

# Retinal Thickness Study with Optical Coherence Tomography in Patients with Diabetes

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**PURPOSE.** To quantitatively assess retinal thickness by optical coherence tomography (OCT) in normal subjects and patients with diabetes. This study was intended to determine which retinal thickness value measured with OCT best discriminates between diabetic eyes, with and without macular edema.

**METHODS.** OCT retinal thickness was measured by a manual technique in a total of 26 healthy volunteers (44 control eyes) and 85 patients with diabetes (148 eyes) with the clinical diagnosis of no diabetic retinopathy (45 eyes), nonproliferative diabetic retinopathy without clinically significant macular edema (CSME; 54 eyes), proliferative diabetic retinopathy without CSME (21 eyes), and 28 eyes with diabetic retinopathy with CSME. Independent predictors of the presence of CSME were quantified by using univariate and multivariate logistic regression analyses. Receiver operating characteristic (ROC) curves were generated to evaluate and compare the predictor variables. The correlation of retinal thickness measurements and visual acuity was calculated.

**RESULTS.** There were statistically significant differences in foveal thickness between control eyes and all the other eye groups ( $P = 0.001$ ). Diabetic eyes with CSME had a statistically significant greater thickness in each of the areas compared with the other groups. In a multivariate logistic regression model, foveal thickness was a strong and independent predictor of CSME (odds ratio [OR], 1.037; 95% confidence interval [CI] 1.02–1.05). The area under the ROC curve of this predictor variable was 0.94 ( $P = 0.001$ ). For a cutoff point of 180  $\mu\text{m}$ , the sensitivity was 93%, and specificity was 75%. Foveal thickness correlated with visual acuity in a log minimum angle of resolution (logMAR) scale (Spearman's  $\rho = 0.9$ ,  $P = 0.001$ ).

**CONCLUSIONS.** These results suggest that foveal thickening over 180  $\mu\text{m}$  measured by OCT may be useful for the early detection of macular thickening and may be an indicator for a closer follow-up of the patient with diabetes. (*Invest Ophthalmol Vis Sci.* 2002;43:1588–1594)

Traditional methods of evaluating macular thickening, including slit lamp biomicroscopy and stereo fundus photography, are relatively insensitive to small changes in retinal thickness. Thus, several new techniques for quantitatively measuring retinal thickness have been explored.<sup>1</sup> Recent imaging techniques can provide tomographic or cross-sectional images of intraocular structures and can yield powerful diagnostic

information, which is complementary to conventional fundus photography and fluorescein angiography.<sup>2</sup>

Optical coherence tomography (OCT) is a new medical diagnostic imaging technology which can perform micrometer resolution cross-sectional or tomographic imaging in biologic tissues.<sup>3</sup> The operation of OCT is analogous to ultrasound B-mode imaging, except that light is used rather than acoustic waves. OCT application has been demonstrated in the normal human anterior eye and retina in patients with selected macular abnormalities and glaucoma.<sup>2,4,5</sup> In patients with diabetes and diabetic retinopathy, single measurements of central foveal thickness using OCT correlate with visual acuity and are a successful means of monitoring macular thickening before and after laser therapy.<sup>2,6,7</sup>

In this study, we used OCT to quantify retinal thickness in patients with diabetes with no retinopathy and patients with different degrees of diabetic retinopathy, with and without clinically significant macular edema (CSME). We assessed the validity of OCT measurements of macular thickness for evaluating the presence of macular edema. Particularly, we intended to determine which retinal thickness best discriminates the severity of macular edema. We also evaluated the correlation between the retinal thickness at the central fovea and best corrected visual acuity.

## PATIENTS AND METHODS

We performed OCT in 44 eyes of 26 healthy nondiabetic volunteers (control group) and in 148 diabetic eyes of 85 patients: 45 eyes of 23 patients with diabetes but no ophthalmoscopic evidence of retinopathy (no diabetic retinopathy [NDR]), 54 eyes of 30 patients with nonproliferative diabetic retinopathy and without CSME (NPDR without CSME), 21 eyes of 12 patients with proliferative diabetic retinopathy without CSME (PDR without CSME), and 28 eyes of 20 patients with diabetic retinopathy and CSME (DR with CSME).

We considered macular edema to be clinically significant as defined by the Early-Treatment Diabetic Retinopathy Study (ETDRS) protocol<sup>8</sup>—that is, if there was retinal thickening or hard exudate associated with adjacent retinal thickening observed within  $500 \pm 50 \mu\text{m}$  of the center of the foveal avascular zone or a zone or zones of retinal thickening 1 disc area or larger, any part of which was within 1 disc diameter of the center of the macula.

All patients underwent a complete ophthalmic evaluation at the University Clinic of Navarra, including indirect ophthalmoscopy, posterior segment biomicroscopy with slit lamp and a fundus lens, and best corrected Snellen visual acuity. The visual acuities were converted to the logarithm of the minimum angle of resolution (logMAR) scale. Optical coherence tomograms were acquired through a dilated pupil by an experienced examiner. The tenets of the Declaration of Helsinki were followed with regard to study subjects. Informed consent was obtained from each subject before enrollment in the study.

OCT is a high-resolution technique that permits cross-sectional visualization of the retinal structure in which the time delays of light reflected from different depths within the retina are located by means of low-coherence interferometry. A commercially available OCT unit (Zeiss-Humphrey Instruments, San Leandro, CA) was used. The basic principles and optical properties of the OCT system have been de-

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Submitted for publication April 27, 2001; revised December 12, 2001; accepted January 2, 2002.

