Associations between Local Retinal Thickness and Function in Early Diabetes

Kavita P. Dhamdhere,[1] *Marcus A. Bearse Jr,*[1] *Wendy Harrison,*[2] *Shirin Barez,*[1] *Marilyn E. Schneck,*[1] *and Anthony J. Adams*[1]

Purpose. To investigate, using multifocal electroretinography (mfERG) and optical coherence tomography (OCT), potential spatial associations between local neuroretinal function and local retinal thickness in patients with diabetes.

Methods. Forty-five patients without retinopathy (10 with Type 1 diabetes; 35 with Type 2 diabetes; 49.9 ± 10.9 years old) and 29 age-similar controls (47.0 ± 12.8 years old) were studied. N1-P1 amplitude (AMP) and P1 implicit time (IT) of mfERGs within the central approximately 20° diameter were compared to spatially corresponding full retinal thickness measurements acquired by Stratus OCT3. AMP and IT were converted to *Z*-scores and retinal thickness was converted to percentile values. Local abnormalities were defined as $P \leq 0.023$. Subject group differences were examined using *t*-tests. Retinal thickness was compared to mfERGs to determine spatial associations.

Results. Average retinal thicknesses were similar for all subject groups. The Type 1 group and controls had similar IT and AMP. The Type 2 group had reduced AMP and longer IT than the controls and the Type 1 group ($P < 0.001$). Local associations between retinal thickness and mfERGs were not significant within any subject group or individuals, even for abnormal locations ($P \geq 0.09$). Abnormalities in most measures were greater in the patient groups than in the controls ($P < 0.008$) except retinal thinning in the Type 1 group.

Conclusions. Local neuroretinal function is not associated with full retinal thickness measured locally in patients with diabetes and no retinopathy, even in abnormal locations. Full retinal thickness measured locally by OCT is not a surrogate for mfERGs in early diabetes. Neuroretinal function in Type 2 diabetes is worse than in Type 1 diabetes and controls. Fewer subjects in the Type 1 group could be a potential limitation. (*Invest Ophthalmol Vis Sci.* 2012;53:6122–6128) DOI: 10.1167/iovs.12-10293

Diabetes affects the eye in many ways, and diabetic retinopathy is the most common and serious ocular complication.[1] As the worldwide prevalence of diabetes continues to increase, diabetic retinopathy remains a leading cause of vision loss and blindness in many countries.[2] Of the 346 million people worldwide with diabetes, approximately a third have signs of diabetic retinopathy, and a third of these might develop vision-threatening retinopathies. In the United States alone, 24,000 new cases of preventable blindness due to diabetes occur every year.[3–5]

Contemporary treatment modalities for diabetic retinopathy are aimed at preserving vision once diabetic retinopathy is clinically evident, as opposed to preventing diabetic retinopathy. Laser photocoagulation and intraocular injections of steroids and anti-VEGFs remain the mainstay of ophthalmic therapy for vision-threatening retinopathies. Despite the often remarkable efficacy of these therapies in slowing further vision loss, they are either associated with significant ocular side effects or they are invasive and destructive. Additionally, even with adequate therapy, reversal of vision loss and prevention of further retinal damage is uncommon.[6] Therefore, researchers continue to search for new and increasingly effective therapeutic strategies, aiming to improve and save vision at an earlier or even subclinical stage of the disease.

The pathophysiology of diabetic retinopathy has two important components: functional and structural. However, the current definitions of retinopathy, its treatment protocol, and the end points for clinical trials focus on either the structural aspects of the disease or visual acuity. There is a growing body of clinical and experimental evidence pointing to the presence of neuronal and glial abnormalities in early stages of diabetes, before vascular lesions are clinically apparent, resulting in dysfunction and even degeneration of these retinal cells.[7–11] By the time neuronal injury is reflected in routine clinical visual acuity testing, retinopathy has usually progressed to advanced stages. Unfortunately, it is unclear at this time how changes in neuronal function or vision function are related to structural changes in retinopathy, such as retinal thickness changes.

