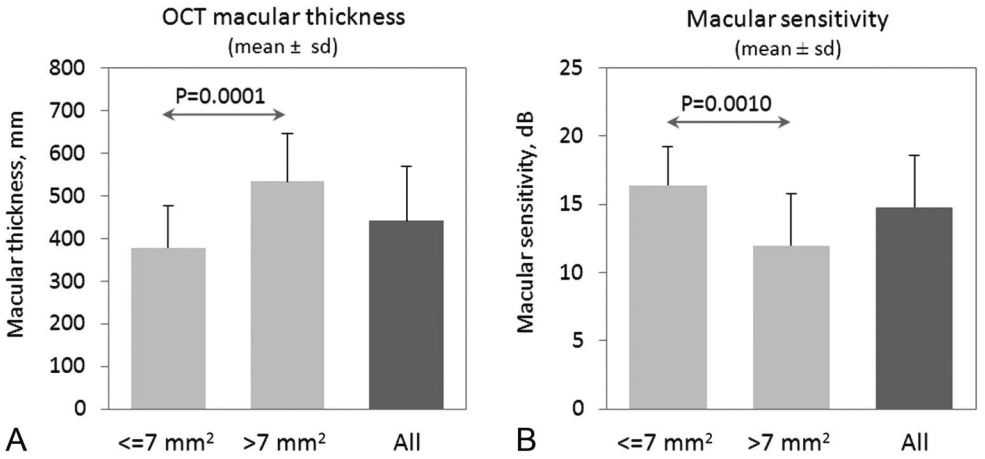

Fig. 5. Correlation between central macular thickness measured by OCT (**A**) and mean macular sensitivity measured by microperimetry (**B**) with the extent of DME. ≤7 mm^2, small DME areas; >7 mm^2, large DME areas; sd, standard deviation.

In conclusion, RM-SLO can improve the noninvasive diagnostic interpretation of different aspects of DME, avoiding in most of the cases invasive tests. Retromode SLO allows for an early detection of DME, quantifies its extent, and differentiates specific patterns. The extent of edema may become a new parameter in the clinical evaluation of DME. The use of RM-SLO should be evaluated in larger population to allow this technique to enter the routine clinical practice of DME evaluation.

Key words: diabetic macular edema, extent, fluorescein angiography, microperimetry, OCT, retromode scanning laser ophthalmoscope.

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