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ABSTRACT

Aims: To investigate the correlation between increased retinal thickness (RT) measured with spectral domain high-definition OCT (Cirrus HD-OCT) and best-corrected visual acuity (BCVA) in eyes with clinically significant macular edema (CSME) and type-2 diabetes.

Methods: Seventy CSME eyes were included in this observational study. Sixty-two eyes were considered for analysis and were classified as having/not having retinal thickening in the central fovea (central 500-µm in diameter circle) by Cirrus HD-OCT. RT measurements were computed and correlated with BCVA. For comparison purposes the Stratus OCT central point thickness was also obtained in these eyes.

Results: In the 19 CMSE eyes identified by Cirrus HD-OCT without increased RT in the central fovea (500-µm in diameter circle) no correlation was found between RT and BCVA (R=+0.062; 95%CI=[-0.404;+0.502]). In the 43 eyes where the Cirrus HD-OCT identified an increased RT in the central fovea (central 500-µm in diameter circle) only a moderate correlation between RT and BCVA was found (R=-0.459; 95%CI=[-0.667;-0.184]).

Conclusion: Correlations between RT and BCVA in CSME are only present when the central 500-µm in diameter circle is involved. However, even in this circumstance, in only 48.8% of the cases a correlation was found. RT cannot, therefore, be used as a surrogate outcome for visual acuity changes.

INTRODUCTION

Diabetic macular edema (DME) has been considered the most frequent cause of visual loss in patients with diabetes. This concept is due mainly from the perception that a decrease in macular edema obtained by treatment is associated with an improvement in visual acuity.

Objective methods of measuring retinal thickness have recently become available, and studies are being performed to investigate the relationship between the degree of DME and visual acuity.

Different studies have reported different results, ranging between 0.28 and 0.73 for the correlation between OCT-measured retinal thickness (OCT – Optical Coherence Tomography) and visual acuity. [1-5].

The verification of such a correlation, or the lack of it, has obvious clinical relevance. Is increased retinal thickness, which equals macular edema, a good indicator of visual acuity loss? Can OCT be used as a surrogate outcome for changes in visual acuity?

There are, now, commercially available improved versions of the OCT with increased sampling allowing a clear identification of the central 500-μm in diameter circle, such as the high-definition spectral domain Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA).

In this paper, we compared best-corrected visual acuity (BCVA) with retinal thickness measurements, performed with the recently available Cirrus HD-OCT, in a series of patients with diabetes type 2 classified on stereocolor fundus photography, at an independent reading center, as having clinically significant macular edema (CSME) using the Early Treatment Diabetic Retinopathy Study (ETDRS) classification.

MATERIALS AND METHODS

Patients and Study Design

Seventy CSME eyes from 37 diabetic type 2 patients, classified according to the ETDRS definition, were included in this observational study.

All eyes were classified as having CSME at an independent reading center using stereocolor fundus photography according to the ETDRS definition. Eyes receiving this classification comply with one or more of the following criteria: [6, 7]

1. thickening of the retina at or within 500 µm of the center of the macula;
2. hard exudates at or within 500 µm of the center of the macula, if associated with thickening of the adjacent retina;
3. a zone or zones of retinal thickening 1 disc diameter (DD) or larger, of which any part is within 1 DD of the center of the macula.

In addition to the CSME classification, according to the ETDRS criterion of "*thickening of the retina at or within 500 µm of the center of the macula*", these eyes were also classified as being with or without retinal thickening in the central fovea based on Cirrus HD-OCT measurements and stereocolor fundus photography.

Exclusion criteria included eyes with photocoagulation treatment within the 3 months prior to inclusion in the study and eyes with cataract or any other eye disease that may interfere with fundus examination.

The tenets of the Declaration of Helsinki were followed and approval from the institutional ethics and review board was obtained. Informed consent was obtained from all the patients (clinical trial identifier at www.clinicaltrials.gov: NCT00797134).

All 70 eyes underwent retinal thickness measurements using the Cirrus HD-OCT, best-corrected visual acuity according to the ETDRS score and 7-field stereocolor fundus photography. Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA) central point thickness was additionally collected.