Commercial relationships policy: N.

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scribed in detail.<sup>2,6,9</sup> Cross-sectional tomographic images integrate 100 axial measurements in 1 second while the probe beam scans across the retina.<sup>4,9</sup> We used the scanning protocol first proposed by Hee et al.<sup>2,6</sup> Scanning was performed through the macula of each eye by the same experienced examiner masked to the conditions of the patients. The scanning and the video image were displayed simultaneously on separate monitors to verify constant fixation and scanning location. Three vertical and horizontal OCT scans were obtained at the center of the macula and analyzed from each studied eye, in a masked fashion.

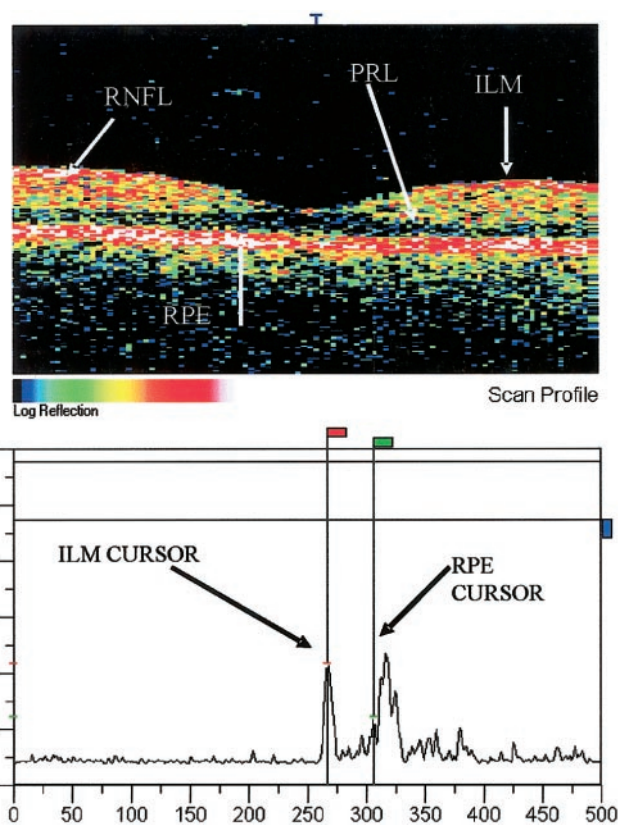
In view of the controversy that using either a manual or an automated measurement technique may generate, we conducted an additional comparison study with 10 representative patients covering the whole spectrum of the percentile distribution of macular thickness values in our series. In these eyes, we used the automated processing software and the manually assisted technique, and we took measurements at foveal, temporal, nasal, superior, and inferior areas. The goal of this pilot study was twofold: to know whether these two methods are interchangeable and to verify the ability of each method to measure the thickened macula.

Analysis of the agreement between the two techniques was performed with the method described by Bland and Altman.<sup>10</sup> The Bland-Altman plots showed in normal patients with lower macular thicknesses that differences between both measurements were smaller than 20  $\mu\text{m}$ , but when we analyzed patients with diabetes who had eyes with higher macular thickness and CSME, differences were in the range of 60  $\mu\text{m}$  at the foveal, superior, and temporal areas and were in the range of 80  $\mu\text{m}$  in the inferior area. These differences are not clinically or statistically acceptable. Moreover, the automated program was unable to detect and measure some foveas in patients with diabetes with more significant macular edema.

For the above-mentioned reasons, measurement of retinal thickness was performed using a manually assisted technique of the program contained within the system software (version A-5; Zeiss-Humphrey). Several scans were made to check that the probe beam was situated in the fovea. The observer visualized the representative A-scan and manually placed measurement cursors: one at the first signal that rose above a noise threshold, which denotes the internal limiting membrane (ILM), and the other one at the signal that identifies the anterior boundary of the red reflective layer corresponding to the retinal pigment epithelium (RPE), which is also the first signal posterior to the low scattering photoreceptor layer (Fig. 1).<sup>3,11,12</sup> The deepest portion of the foveal pit was taken as the center. When macular edema prevented adequate foveal pit location in the scan, the OCT was centered on the patient's fixation. Three representative vertical and horizontal scans for each eye, characterized by strong signal quality and transecting the deepest portion of the foveal pit, were used in the data analysis. Sections were assigned numerical subscripts based on their distances from fixation  $800 \pm 50 \mu\text{m}$  superior and inferior to fixation on the vertical scans and  $800 \pm 50 \mu\text{m}$  temporal and nasal to fixation on the horizontal scans. For each scan, images were optimized to obtain the highest intensity and definition of the inner and outer band by altering the intensity of the incidence light.

Because data for macular thickness were non-normally distributed, they are presented as median (interquartile range [IQR]). Differences in thickness in each of the regions among groups were compared using the Kruskal-Wallis test one-way analysis of variance, as appropriate, and paired comparisons between groups were performed using the Mann-Whitney test with the Finner adjustment (Abramson JH, Gahlinger PM. Computer Program for Epidemiologists [PEPI] <http://sagebrushpress.com/pepibook.html>).<sup>13</sup> We used the Finner adjustment because it is more sensitive for selected comparisons than is the Bonferroni adjustment.<sup>14</sup>

The univariate association between each retina measurement and the presence of CSME were quantified by using odds ratios (OR) and 95% confidence intervals (CR). All determinants with  $P < 0.25$  were then entered together in a multivariate logistic regression model to evaluate which were independently associated with the presence of CSME.<sup>15</sup> The model was reduced by excluding variables with  $P > 0.05$



