SCANNING LASER-DERIVED EDEMA INDEX TOPOGRAPHIC MAPS
Correlation with visual function assessment in patients undergoing laser photocoagulation for clinically significant diabetic macular edema

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Abstract

Purpose: To establish the correlation between change of the edema index analysis and change of visual function over the time course of the study in patients undergoing laser photocoagulation for clinically significant diabetic macular edema (DME).

Methods: The sample included 12 diabetic subjects, mean age 60 years (range 45-75 years) with clinically significant DME, and 16 normal subjects, mean age 60.5 years (range 48-75 years). Inclusion criteria for both groups included a logMAR visual acuity of 0.25 or better, while exclusion criteria included lenticular opacity. One eye of each subject was selected. Diabetic subjects were assessed twice prior to treatment, within one week of, and at one, two, four and 12 weeks after treatment, while normal subjects were assessed on two occasions. At each visit, subjects underwent logMAR visual acuity, conventional and short-wavelength automated perimetry (SWAP) and scanning laser tomography using the Heidelberg Retina Tomograph (HRT). The Z-profile of the HRT has been shown to exhibit a localized increase of signal width, SW, within areas of DME. Also, empirical observation of the Z-profile has demonstrated a localized reduction of maximum reflectance intensity, Imax, within areas of DME. An index of retinal edema has been developed by dividing the SW by Imax at each pixel (i) within the HRT image; edema index topographic maps were generated which provide an objective measure of DME. In addition, a global summary index that averaged all the edema index values across each topographic map was calculated, i.e., the mean edema map value (arbitrary units).

Results: At baseline, the group mean edema map value was significantly higher for the diabetic subject group than for the normal subject group both for the 10×10° and the 20×20° scan fields (two-tailed t test, p<0.05). Unlike normal subjects, all diabetic subjects exhibited a localized area of increased mean edema index values within the 20×20° scan field. Nine diabetic subjects exhibited a peak mean edema index value within four weeks of treatment. A transient increase of the mean edema index value within four weeks of treatment was not detected clinically in any of the patients. Correlation of change of the mean edema map value and change of visual function over the time course of the study was found in six of the 12 diabetic subjects.

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Conclusions: The transient post-laser increase of DME in nine of the diabetic subjects following grid laser photocoagulation provides insight into the mechanism underlying the re-absorption of retinal edema. Change of the mean edema map value over the time course of the study correlated with the change of visual function for six of the 12 diabetic subjects. The localized distribution and relatively slow period of development of DME explained the failure to establish a significant correlation between the mean edema map value and visual function in other diabetic subjects.

Introduction

Diabetic macular edema (DME) is the largest single cause of visual impairment and blindness in diabetics. The assessment of DME, using non-contact or contact lens stereo fundus biomicroscopy, relies upon the subjective interpretation of retinal thickening. Consequently, early retinal thickening can be difficult to distinguish from normal between-subject variation in retinal thickness, and the subjective evaluation of change in retinal thickness over repeated examinations is difficult. The development of an objective measure to monitor change in retinal thickness is necessary both for the clinical management of retinal diseases such as DME and for the evaluation of therapeutic protocols.

In a recent publication, Hudson et al. demonstrated that analysis of the Z-profile signal width of a scanning laser tomographer (i.e., the width at 50% maximum reflectance of a function describing change in reflectance intensity as a function of scan depth) provides an objective, topographic measure of macular retinal thickening. This basic methodology has been developed further; empiric observation of scanning laser tomography images has demonstrated that the maximum reflectance intensity exhibits a localized decrease within areas of DME relative to the reflectance values of surrounding pixels. Consequently, an edema index has been derived which is sensitive both to the localized increase in Z-profile signal width and the localized decrease of maximum reflectance intensity, such that:

$$\text{edema index} = \frac{SW_{\text{norm}}}{I_{\text{max}}}$$

where SW is the signal width of the normalized Z-profile (i.e., to minimize the variation of reflectance intensity between successive images) at 50% maximum reflectance intensity, and $I_{\text{max}}$ is the maximum reflectance intensity (arbitrary units). Using the edema index methodology, topographic maps can be derived which illustrate the extent and magnitude of edema across a whole scanning laser image.