Our previous work along with other studies have shown that the mfERG is sensitive and specific to the neurodegenerative or functional changes that precede clinical signs of diabetic retinopathy.[12–17] Multifocal electroretinography (mfERG) implicit time (IT) delays are locally predictive of future nonproliferative retinopathy.[18–22]

Optical coherence tomography (OCT) is a sensitive and reliable technique that enables us to acquire high-resolution, in vivo images of the central retina. It has the potential to enhance early diagnosis and objective evaluation of structural damage in retinopathy. OCT noninvasively generates tomographic images that are similar to tissue sections and permits visualization of morphological changes in the retina due to diabetes that had, previously, been possible only with histopathology.[23,24] It has recently become the state-of-art technique to evaluate retinal thickness and changes in diabetes and other diseases.

From the [1]University of California Berkeley, Berkeley, California; and [2]Midwestern University, Arizona College of Optometry, Glendale, Arizona.

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Corresponding author: Kavita P. Dhamdhere, University of California Berkeley, School of Optometry, Rm 411 Minor Hall, Berkeley, CA 94720-2020; drkpd@berkeley.edu.

Table 1. Subject Demographics

Subject Group	Sex		Mean Age, y	Mean Diabetes Mellitus Duration, y	Mean HbA1c %
	Males	Females			
Control	13	16	47.0 ± 12.8	NA	NA
Type 1	3	7	46.6 ± 13.2	17.2 ± 13.5	8.2 ± 1.4
Type 2	17	18	53.2 ± 8.7	7.81 ± 4.8	8.6 ± 1.6

Although both mfERG and OCT techniques are effective and sensitive in detecting "subclinical" functional and structural changes in the retina due to diabetes, their relationships, especially at preretinopathy stages of the disease, have not been explored. A better understanding of their possible relationships is important for advancing the development of better diagnostics, preventatives, and therapeutic interventions at early stages of diabetic retinopathy.

In this study, we compare these techniques: mfERG to assess the functional neural health of the retina, and OCT to assess full retinal thickness. One of our motivations is to determine whether mfERG and OCT can serve as surrogate measures for each other of early retinal effects of diabetes. We investigate potential local relationships between these two measures and examine whether the type of diabetes influences any relationship. Specifically, we test whether mfERG and full retinal thickness abnormalities show spatial agreement with each other. We analyze local retinal thickness with novel methodology developed in one of our previous studies that allows us to compare retinal structure and function at 37 locations in the central 20° diameter.[25]

Methods

Subjects

This cross-sectional observational study involved 74 participants made up of 29 nondiabetic healthy controls (Control group; 13 males and 16 females), and 45 patients (20 males and 25 females) with clinical diagnosis of diabetes and no diabetic or other form of retinal or ocular pathology (Table 1). Ten patients with Type 1 diabetes (Type 1 group) and 35 patients with Type 2 diabetes (Type 2 group) were examined. All subjects were between 25 and 65 years of age with a mean age of 47.0 ± 12.8, 46.6 ± 13.2, and 53.2 ± 8.7 years for the Control, Type 1, and Type 2 groups, respectively. Subjects had best-corrected visual acuity of 20/20 or better, clear ocular media, and refractive errors within the range of ±6 D. The purpose of the study and potential risks were explained to the subjects before obtaining their informed written consent to participate in the study. The protocol follows the tenets of the Declaration of Helsinki and was approved by the University of California Committee for Protection of Human Subjects.