**FIGURE 1.** *Top:* OCT image through the center of fixation. The ILM, retinal nerve fiber layer (RNFL), photoreceptor layer (PRL), and RPE are imaged. *Bottom:* representative A-scan with two measurement cursors placed at the vitreoretinal surface and the anterior surface of the RPE. The ILM's and RPE's reflectivity measurements are indicated.

to retain a simpler diagnostic model containing only the strongest determinants of the presence of CSME. The reliability goodness-of-fit statistic for significance ( $P > 0.05$ ) of each of the diagnostic models was assessed by using the Hosmer and Lemeshow test.<sup>15</sup> The ability of predictor variables to discriminate between diabetic eyes, with and without edema, was investigated with receiver operating characteristic (ROC) curves, which were plotted with the predictor variables singly.<sup>16</sup> Areas under the ROC curve were calculated and statistical comparisons of the areas under the ROC curves were performed. Calculations were obtained with the expression

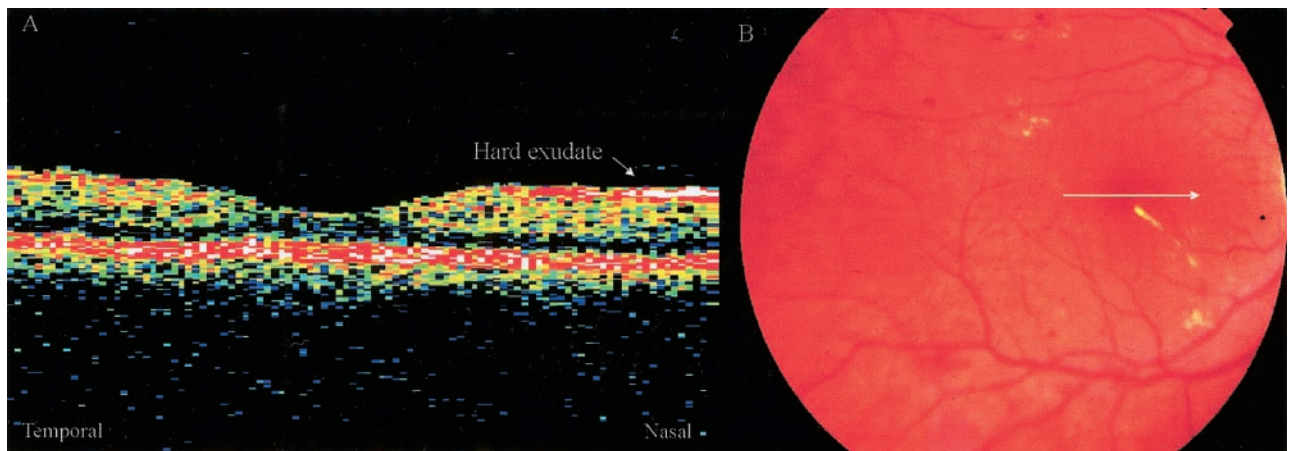
$$Z = (\text{AUC}_1 - \text{AUC}_2) / (\text{SE}_1^2 + \text{SE}_2^2)$$

where  $Z$  represents Fisher's  $Z$  test, AUC is the area under the curve, and SE is the standard error.

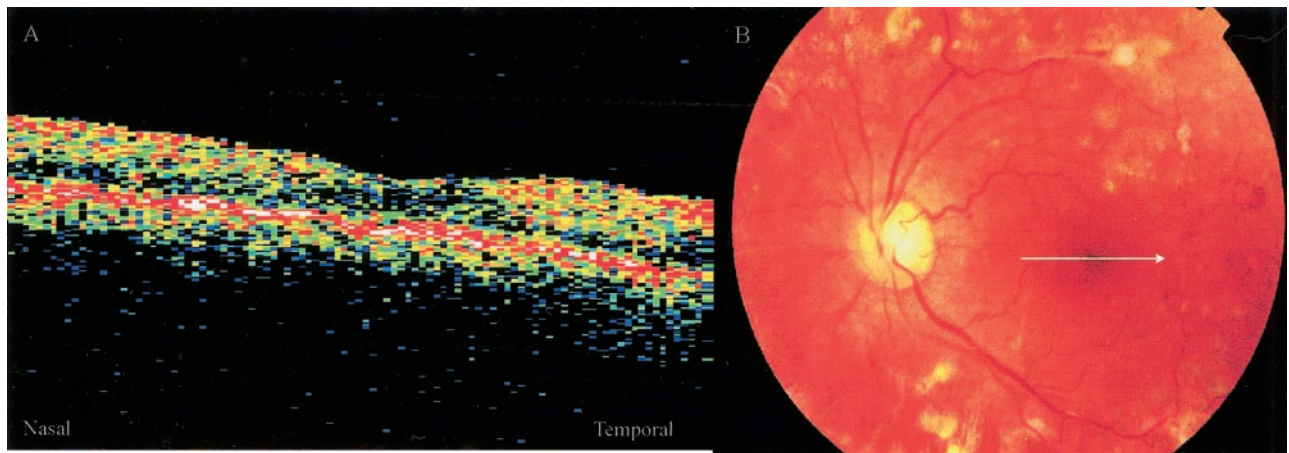
We then selected the best model (i.e., largest area under the ROC curve) and cutoff (best trade off between sensitivity and specificity). Sensitivities, specificities, and diagnostic precisions for predictor variables were calculated. Diagnostic precision is the overall proportion of correct diagnostic assignments to the diabetic eyes, with and without edema.<sup>16</sup> OCT measurements of foveal thickness were compared with best corrected visual acuity on a logarithmic scale using linear regression. Data were entered onto a computerized database, and statistical calculations were performed using a commercially available statistical package (SPSS ver. 9.0 for Windows; SPSS Sciences, Chicago, IL). Two tailed  $P < 0.05$  was considered significant in all statistical analyses.