The aim was to establish any correlation between change of the edema index analysis and change of visual function over the time course of the study in patients undergoing laser photocoagulation for clinically significant DME. Visual function was assessed using logMAR visual acuity and conventional and short-wavelength (SWAP) automated static perimetry. In particular, SWAP has been proven to offer improved sensitivity in the detection of psychophysical abnormality in patients with clinically significant DME, while conventional perimetry indicates postoperative localized visual field loss resulting from grid laser photocoagulation.
Methods

The sample was comprised of 12 subjects, mean age 60 years (SD 9.51 years, range 45-75 years), with clinically significant DME. All diabetic subjects exhibited clinically significant DME using the ETDRS criteria \( i.e. \), retinal thickening within 500 \( \mu \text{m} \) of the center of the macula) and a logMAR visual acuity of 0.25 or better. The diagnosis of clinically significant DME was independently confirmed by two medical retina specialists. Exclusion criteria for the diabetic group included a refractive error greater than 6.00 diopter sphere and/or greater than 1.00 diopter cylinder, a family history of glaucoma in a first degree relative, any other eye disease or disorder, including lenticular opacity \( i.e. \), LOCS III grades \( \geq \text{NC2}, \geq \text{NO2}, \geq \text{C2} \) and \( \geq \text{P1} \), the presence of proliferative retinopathy and its sequelae, and any previous laser treatment. Diabetic subjects were assessed twice prior to argon green grid laser photocoagulation and within one week of and at one, two, four and 12 weeks after treatment. The results of the diabetic subjects were compared to a sample of 16 normal subjects, mean age 60.5 years (SD 8.17 years, range 48-75 years). Inclusion criteria for the normal subjects included a logMAR visual acuity of 0.25 or better, while exclusion criteria were similar to those of the diabetic group, but also included any eye disease or disorder and a family history of diabetes in a first degree relative. Normal subjects were assessed on two separate occasions.

One eye of each subject was entered into the study. At each visit, subjects underwent logMAR visual acuity, conventional and SWAP12,13 and scanning laser tomography. Visual acuity was assessed using the 96, 25 and 11% contrast Regan charts in conjunction with a by-letter scoring system. Automated perimetry was assessed using Program 10-2 of the Humphrey Field Analyzer. Visual function assessment was always undertaken before scanning laser tomography. Seven scanning laser tomography images were acquired, using the Heidelberg Retina Tomograph (HRT), for both the 10×10° and 20×20° scan fields at each visit. The scan parameters (depth and focus) were kept constant for each patient between visits. Steady patient fixation was achieved using a 60-watt light viewed by the fellow eye at a distance of 3 m through a periscope, thereby allowing the subject to see around the HRT during the acquisition of macular images.

Analysis

A normalization procedure was undertaken on the scanning laser tomography data that expressed reflectance intensity as a function of the minimum and maximum reflectance intensity values within a given image. The normalization procedure reduced the influence of variation in reflectance intensity between successive images on the signal width calculation. The signal width was measured at 50% of maximum reflectance intensity following fitting of the Z-profile with a 16th order polynomial that was found to give the most satisfactory fit of the Z-profile function. Custom image alignment software (TView) was used to generate mean edema index topographic maps of macular scanning laser images. Super-pixel edema index values were averaged from each set of 4×4 pixels. The resulting resolution of the edema index topographic map was 64×64 super-pixels, rather than 256×256 pixels of the original scanning laser image. Mean edema index topographic maps were generated which comprised a maximum of seven separate scanning laser images. In addition, a global summary index that averaged all of the edema index values across the complete mean topographic map, termed the mean edema map value (arbitrary units), was calculated. The coefficient of repeatability (COR),
which defines the 95% confidence limits for the repeatability of the measurement procedure, was calculated for the mean edema map value using the two baseline visits of the diabetic subjects and the two visits of the normal subjects.

A Pearson correlation coefficient was undertaken on the data set of each diabetic subject to establish any correlation between change of the mean edema map value and change of visual function over the time course of the study. For each of the diabetic subjects, the following visual function parameters were correlated with the mean edema map value derived from the 10×10° and from the 20×20° HRT scan fields: 1. Regan logMAR visual acuity at 96%, 25% and 11% contrasts; 2. mean deviation (MD) and corrected pattern standard deviation (CPSD) of conventional perimetry; and 3. SWAP cluster volume\textsuperscript{11} of stimulus locations reaching statistical probability levels of $p<0.05$ and $p<0.001$. A Bonferroni correction was applied to the data to correct for Type I experimental error, since multiple comparisons were undertaken on the mean edema map value to establish any significant correlation with the various parameters of visual function. Consequently, a $p<0.001$ was taken to indicate significant correlation.

Results

At baseline, the group mean edema map value for the complete 10×10° scan field was 1.258 (SE 0.076) and 1.688 (SE 0.195) in the normal and diabetic subject groups respectively; similarly, the group mean edema map value for the 20×20° scan field was 1.624 (SE 0.092) and 2.095 (SE 0.180), respectively. The group mean edema map value was significantly higher for the diabetic subject group than for the normal subject group both for the 10×10° and the 20×20° scan fields (two-tailed $t$ test, $p<0.05$). Unlike normal subjects, all diabetic subjects exhibited a localized area of increased mean edema index values within the 20×20° scan field.