mfERG Recordings

mfERGs were recorded according to International Society for Clinical Electrophysiology of Vision guidelines[26] using a visual evoked response imaging system (VERIS Science 4.3; EDI, San Mateo, CA) and dilated pupils (6–8-mm diameter). Dilation was achieved using 1.0% tropicamide and 2.5% phenylephrine hydrochloride. The stimulus array consisted of 103 hexagonal elements that were displayed at a 75-Hz frame rate on a monochrome cathode ray tube. The sizes of the hexagons were scaled with eccentricity to account for cone density (Fig. 1). The luminance of each hexagon was independently alternated between black (<2 cd/m^2) and white (200 cd/m^2) according to a pseudorandom binary m-sequence. The stimulus array subtended approximately 45° on the retina, centered on the fovea. Each recording was made up of 16 segments of approximately 25 seconds each. Retinal activity was recorded with a Burian-Allen bipolar contact lens electrode (Hansen Ophthalmic,

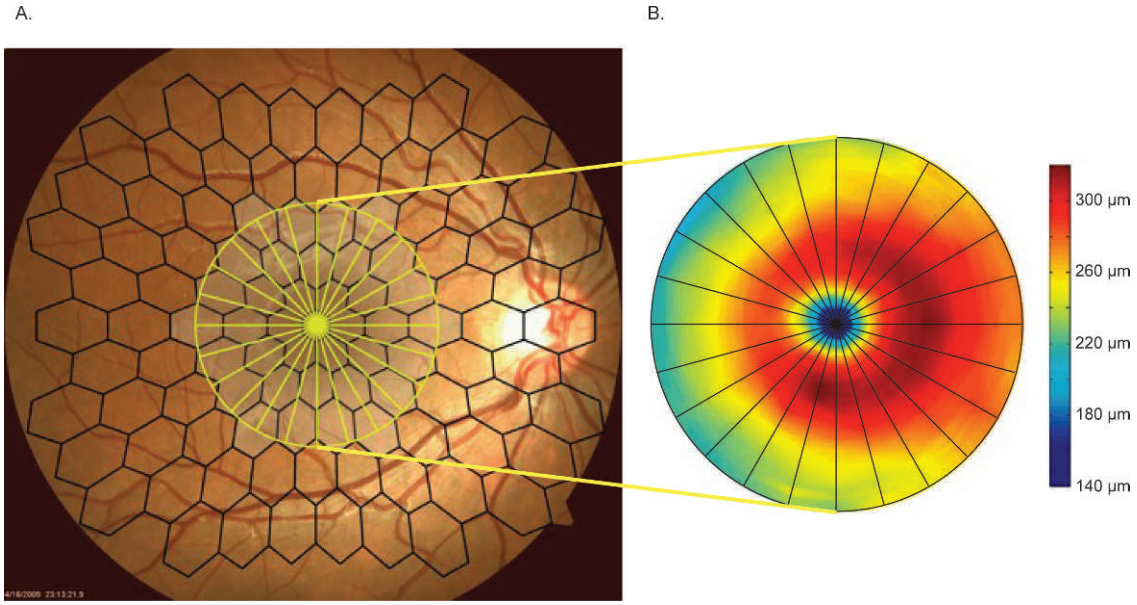

Figure 1. The central 37 mfERG stimulus hexagons corresponding to the central 20° of OCT radial scans (**A**). Pseudo-color map of retinal thickness generated by interpolating the points between each scan using triangle-based linear interpolation (**B**).

Solon City, IA) filled with 1% carboxymethylcellulose sodium (Refresh Celluvisc; Allergan Inc., Irvine, CA), which was placed on the anesthetized (0.5% proparacaine) cornea. A ground electrode was clipped to the right earlobe and electrode impedance was kept below 5 kΩ. Fixation was controlled by a fixation target "X" in the center of the stimulus and by monitoring displacements of the lens and eye movements using an in-line infrared camera. Contaminated recording segments were discarded and rerecorded. The signals were amplified 100,000 times, filtered 10 to 100 Hz and sampled at 1200 Hz. The fellow eye was covered with an eye patch.