## RESULTS

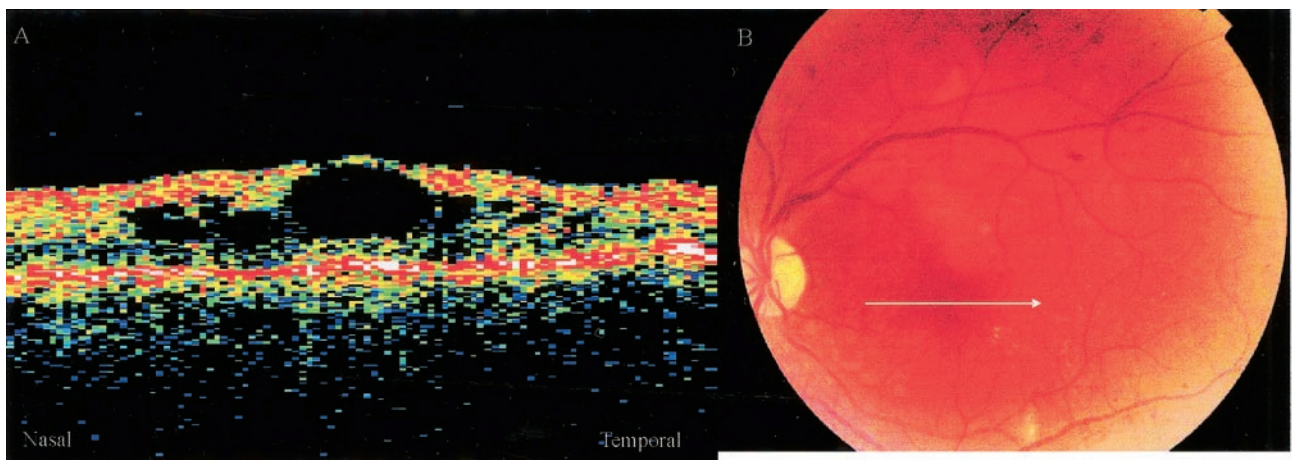
Cross-sectional images were obtained in 44 eyes of 26 healthy volunteers. The mean  $\pm$  SD of foveal thickness was  $145.1 \pm$



**FIGURE 2.** Hard exudates. Optical coherence tomograph (A) and fundus photograph (B) of an eye with NPDR. The fundus photograph showed hard exudates that were observed as spots of high reflectivity with low reflective areas behind them in OCT images (at 1250  $\mu\text{m}$  from the foveal pit). The retinal thickness at the fovea measured 156  $\mu\text{m}$ . *Arrow* represents the OCT section obtained through the fovea and the direction of the scan.



**FIGURE 3.** Optical coherence tomograph (A) and fundus photograph (B) of an eye with proliferative retinopathy without macular edema. OCT showed mild retinal thickness at the fovea. Retinal thickness measured 216  $\mu\text{m}$ . *Arrow* represents the OCT section obtained through the fovea and the direction of the scan.



**FIGURE 4.** Cystoid macular edema. OCT (A) and fundus photograph (B) of an eye with nonproliferative diabetic retinopathy and macular edema. OCT showed round cystoid spaces, mainly in the outer retinal layers that caused the fovea to protrude. The retinal thickness at the fovea measured 410  $\mu\text{m}$ . *Arrow* represents the OCT section obtained through the fovea and the direction of the scan.

TABLE 1. Characteristics of the Study Population

	Age (y)*	Eyes (n)
Control group (n = 26)	52 (21-79)	44
NDR (n = 23)	56 (29-77)	45
NPDR without CSME (n = 30)	60 (21-77)	54
PDR without CSME (n = 12)	56 (32-75)	21
DR with CSME (n = 20)	60 (29-81)	28

\* Mean (range).

15.8 μm and never exceeded 180 μm in any of the normal eyes. As expected, retinal thickness reached a minimum at the fovea, and measured thicker 850 ± 50 μm from the center. The temporal area was the thinnest in relation to nasal, superior, and inferior areas (P = 0.001).

OCT was used to examine 148 eyes of patients with diabetes. Classification was based on slit lamp examination: 45 eyes with no diabetic retinopathy (NDR), 54 with nonproliferative diabetic retinopathy without CSME (NPDR without CSME; Fig. 2), and 21 eyes with proliferative diabetic retinopathy without CSME (PDR without CSME; Fig. 3). Some of these (29 eyes) had been treated with panretinophotocoagulation (PRP) and in some cases focal photocoagulation (9 eyes). Diabetic retinopathy with CSME (DR with CSME) was diagnosed in 28 eyes, of which 22 eyes had been treated with focal and/or PRP (22 eyes; Fig. 4). The characteristics of the study population are detailed in Table 1. The mean ± SD, median, and IQRs of retinal thickness by area in these eyes are reported in Table 2, Figure 5.

The SD in thickness in each area was greater in eyes with nonproliferative (34 eyes) and proliferative diabetic retinopathy (37 eyes) than in normal eyes (17 eyes; P = 0.001). The largest differences were found in eyes with CSME (Table 2, Fig. 1).