Methods

Best-Corrected Visual Acuity

Best-corrected visual acuity in each eye was assessed according the ETDRS protocol [6, 8] using Precision Vision charts “R”, “1”, and “2” (Precision Vision, Bloomington, IL, USA) at a distance of 4 meters.

Retinal Thickness

Retinal thickness was assessed by stereocolor fundus photography, for CSME classification according to the ETDRS criteria, and objectively measured by Cirrus HD-OCT and by Stratus OCT (central point thickness only).

Stereocolor Fundus Photography

Stereocolor fundus photography was performed according to the ETDRS guidelines for CSME classification – field 2 of 7-field stereocolor fundus photography.

Cirrus HD-OCT

A major advantage of the Cirrus HD-OCT, as compared to the Stratus version and besides the increase in sampling (65536 readings for the Macular Cube 512x128 Combo Protocol), is the availability of two distinct fundus references: a C-scan computed from

the tomographic data, and; a reference obtained by scanning the eye fundus through scanning laser ophthalmoscopy (SLO). Although none of these two references excels in image quality, both outperform the Stratus OCT fundus reference which is unusable for the large majority of scans.

To increase the accuracy in detecting the center of the fovea, this location was identified in color fundus photographs of the same eye. Through an image co-registration procedure (projective transformation), Cirrus HD-OCT fundus references were co-registered to the respective color fundus photographs. This procedure allows the center of the fovea to be identified in the thickness map based on its easier identification in the respective color fundus image. Also, because of sampling, the average retinal thickness for the 500-μm in diameter circle, centered at the identified foveal location, was computed resorting to thin plate spline (TPS) interpolation, [9, 10] a procedure that allows data to be interpolated by defining a smooth surface passing through all control points.

A Cirrus HD-OCT map over the fundus reference can be seen in figure 1.

To establish a reference value for the central 500-μm in diameter circle, an age-matched control population of 29 eyes, from healthy volunteers with ages ranging from 40 to 85 years (mean±SD: 52.9±10.7 years), underwent retinal thickness measurements with the Cirrus HD-OCT. The reference value, ie the value above which retinal thickness was considered increased, was defined as the mean + 2 SD. Based on this thickness-value reference, retinal thickness in the central fovea was considered increased whenever the measured retinal thickness in the central 500-μm in diameter circle was above 261.8 μm (ie 231.5 + 2x15.1 μm).

Cirrus vs. Stratus OCT

While for the Stratus OCT the average retinal thickness for the central 1000-µm in diameter circle and the central point thickness – CP values are the only options available, when using the 6 radial line-scans (Fast Macular Protocol), for the Cirrus HD-OCT a detailed retinal-thickness map is provided, allowing access to detailed information. The number (density) of retinal-thickness measures by Stratus and Cirrus HD-OCT for the central 1000-µm in diameter circle is of 128 and more than 5600 readings, respectively (ie a sampling factor over 40).

Statistical analysis

To analyze the correlation between retinal thickness measured with the Cirrus HD-OCT in the central 500-µm in diameter circle and best-corrected visual acuity, a regression analysis was performed, with the BCVA being it considered the dependent parameter.

Regression analyses were performed for the eyes with and without retinal thickening in the central fovea (increased RT in the central 500-µm in diameter circle based on the Cirrus HD-OCT retinal thickness classification or based on the stereocolor fundus photography classification). The normal distribution of the different parameters, tested using the Kolmogorov-Smirnov test, was ensured by removing 4 outliers and by applying the logarithmic function to the retinal-thickness parameters (logRT), which initially presented a skewed distribution.

The correlation between the central retinal thickness values and patients' age, diabetes duration and HbA_{1C} levels was also analyzed using the Pearson correlation coefficient.

The agreement between the Cirrus HD-OCT and the stereocolor fundus photography classifications, for retinal thickening in the central fovea (ie for the presence of an increased RT in the central 500-µm in diameter circle) was assessed using the Cohen's Kappa coefficient (Kappa).