mfERG Analysis

Each of the 103 first-order local mfERG responses was analyzed with one iteration of artifact removal and spatial averaging with one-sixth of the surrounding responses. The responses were measured using the template scaling method described in detail by Hood and Li.[27] Each of the local responses was compared to a waveform template constructed by averaging the corresponding local waveforms of the control subjects (right eye response arrays were converted to left eye orientation). Each template was independently scaled in amplitude and time dimensions so that the subject's local waveform and local template had minimal least-squares difference. Statfit, a measure of goodness of fit, was generated and responses with statfits greater than or equal to 0.8 were not included in the analysis.[20] The first negative peak (N1) and the first positive peak (P1) of the local mfERG response waveforms were identified and the N1- P1 amplitudes (AMPs) and P1 ITs were measured. The P1 ITs were measured from the onset of the local stimulus flash to the P1 peak. The Control group's mean and SD for each local mfERG measure were used to compute *Z*-scores for the patients' corresponding mfERG responses at each location.

Retinal Thickness Measurements

The Stratus OCT3 (Zeiss Meditec, Dublin, CA) was used to measure retinal thickness. Twelve radial B-scans (6-mm-long central 20°, 512 A-scans, 10-μm axial and 11-μm longitudinal resolution) centered at the foveola were acquired from the eyes fixating a green target (Fig. 1). Scans contaminated by fixation loss, blink, or eye movement were discarded and recaptured. Only scans with a signal strength of 6 or more of a possible 10 were included for analysis (mean signal strength was 7.1 ± 1.3). The scan acquisition time ranged from 1 to 2 seconds. Retinal thickness was calculated as the distance between the first signal from the vitreoretinal interface and the signal from the outer border of the retinal pigment epithelium.

Retinal Thickness Analysis

Retinal thickness was analyzed as previously described.[19] Thickness measurements were exported from the OCT instrument and processed in Matlab (MathWorks, Natick, MA). A continuous 360° pseudocolor retinal thickness map was generated by interpolating the points between each scanned point using triangle-based linear interpolation and fitting this to a 1024 × 1024 grid. The thickness map was then divided into 37 hexagons such that they correspond to the central 37 hexagons in the mfERG stimulus (Fig. 1). To correct for the ambiguous assignment of thickness values falling on a hexagonal boundary, a uniform exclusion zone of six samples wide was created at each hexagonal border. The number of A-scans within each hexagon ranged from 63 at a peripheral location to 707 at the center hexagon. The total number of data points within a hexagon, including interpolated points, ranged from 5020 to 17,637.[19] An average thickness of each hexagon was computed. Retinal thickness values were converted to percentile ranks based on the retinal thickness values from controls (which were not normally distributed).

Statistical Analysis

We used *t*-tests to examine whether the subject groups differed significantly from each other in any of the measurements (IT, AMP, and full retinal thickness). An abnormal mfERG response for each hexagon was defined as a *Z*-score value greater than or equal to 2 ($P < 0.023$) for IT, and a *Z*-score less than or equal to −2 ($P < 0.023$) for AMP. Retinal locations with thickness values beyond or equal to the 97.7th percentile of the Control group were defined as abnormally thick and values below or equal to the 2.3rd percentile of the Control group were defined as abnormally thin ($P < 0.023$). Eyes having four or more abnormal locations ($P \leq 0.01$) were defined as abnormal eyes for each particular measure (e.g., four abnormally thin retinal locations made the eye abnormally thin). Proportions tests were performed to examine whether the subject groups differed in their frequencies of abnormalities.

One eye of each subject was included in the analysis, the eye with both a better statfit value (defined in mfERG methods section above) and a better OCT scan quality (minimum signal strength of 6). If both eyes of a subject had equal statfit and scan strength values, the left eye was included. Spatial associations between the mfERG and retinal thickness were examined locally within the subject groups and also within individual subjects. A 2 × 2-cell Fisher exact test for significance was performed to identify any association between local retinal thickness and either IT or AMP. Linear regression analysis was not used because a linear relationship was not assumed.