There were statistically significant differences in each of the areas when all groups were compared (Kruskal-Wallis test; P = 0.001). We found statistically significant differences between the control group and all the other diabetic groups in the foveal center (Mann-Whitney test with Finner adjustment), but not in the superior, inferior, nasal, and temporal areas (Table 3). Statistically significant differences were found only between control subjects and patients with diabetes who had proliferative diabetic retinopathy without CSME in the temporal area (P = 0.011). There were statistically significant differences between control subjects and patients with diabetes with CSME in each one of the areas.

We did not find significant differences in average thickness in any area between eyes with no diabetic retinopathy (NDR) and eyes with nonproliferative (NPDR without CSME) or pro-

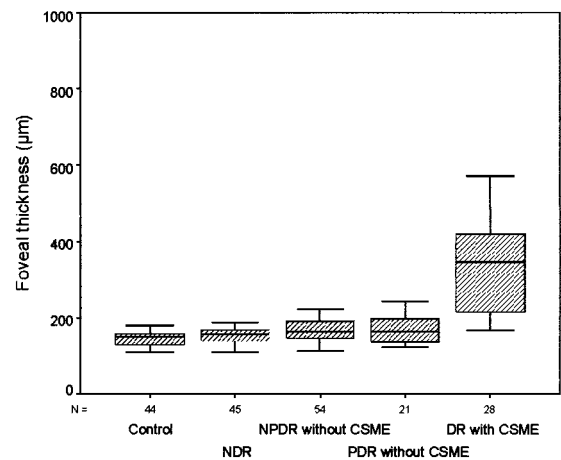


FIGURE 5. Box plot of OCT measurement of central macular thickness in patients without diabetes (control group) and patients with diabetes with different levels of retinopathy. NDR, patients with diabetes with no diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; DR, diabetic retinopathy; CSME, clinically significant macular edema. In each box, the longitudinal bar represents the median; box height represents the IQR (25%–75% percentiles).

liferative retinopathy without CSME (PDR without CSME). Neither were there significant differences in thickness in any area between eyes with nonproliferative (NPDR without CSME) and eyes with proliferative retinopathy without CSME (PDR without CSME). As expected, the macular thickness was greater in all areas in eyes with CSME than in all the other diabetic groups and the control group. These differences were statistically significant (Mann-Whitney test, P = 0.001).

Table 4 lists the results of logistic univariate and multivariate regression. In univariate analysis, each one of the measures was a statistically significant predictor of macular edema. We wanted to examine whether a combination of some of these variables would improve the predictive ability of macular thickness. The result of multiple logistic regression was that foveal thickness was the only independent predictor.

Table 5 shows the area under the ROC curves and SE for each one of the five macular measures. There were no statistically significant differences among the areas under the ROC curves for the superior and inferior macular location compared with the foveal one. Foveal thickness had the ROC curve with the highest diagnostic value, and it represents the best discriminator between diabetic eyes with and without edema (Fig. 6). Diagnostic precision, sensitivity, and specificity with 95% CI for a cutoff point of 180 μm were 68% (56%–80%), 93%

TABLE 2. Macular Thickness in Healthy Control Eyes and Diabetic Eyes

	Foveal	Superior	Inferior	Temporal	Nasal
Control (n = 44)	145 ± 16*	267 ± 18*	264 ± 16*	242 ± 18*	258 ± 20*
NDR (n = 45)	148 ± 25†	268 ± 25†	263 ± 21†	241 ± 30†	255 ± 27†
NPDR without CSME (n = 54)	156 ± 28*	265 ± 18*	265 ± 17*	246 ± 18*	258 ± 19*
PDR without CSME (n = 21)	155 ± 25†	268 ± 24†	263 ± 29†	249 ± 21†	263 ± 19†
DR with CSME (n = 28)	169 ± 33*	267 ± 27*	263 ± 26*	251 ± 29*	264 ± 26*
	163 ± 46†	269 ± 29†	263 ± 27†	251 ± 37†	265 ± 33†
	170 ± 37*	271 ± 32*	269 ± 28*	264 ± 34*	261 ± 26*
	163 ± 668†	269 ± 36†	270 ± 26†	258 ± 41†	259 ± 29†
	371 ± 180*	379 ± 141*	357 ± 108*	367 ± 133*	380 ± 1413*
	346 ± 203†	311 ± 149†	309 ± 119†	329 ± 1177†	318 ± 199†

\* Data are mean micrometers ± SD.

† Data are median micrometers ± IQR (interquartile range).

TABLE 3. Probabilities of Group Differences in Foveal Thickness

Group	Control	NDR	NPDR without CSME	PDR without CSME	DR with CSME
Control	—	0.043*	0.001*†	0.018*	0.001*†
NDR	—	—	0.061	0.229	0.001*†
NPDR without CSME	—	—	—	0.925	0.001*†
PDR without CSME	—	—	—	—	0.001*†

Probabilities are by Mann-Whitney test, with the Finner adjustment.

\* Statistically significant at  $P < 0.05$ .

† Statistically significant at  $P < 0.001$ .

(78%–99%) and 75% (67%–82%), respectively. The area under the ROC curve was 0.94 ( $P = 0.001$ ).

We considered that an eye had suspected edema detected by OCT when foveal thickness was greater than the cutoff point. Shifting this cutoff point just 200  $\mu\text{m}$  in the direction of edema increases the specificity to 85%, but reduces the sensitivity to 86%, illustrating the trade-off between sensitivity and specificity.