Additionally, Stratus OCT central point thickness was correlated with the BCVA.

Statistical analyses (estimates and 95%CI) were performed using the SPSS software version 13.0 (SPSS Inc., Chicago, USA). Good agreements were considered for Kappa values over 0.75 (based on the Landis and Koch criteria [11]). For the Pearson correlation coefficient (R), from the regression analyses between logRT and BCVA, the criteria defined by Swinscow and Campbell were used. [12]

RESULTS

From the initial 70 eyes included in this study 8 eyes were excluded, 4 eyes with segmentation errors on Cirrus HD-OCT and another 4 considered as outliers on the statistical analysis.

Increased retinal thickness, in the central 500-µm in diameter circle (retinal thickness above 261.8 µm) was detected in 43 eyes using the high-definition Cirrus HD-OCT. Therefore, 43 eyes were considered to have increased RT in the central fovea (central 500-µm in diameter circle), and 19 eyes were considered as not having increased RT in the central fovea.

On the basis of stereocolor fundus photograph grading, 40 of the 62 eyes were considered, by the independent reading center, to have retinal thickening in the central fovea and 22 eyes were considered as not having retinal thickening in the central fovea.

Table 1 provides demographic and clinical characteristics for patients and study eyes.

No correlations were found between Cirrus HD-OCT retinal thickness in the central 500-µm in diameter circle and, patients' age (R= +0.044; 95%CI=[-0.208; +0.291]); diabetes duration (R= -0.055; 95%CI=[-0.301; +0.197]) and; HbA_{1C} levels (R= +0.031; 95%CI=[-0.220; +0.279]).

Table 1. Patients' characteristics.

Patients/eyes	
Patients/Eyes, n/n	36/62
Sex (Men/Women), n/n	22/14
Age (yr), mean ± SD [min; max]	64.1 ± 8.7 [44; 79]
Diabetes duration (yr), mean ± SD [min; max]	10.8 ± 6.8 [1; 30]
HbA_{1C} (%), mean ± SD [min; max]	8.4 ± 1.8 [5.9; 12.8]
BCVA (letters), mean ± SD [min; max]	73.3 ± 11.0 [45; 92]
Retinal Thickness – Cirrus HD-OCT	
Ø 500-µm area (µm) , mean ± SD [min; max]	326.2 ± 100.1 [169.6; 621.7]

Retinal Thickness vs. BCVA

Considering, separately, the eyes with and without increased RT in the central fovea by Cirrus HD-OCT (central 500-µm in diameter circle), the correlation between logRT and BCVA is absent for the eyes without increased RT in the central fovea and is only moderate for the eyes with increased RT in the central fovea (Table 2).

For eyes with increased RT in the central fovea (central 500-µm in diameter circle) the correlation coefficient is R=-0.459 (95%CI=[-0.667; -0.184], Figure 2), while for eyes without increased RT in the central fovea the correlation coefficient is R= +0.062 (95%CI=[-0.404; +0.502]).

The moderate correlation in the eyes with increased RT in the central fovea is well demonstrated by the fact that only 48.8% of the eyes (21 out of the 43) are within the 99% mean prediction interval for the regression line.

The lack of a correlation between the more increased values of RT and worst BCVA is shown in Table 3 (number of eyes with an observed BCVA different, better or worst, than the predicted value, ie than the BCVA predicted by the regression line).

Foveal involvement classifications: Cirrus HD-OCT vs. stereocolor fundus photography

A moderate agreement was found between the classifications for CSME with or without increased RT in the central fovea (central 500-µm in diameter circle) based on the Cirrus HD-OCT (ie retinal thickness in the 500-µm in diameter circle over 261.8 µm) and the stereocolor fundus photography (Kappa=0.673; 95%CI=[0.478; 0.868]).

Fifty-three of the 62 CSME eyes (85.5%) received the same classification by both Cirrus HD-OCT and stereocolor fundus photography. Thirty-seven eyes (59.7%) were classified with increased RT in the central fovea (central 500-µm in diameter circle) by Cirrus HD-OCT and stereocolor fundus photography, and 16 eyes (25.8%) were classified without increased RT in the central fovea by both methods.