In a second analysis, abnormal full retinal thinness or thickness was examined locally to investigate any spatial agreement with either abnormally delayed IT or abnormally diminished AMP. A 2 × 2-cell Fisher exact test for significance was performed to identify any spatial agreement between the abnormalities.

Results

To preview the main findings of this study, retinal function was worse in the Type 2 group than in the Type 1 group, and the two groups differed in retinal thickness abnormalities. There were no local associations between full retinal thickness measured with OCT and retinal neural function measured with mfERG in the adult patients with diabetes who had no diabetic retinopathy. There was also no spatial correspondence of functional and anatomical abnormalities. These results were obtained in subject group comparisons and also within individual eyes.

Subject Group Differences

Potential differences among the three subject groups were examined. The Type 1 group was significantly younger ($P < 0.001$) with almost double the duration of diabetes than the Type 2 group. The Type 1 and Type 2 subject groups were significantly different ($P < 0.001$) from each other in both IT and AMP measures (Fig. 2), with the Type 2 group having more delayed IT and reduced AMP. The Type 2 group had significantly delayed IT and diminished AMP ($P < 0.001$) compared with the controls, but subjects with Type 1 diabetes and controls had similar IT and AMP. Mean retinal thickness was similar in all three subject groups.

Figure 3 shows the percentages of abnormalities for the functional and anatomical measures. Abnormalities are defined as explained in the method section. We found only one eye with mixed thickness abnormalities (two abnormally thin and two abnormally thick hexagons in same eye). The frequency (percentage) of mfERG IT and AMP abnormalities in the Type 2 group was greater than that in the Control and Type 1 groups (Fig. 3; $P < 0.001$ for both). The Type 1 group had a larger percentage of AMP abnormalities

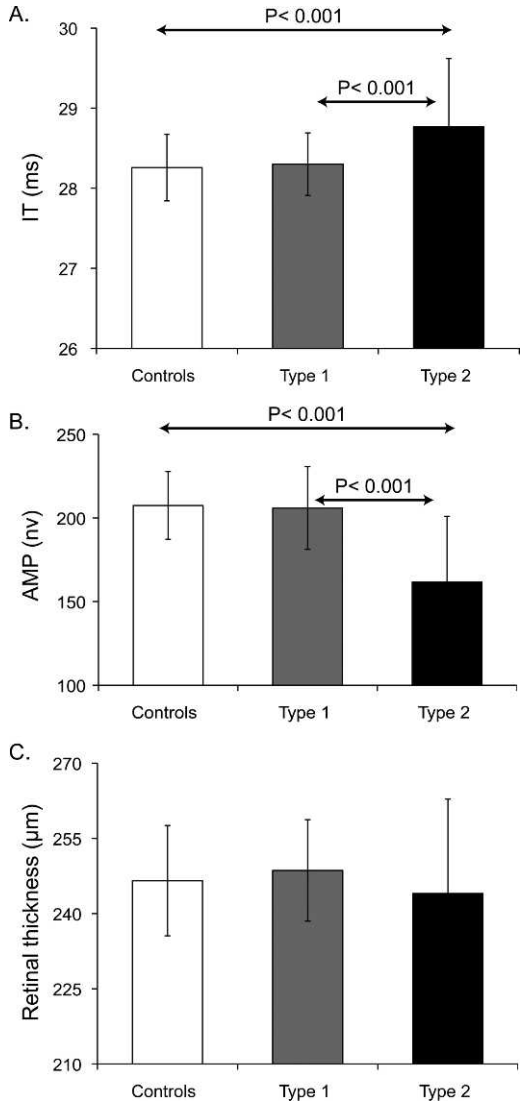

Figure 2. Group differences for IT, AMP, and full retinal thickness. The Type 2 group had longer IT and lower AMP than the Type 1 and Control groups. Total retinal thicknesses of the three groups were similar.