The maximum thickness observed in normal eyes was 180  $\mu\text{m}$ . OCT evaluation agreed with slit lamp examination results in diabetic eyes with CSME (foveal thickness between 167–838  $\mu\text{m}$ ; mean, 371.3). Therefore, only two diabetic eyes with CSME by slit lamp had foveal thicknesses less than 180  $\mu\text{m}$  (167–175  $\mu\text{m}$ ). These eyes had one disc area of thickening within one disc diameter from the center of the fovea, but no thickening within 500  $\mu\text{m}$  of the center.

There were 13% (six eyes) with no diabetic retinopathy in which foveal thickness was superior to 180  $\mu\text{m}$ , between 185 and 217  $\mu\text{m}$ . In diabetic eyes with retinopathy without CSME by slit lamp examination, the foveal thickness determined by OCT was superior to 180  $\mu\text{m}$  in 32% (17 eyes) and in 33.3% (7 eyes) of eyes with nonproliferative and proliferative retinopathy (NPDR and PDR without CSME), respectively.

There was no significant correlation between age and foveal thickness among all the eyes or in each one of the groups. OCT measurements at the foveal center were plotted against visual acuities in normal and diabetic eyes. The foveal thickness, averaged over eyes with the same visual acuity, correlated with best corrected visual acuity on a logMAR scale (Spearman  $\rho = 0.94$ ,  $P = 0.001$ ). Linear regression analysis showed that changes in macular thickening at the central fovea can explain 65% of the variations in visual acuity reported on a logMAR scale (adjusted  $R^2 = 0.65$ ; Fig. 7). For comparison, the correlation was also performed with each data point considered separately, and then a Spearman  $\rho = 0.4$  ( $P = 0.001$ ) was obtained.

## DISCUSSION

Although fluorescein angiography is highly sensitive for the qualitative detection of fluid leakage, which causes macular

edema, measurements of retinal thickening may correlate better with areas of retinal dysfunction than does the amount of fluorescein leakage.<sup>1</sup> OCT enables the clinician to show accurately subclinical retinal changes in the absence of CSME or in the absence of any signs of diabetic retinopathy by detectable fluorescein leakage.<sup>2</sup> In this study, we found a statistically significant difference in thickness at the foveal center in diabetic eyes, even with no ophthalmoscopic evidence of retinopathy compared with normal eyes. In a previous study,<sup>17</sup> we reported a significant increase in the foveal thickness in patients with diabetes who had undergone PRP even a year before. Moreover, these eyes had not shown CSME.

In the present study, the scanning protocol is identical with the one in the cited previous studies,<sup>2,3,6,9</sup> but a different measurement technique was used. In contrast to using a computed algorithm to construct a retinal thickness map, we measured retinal thickness by looking at the A-scans as well as the two-dimensional cross-sectional images. We took manual measurement on nonaligned data. We conducted an additional comparison study of 10 representative patients, in whom we used automated processing software and a manually assisted technique. The Bland-Altman plots showed in normal eyes with lower macular thicknesses that differences between both measurements were smaller than 20  $\mu\text{m}$ ; but when we analyzed eyes in patients with diabetes with higher macular thicknesses and with CSME, differences were in the range of more than 60  $\mu\text{m}$ , which is not clinically or statistically acceptable. Moreover, the automated program was unable to detect and measure some foveas in patients with diabetes with more significant macular edema. For these reasons, we performed manually assisted measurements of the scans using the A5 version.

Retinal thickness was measured in the center of the fovea and at two locations on either side outside the foveal rim in three horizontal and vertical scans. This procedure ignores a large part of the information obtained by each scan, which is a potential shortcoming, but because measurements are taken from actual raw data and checked on single A-scans, potential errors are widely excluded. Other investigators have reported reproducible results, using manually assisted computer software and decreased measurement reproducibility using auto-

TABLE 4. Univariate and Multivariate Logistic Regression for Variables of Potential Prediction Value

Thickness	Univariate Model			Multivariate (Adjusted)		
	e <sup>b</sup> (OR)	95% CI	P	e <sup>b</sup> (OR)	95% CI	P
Foveal	1.037	(1.02–1.05)	0.001*†	1.037	(1.02–1.05)	0.001*†
Superior	1.041	(1.02–1.06)	0.001*			0.24
Inferior	1.047	(1.03–1.07)	0.001*†			0.22
Temporal	1.033	(1.02–1.05)	0.001*†			0.63
Nasal	1.037	(1.02–1.06)	0.001*†			0.84

Log likelihood test, univariate and multivariate model at \* $P < 0.005$  and † $P < 0.001$ .

**TABLE 5.** Point Estimates and Standard Errors for Area under the ROC Curves

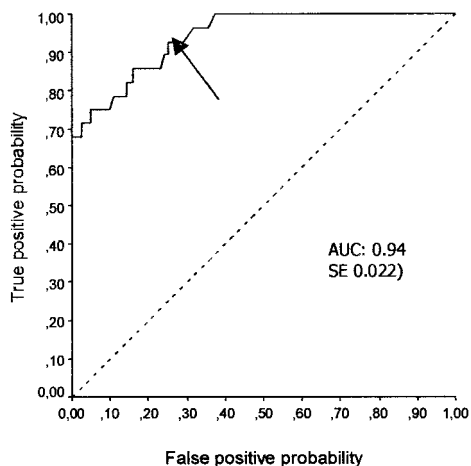
Thickness	AUC	SE	95% CI for AUC	P*
Foveal	0.94	0.022	0.90, 0.98	—
Superior	0.84	0.051	0.74, 0.94	0.07
Inferior	0.86	0.044	0.78, 0.95	0.11
Temporal	0.82	0.052	0.71, 0.92	0.03
Nasal	0.81	0.055	0.71, 0.92	0.03

\* Z double-tailed, statistically significant at  $P < 0.05$ . Compared with AUC at the foveal measures.