When considering the stereocolor fundus photography classification for retinal thickening in the central fovea, the strength of the correlation between logRT and BCVA decreases. For these eyes the correlation becomes weak (R=-0.342; 95%CI=[-0.591; -0.034]), whereas for eyes without retinal thickening in the central fovea the correlation remains absent (R =-0.005; 95%CI=[-0.426; +0.417]) (Table 2).

Table 2. Pearson correlation coefficient and 95%CI for the regression analysis between Cirrus HD-OCT retinal thickness in the 500-µm in diameter circle (LogRT) and best-corrected visual acuity (BCVA).

Central fovea (Ø 500-µm)	Retinal thickening in the central fovea based on	
	Cirrus HD-OCT	Stereocolor fundus photography
With increased RT	-0.459 [-0.667; -0.184] (n=43)	-0.342 [-0.591; -0.034] (n=40)
Without increased RT	+0.062 [-0.404; +0.502] (n=19)	-0.005 [-0.426; +0.417] (n=22)

Table 3. Number of eyes with increased RT in the central fovea (central 500-µm in diameter circle) (n=43), with an observed BCVA different (worst, or better) than the predicted value (from the regression line).

		BCVA		Total
		Worst	**Better**	
Cirrus HD-OCT RT in the 500-µm in diameter circle (µm)	[261.8; 300]	6	4	10
	]300; 350]	5	8	13
	]350; 400]	2	3	5
	] 400; 450]	5	4	9
	> 450	3	3	6
Total		21	22	43

Stratus OCT central point

The correlation between logRT and BCVA, when using the Stratus OCT central point thickness, was found to be moderate (as well) for the eyes with increased RT in the central fovea (R=-0.460; 95%CI=[-0.668; -0.185]), ie in the same range of the correlation found for the Cirrus HD-OCT.

DISCUSSION

Central retinal thickness, as measured by OCT Stratus, has been proposed by several authors as a surrogate outcome for visual function, while recent findings reported by the DRCR.net in a large series of 251 eyes with DME, before and after laser treatment, [1] documented only a modest correlation between BCVA and Stratus OCT-measured central point thickness.

We examined a series of 62 eyes with DME, correlating BCVA with high-resolution spectral domain Cirrus HD-OCT measurements of retinal thickness for the inner 500-µm in diameter circle.

Evaluation of the central 500-µm in diameter circle is particularly relevant taking into consideration the accepted definition of CSME and the current understanding that visual acuity values are mainly dependent on the function of the central fovea. [6, 7]

The separation of the eyes into two different groups based on retinal thickening in the central fovea, using the Cirrus HD-OCT retinal thickness maps (allowing a clear identification of the central 500-µm in diameter circle), offers a better insight into any correlation between RT and BCVA. [13]

This study confirms the DRCR.net study findings, [1] which showed only a moderate correlation between Stratus OCT thickness values and BCVA, even when considering the central 500-µm in diameter circle.

Correlations between retinal thickness, measured by the Cirrus HD-OCT, and BCVA were only identified in eyes with retinal thickening in the central fovea (central 500-µm in diameter circle).

No clear association could be found between higher ranges of increased thickness and worst visual acuities, nor the reverse. Worst than expected visual acuities were

predominant in the group of eyes that had edema of the central 500-µm diameter circle lower than 300 µm and in the group that had increased retinal thickness values in the central macula between 400 and 450-µm.

It is interesting that stereocolor fundus photography classification of retinal thickening in the central 500-µm circle performed by trained graders showed only a moderate agreement with the classification based on the Cirrus HD-OCT thickness in the 500-µm in diameter circle.

Our findings show that OCT retinal thickness measurements, although able to quantify the height and volume of macular edema, cannot be used alone as a reliable outcome when evaluating progression of diabetic retinal disease and/or progression of visual acuity loss.

Assessment of macular thickness using OCT is clinically useful and demonstrates objectively the degree of macular edema. Macular thickness, however, does not, *per se*, correlate well with visual acuity in eyes with DME.