($P < 0.001$), but not IT abnormalities, than the Control group. Type 1 and Type 2 diabetes were observed to affect retinal thickness differently. The Type 2 group had a larger percentage of retinal thinning abnormalities than the Control group ($P < 0.001$). In contrast, the Type 1 group had a larger proportion of retinal thickening abnormalities compared with the Control and Type 2 groups ($P < 0.001$ for both).

Associations between Local Retinal Thickness and Local mfERG IT

The potential local retinal associations between function and full thickness were examined separately for each subject group. No spatial associations between full retinal thickness and IT were found in any subject group. Figure 4 shows the results from the Type 2 subject group as an example. In this figure, IT *Z*-scores from 37 retinal locations are plotted against retinal thickness percentiles in the 37 corresponding locations for all patients with Type 2 diabetes. This distribution does not reveal an association. This finding represents what we also observed in the Control and Type 1 subject groups.

Table 2. Percentages of Eyes with Significant Associations between Full Retinal Thickness and mfERG IT

Subject Group	Positive Association (%)	Negative Association, %
Control	10.3	10.3
Type 1	0.0	0.0
Type 2	5.7	11.4

When individual retinas were examined, no consistent associations were found between full retinal thickness and mfERG measured locally within any subject group. None of the subjects in the Type 1 group had a significant association between local full retinal thickness and IT. Some of the subjects in the Type 2 and Control groups showed a significant association, but the association was positive for some subjects (retinal thickening is associated with longer IT or larger AMP and retinal thinning is associated with shorter IT or reduced AMP) and negative (retinal thinning is associated with longer IT or larger AMP and retinal thickening is associated with shorter IT or reduced AMP) for others. In fact, the number of subjects with a positive association was equal to the number of subjects with a negative association in the Control group. Table 2 summarizes the percentage of subjects in each group who had significant associations ($P < 0.001$) between full retinal thickness and IT.

Associations between Local Retinal Thickness and Local mfERG AMP

Spatial associations within the subject groups were examined first. There were no significant spatial associations between full retinal thickness and AMP in any of the three subject groups. Figure 5 shows the results obtained from the Type 2 group as an example. AMP *Z*-scores from 37 retinal locations are plotted against the retinal thickness percentiles of the 37 locations for all subjects with Type 2 diabetes. The distribution does not reveal an associative trend. This was also observed in the Type 1 and Control subject groups.

Next, potential associations between full retinal thickness measured locally and AMP were tested within each individual of each subject group. Some of the subjects in each group showed a significant association but this finding was not consistent. For example, the percentages of subjects with positive and negative associations were equal (10.0%) in the Type 1 group. The percentages of subjects with a positive association were also low and approximately equal to the number of subjects with a negative association in the Control and Type 2 subject groups, although in these groups positive associations were slightly more likely than negative associations. Table 3 summarizes the percentages of subjects

Table 3. Percentages of Subjects Showing Significant Associations between Local Retinal Thickness and mfERG AMP

Subject Group	Positive Association, %	Negative Association, %
Control	10.3	6.9
Type 1	10.0	10.0
Type 2	17.1	11.4