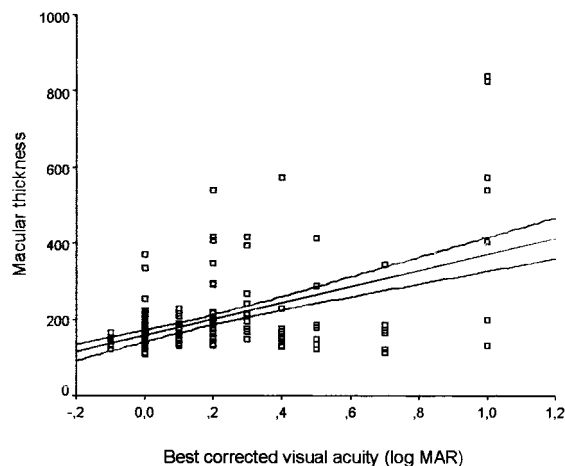
mated software.<sup>10</sup> Schaudig et al.<sup>18</sup> reported falsely aligned images when using the automated computer program, with the impairment caused by reflection from the RPE.

As expected, in eyes without CSME, retinal thickness reached a minimum in the fovea and was largest 850  $\mu\text{m}$  away from the center of the fovea. The temporal area was thinnest. The superior and inferior areas were thicker because of the superior and inferior arcuate bundling of nerve fibers. Our measurement results were slightly lower than those previously reported,<sup>2</sup> which may be because of the measurement procedure or differences characteristic of the study group. More important, however, the same distribution was present in patients with diabetes.

In the current investigation, eyes with NPDR or PDR had greater macular thickness in all regions than that in normal eyes. However, differences were not statistically significant in any of the areas. There were no significant differences in average thickness in any area between NPDR and PDR without CSME. Other investigators have reported similar results, finding differences in central foveal thickness between normal eyes and eyes with diabetic retinopathy and no significant differences in average thickness between eyes with nonproliferative and proliferative diabetic retinopathy.<sup>2</sup> However, they did not compare diabetic eyes with no diabetic retinopathy (NDR) with normal eyes in healthy control subjects. Schaudig et al.<sup>18</sup> reported significant differences between eyes in patients with diabetes, with and without diabetic retinopathy, but they found significant differences only in the superior quadrant between diabetic eyes with no diabetic retinopathy and healthy control eyes. They found differences between control eyes and diabetic eyes with retinopathy in the fovea and in the perimacular ring.<sup>18</sup>



**FIGURE 6.** ROC curve of foveal thickness in diabetic eyes. Arrow: cutoff point on the ROC curve for at least 180  $\mu\text{m}$  of thickness where the sensitivity is 93% and 1 - specificity is 25%.



**FIGURE 7.** Central macular thickness versus visual acuity in logMAR scale in all the patients. Linear regression shows a correlation between mean macular thickening in the central fovea and visual acuity.

The ROC curve can be used to test the accuracy of diagnoses that are based on continuous parameters, and the area under the ROC curve measures the goodness of the model. AUCs between 0.50 and 0.70 are considered to represent a low diagnostic accuracy, whereas AUCs of more than 0.90 suggest a high accuracy.<sup>16</sup> Foveal thickness obtained with OCT provided sensitivity of 93% and specificity of 75% for a cutoff point of more than 180  $\mu\text{m}$  of foveal thickness and produced an ROC curve with an AUC of 0.94. Adding superior, inferior, temporal, and nasal thickness did not improve the foveal prediction. Hee et al.<sup>2</sup> found similar results with OCT. They reported 216  $\mu\text{m}$  as the maximum value observed in normal eyes, and they considered that the cutoff point that discriminated between eyes with and without macular edema.<sup>2</sup> In another study, Hee et al.<sup>6</sup> considered central foveal thickness to be abnormal in an OCT examination when it was greater than 185  $\mu\text{m}$ . In 17 of 75 diabetic eyes in their study, the fovea appeared abnormally thickened on OCT, but macular thickening was not observed on biomicroscopy.<sup>6</sup>

In our study, retinal thickening or hard exudate observed in slit lamp biomicroscopy analysis almost always correlated with increased thickness on OCT, but there were some occasions when OCT detected thickening in the absence of any abnormality detected by slit lamp examination. Edema was difficult to detect clinically when there was no hard exudate in the central macula and diffuse rather than focal macular thickening was present.

Both measurements of foveal and macular thickness with OCT may appear to be more sensitive than slit lamp examination for evaluating clinically significant macular edema. Criteria for treatment depend on the presence of retinal thickening and its distance from the center of the fovea, which is clinically assessed by contact lens biomicroscopy or stereophotography. The beneficial effects of photocoagulation for diabetic macular edema demonstrated by the ETDRS suggest that all eyes with CSME should be considered for focal photocoagulation.<sup>19</sup>

Sinclair et al.<sup>20</sup> studied the effects of two methods of grid laser photocoagulation for diabetic macular edema on high-contrast target discrimination in the central visual field. They compared ETDRS-level treatment with threshold-level treatment. Grid laser using threshold-level burns appeared to produce some improvement in thresholded high-contrast vision. They recommended using screening methods other than biomicroscopic perception of retinal swelling to define earlier opportunities for intervention in the diabetic maculopathic process and using threshold or subthreshold methods of laser

grid photocoagulation for treating leakage and/or edema. In this respect, our study suggests an important role for OCT in screening retinal thickening in diabetic eyes. Beyond that, Koozekanani et al.<sup>4</sup> reported that macular thickness measurements were repeatable within a session and over different independent sessions. Intersession repeatability and the high resolution of OCT provide therefore a useful tool for the early diagnosis, analysis, and monitoring of retinopathy in these patients.