The degree of macular edema may only represent the degree of the breakdown of the blood-retinal barrier (BRB) and the associated inflammatory response, and, as such, is just a sign of only one component of disease progression. Subclinical macular edema may be present from the earliest stages of diabetic retinal disease as soon as there is an alteration of the inner BRB that is not compensated by the pumping activity of the outer BRB.

It is necessary to reach a scientific consensus on the definition of the different subtypes of diabetic macular edema. Demonstration of increased retinal thickness, with an objective method such as OCT, should be mandatory. Furthermore, the presence, or absence, of increased RT values in the central 500-µm in diameter circle of the retina should also be indicated. Other factors that should be taken into account are, the total

area of the retina that shows increased RT, the finding of large “cystic” spaces in the retina suggesting large accumulations of extracellular fluid, the duration of the edema and its response to treatment. Another piece of information that may become particularly relevant is the status of the retinal photoreceptors (rods and cones) within the area of edema. [13]

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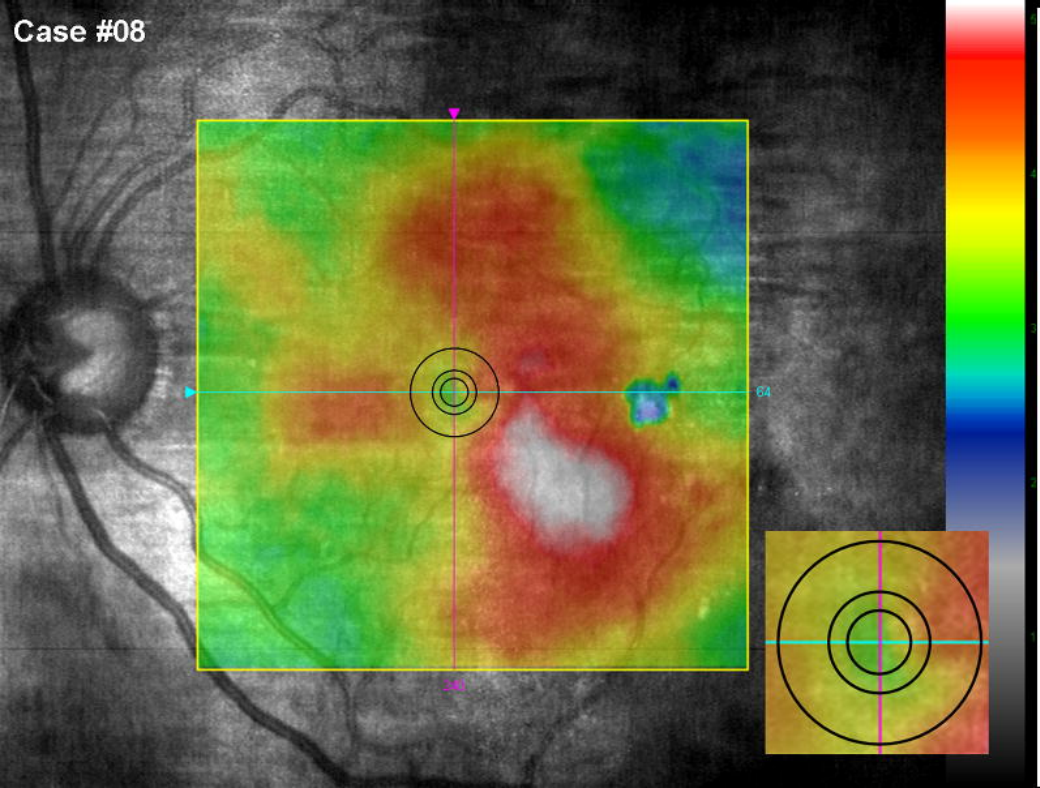
Figures Legends