For the 10×10° scan field, a group mean COR of 0.180 and 0.322 was found for the normal and diabetic subject groups, respectively. Similarly, the group mean COR for the 20×20° scan field was 0.447 and 0.626, respectively.

Nine diabetic subjects exhibited a peak mean edema index value within four weeks of treatment, while three diabetics exhibited a peak mean edema index value at 12 weeks post-treatment (Fig. 1). The transient increase of the mean edema index value within four weeks of treatment was not detected using established clinical techniques, \textit{i.e.}, medical retina assessment utilizing stereo fundus biomicroscopy. At 12 weeks post-treatment, the mean edema index value had decreased relative to baseline in nine diabetic subjects.

Change of the mean edema map value correlated with change of visual function over the time course of the study in six of the 12 diabetic subjects (Fig. 2). Five diabetic subjects exhibited significant correlation of the mean edema map value and of visual function for the 10×10° scan field (Fig. 2a), and three subjects exhibited significant correlation for the 20×20° scan field (Fig. 2b).

Discussion

The group mean edema map value was significantly higher for the diabetic subject group than for the normal subject group. However, considerable overlap of the individual mean edema map values of the two groups was apparent; this is not surprising given that the
The inclusion criteria for the diabetic subjects included any evidence of retinal thickening within 500 µm of the center of the macula (based upon clinical assessment). Using the edema index methodology, the parameter that differentiated diabetic subjects from normal subjects was the presence of a localized area of increased mean edema index values within the 20° topographic map. Unlike normal subjects, all diabetic subjects exhibited a localized area of increased mean edema index values.

The COR for the mean edema map value indicates that in order to reach statistical significance, change of the edema index would typically need to exceed approximately 20% of the mean value for the 10° scan field and 30% of the mean value for the 20° scan field. Caution must be exercised, however, in the interpretation of the COR results for the mean edema map value, since the mean edema map value is a global summary index. Pointwise variation in COR values is likely to occur across a mean edema index topographic map of a subject exhibiting clinically significant DME. Future work will examine the pointwise variation of COR values of the edema index in normal and diabetic subjects.

To the best of our knowledge, no other study which has utilized an objective measure of retinal edema has detected a transient post-laser increase of DME; this can probably be

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**Fig. 1.** Mean edema index topographic maps for diabetic subject #10 (right eye, 10×10° scan field). Each map is auto-scaled to optimize the grayscale, *i.e.*, the whiter the area the greater the magnitude of the edema index. Consequently, the grayscale is not directly comparable between images (a. pretreatment; b, c, d, e and f: three days, one, two, four and 12 weeks post-treatment, respectively). The fovea is located approximately in the center of each scan. a. Pretreatment, there is a localized area of DME located supero-temporally to the fovea (this finding agreed with clinical assessment). b. Immediately post-treatment, a hemorrhage (and associated edema) has arisen inferior to the fovea. c and d. At one and two weeks post-treatment, laser scars are visible as dark (indicating no retinal edema) circular patches supero-temporal to the fovea. e. At 12 weeks post-treatment, further hemorrhages and micro-aneurysms (and associated edema) have arisen, particularly inferior to the fovea.
explained by an insufficient frequency of follow-up of the previous studies. The finding of a transient increase of DME following grid laser photocoagulation provides insight into the mechanism underlying the re-absorption of retinal edema. In this study, clinical assessment failed to detect any transient post-laser increase of DME. However, a transient increase of DME is sometimes apparent following grid laser photocoagulation using clinical assessment and is usually associated with a transient reduction of visual acuity. Interestingly, pan-retinal photocoagulation frequently results in a more apparent transient reduction in visual acuity, which is often associated with the spontaneous development of macular edema, or the worsening of pre-existing DME.

Change of the mean edema map value over the time course of the study correlated with the change of visual function for six of the 12 diabetic subjects. However, correlation of the mean edema map value and of visual function was not found in each possible situation or
Scanning laser-derived edema index topographic maps

in each diabetic subject. This finding is consistent with the localized distribution, and typical period of development, of DME. The mean edema map value represents a mean pixel value over the complete scan field. All the diabetic subjects in this study exhibited localized areas of DME. In effect, localized significant change of the edema index could be obscured in the noise inherent within the complete scan. Obvious differences were also apparent in the time course of change of the various parameters. Grid laser photocoagulation typically resulted in an immediate localized loss of perimetric sensitivity\(^2\), whereas the resulting change of the mean edema map value occurred over a period of weeks. In addition, change in the magnitude of extra-foveal DME had minimal impact on visual acuity. Furthermore, SWAP typically showed extensive and deep localized visual field loss in the diabetic subjects prior to treatment\(^1\) and, consequently, was unable to reflect post-laser change of DME due to dynamic range limitations.

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References

13. Early Treatment Diabetic Retinopathy Study Research group: Treatment techniques and clinical guide-