The retinal thickness at the foveal center correlated with best corrected visual acuity in normal and diabetic eyes (Spearman  $\rho = 0.94$ ). A simple linear regression provided a good fit (adjusted  $R^2 = 0.65$ ) between foveal thickness averaged over eyes with the same visual acuity and visual acuity as reported on a logMAR scale. Hee et al.<sup>6</sup> demonstrated that the variability in thickness between eyes of different visual acuities was significantly greater than the variability in eyes that had the same visual acuity. In another study, Hee et al.<sup>2</sup> found a correlation between paired eyes with the same visual acuity ( $r^2 = 0.79$ )<sup>2</sup> and found an adjusted correlation (adjusted  $R^2 = 0.76$ ) in a similar study.<sup>6</sup> They correlated measurements of macular thickness averaged over eyes with the same visual acuity in patients with diabetes, both with and without retinopathy. Otani et al.<sup>7</sup> reported a correlation between retinal thickness and visual acuity in eyes with diabetic macular edema, with or without cystoid macular edema (correlation coefficients  $r = -0.64$  and  $r = -0.61$ , respectively).<sup>7</sup>

In conclusion, we found that OCT was a useful technique for quantitative measurement of retinal thickness in patients with diabetes. Our study fully supports previous suggestions that early changes in retinal thickness can be detected by OCT despite normal findings in slit lamp biomicroscopy. In addition, our results suggest that abnormal macular thickening may be suspected if the foveal thickness measures more than 180  $\mu\text{m}$  on OCT, which may indicate that the patient is a candidate for more frequent and detailed follow-up. Future long-term studies are needed to investigate whether patients with areas of sub-clinical retinal thickening in specific regions are at higher risk for development of retinopathy than those with normal OCT findings.

## References

- Nussenblatt RB, Kaufman SC, Palestine AG, Davis MD, Ferris FL. Macular thickening and visual acuity. *Ophthalmology*. 1987;94:1134-1139.
- Hee MR, Puliafito CA, Duker JS, et al. Topography of diabetic macular edema with optical coherence tomography. *Ophthalmology*. 1998;105:360-370.
- Chauhan DS, Marshall J. The interpretation of optical coherence tomography images of the retina. *Invest Ophthalmol Vis Sci*. 1999;40:2332-2342.
- Koozekanani D, Roberts C, Katz SE, Herderick ED. Intersession repeatability of macular thickness measurements with the Humphrey 2000 OCT. *Invest Ophthalmol Vis Sci*. 2000;41:1486-1491.
- Munuera JM, García-Layana A, Maldonado MJ, Aliseda D, Moreno-Montañés J. Optical coherence tomography in successful surgery of vitreomacular traction syndrome. *Arch Ophthalmol*. 1998;116:1388-1389.
- Hee MR, Puliafito CA, Wong C, et al. Quantitative assessment of macular edema with optical coherence tomography. *Arch Ophthalmol*. 1995;113:1019-1029.
- Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. *Am J Ophthalmol*. 1999;127:688-693.
- Early Treatment Diabetic Retinopathy Study Research Group. ETDRS report number 7: Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. *Ophthalmology*. 1991;98:741-756.
- Puliafito CA, Hee MR, Lin CP, et al. Imaging of macular diseases with optical coherence tomography. *Ophthalmology*. 1995;102:217-229.
- Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1(8476):307-310.
- Baumann M, Gentile R, Liebman J, Ritch R. Reproducibility of retinal thickness measurements in normal eyes using optical coherence tomography. *Ophthalmic Surg Lasers*. 1998;29:280-285.
- Massin P, Viscaut E, Haouchine B, Erginay A, Paques M, Gaudric A. Reproducibility of retinal mapping using optical coherence tomography. *Arch Ophthalmol*. 2001;119:1135-1142.
- Finner H. On a monotonicity problem in step-down multiple test procedures. *J Am Stat Assoc*. 1993;88:920-923.
- Perneger TV. What's wrong with Bonferroni adjustments. *BMJ*. 1998;316:1236-1238.
- Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York: Wiley & Sons, Inc.; 1989.
- Campbell G. General methodology. I: advances in statistical methodology for the evaluation of diagnostic and laboratory tests. *Stat Med*. 1994;12:499-508.
- García Layana A, Munuera Gil JM, Aliseda Perez de Madrid D, Maldonado M, Moreno Montañés J. Evaluación clínica del grosor macular en pacientes diabéticos con el tomógrafo óptico de coherencia (OCT). *Arch Soc Esp Ophthalmol*. 1999;74:455-460.
- Schaudig UH, Glaefke C, Scholz F, Richard G. Optical coherence tomography for retinal thickness measurement in diabetic patients without clinically significant macular edema. *Ophthalmic Surg Lasers*. 2000;31:182-186.
- Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. *Ophthalmology*. 1987;94:761-774.
- Sinclair SH, Alaniz R, Presti P. Laser treatment of diabetic macular edema: comparison of ETDRS-level treatment with threshold-level treatment by using high-contrast discriminant central visual field testing. *Semin Ophthalmol*. 1999;14:4:214-222.