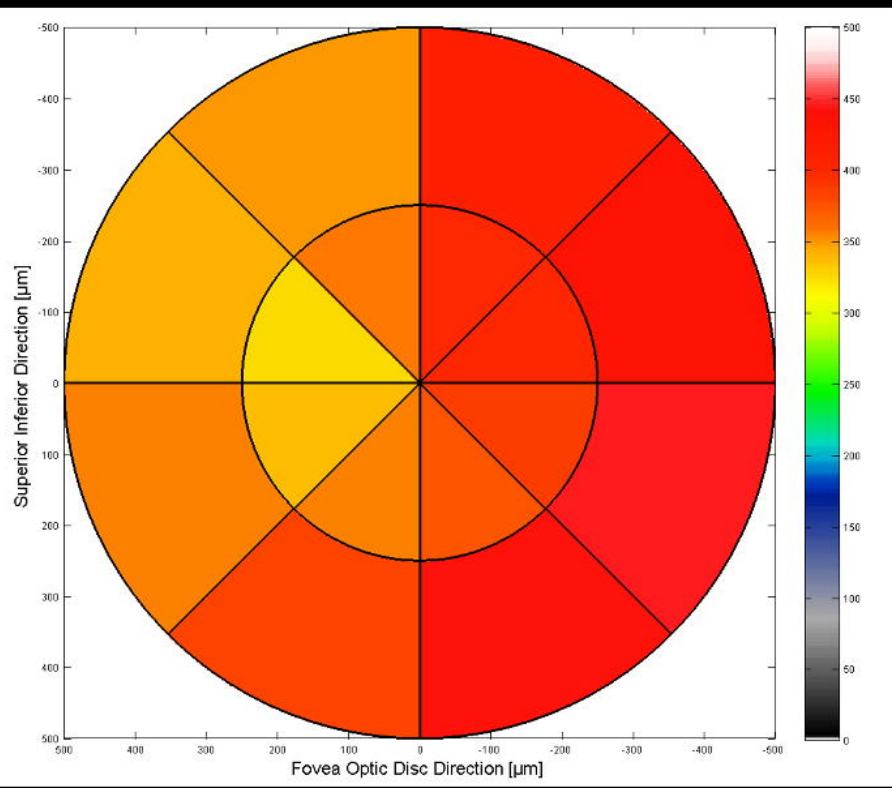
Figure 1.

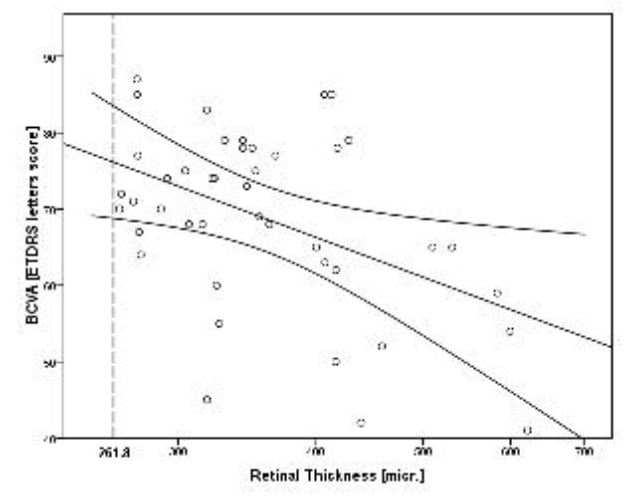
Retinal-thickness maps for case #08. Left: Retinal-thickness map from the Cirrus HD-OCT where the circles indicate the central 300- (the foveola), 500- and 1000-µm diameter circles centered on the fovea, as identified from the respective color fundus photograph. Right: Proprietary retinal-thickness map with circles of 500- and 1000-µm in diameter, each split into 8 equal areas. Retinal thickness (in µm) can be deciphered through the color bar on the right.

Figure 2.

Retinal thickness in the 500-µm in diameter circle (logarithm scale) vs. BCVA for the eyes with increased RT (based on Cirrus HD-OCT) in the central fovea (n=43; regression line with 99% mean prediction interval).


Case #08


Superior Inferior Direction [µm]
Fovea Optic Disc Direction [µm]
500
400
300
200
100
0
-100
-200
-300
-400
-500
450
350
250
150
50


BCVA [ETDRS letters score]
261.8
Retinal Thickness [micr.]