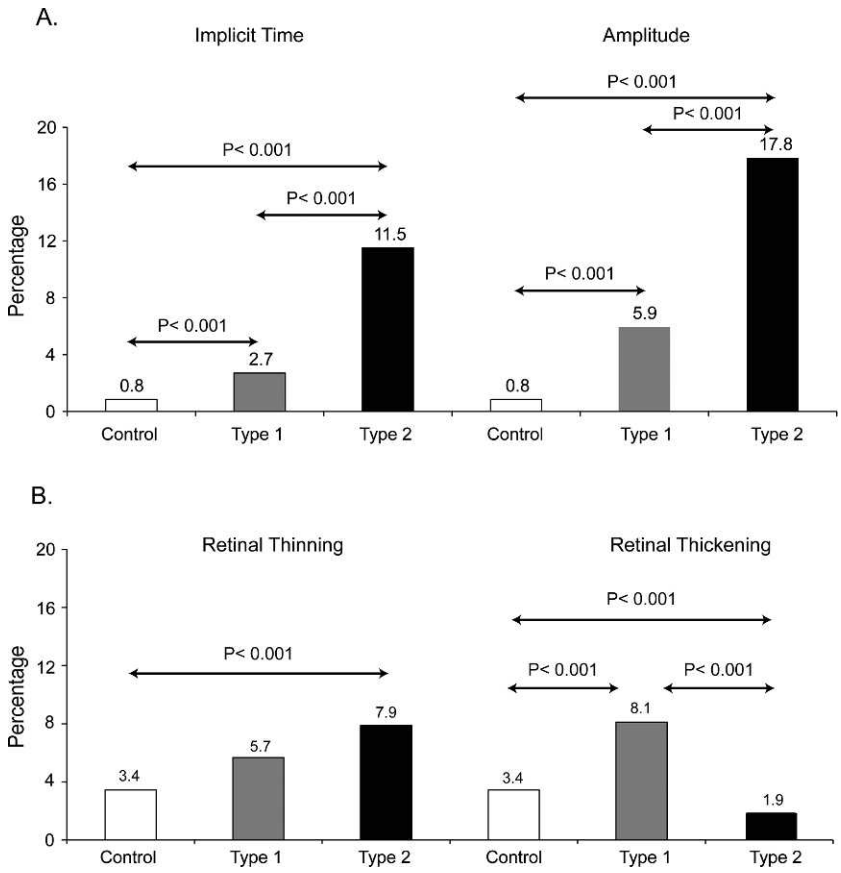

Figure 3. mfERG and full retinal thickness abnormality percentages.

in each group who had significant associations ($P < 0.001$) between full retinal thickness and AMP.

Spatial Associations between Full Retinal Thickness Abnormalities and mfERG Abnormalities

Within all subject groups, retinal thickness abnormalities (both thinning and thickening) did not show evidence of significant spatial agreement with either IT or AMP. The *P* values for the Fisher exact analysis test results are shown in Table 4. The occurrence of abnormalities was low, as shown earlier in Figure 3, and not consistent across the individual subjects. Therefore, the total number of abnormalities in the different measures was too small to allow for statistically valid examination of potential associations within individual subjects.

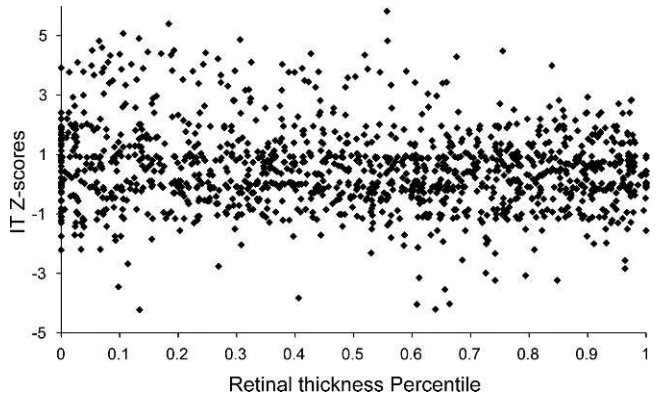

Figure 4. Association between full retinal thickness and mfERG IT in the Type 2 group.

Discussion

Our results indicate that there is no significant spatial correlation or association between full retinal thickness and either mfERG AMP or mfERG IT for any of the study groups. In addition, the absence of spatial coincidence of abnormalities in the two measures suggests that significant mfERG response changes in diabetic patients without retinopathy are not related to significant full retinal thickness changes.

The lack of spatial agreement between retinal thickness and mfERG abnormalities could be related to the fact that these patients are at early stages of diabetic eye disease. More advanced diabetic retinal damage may well show a more direct

Table 4. *P* Values for the Fisher Exact Analyses Are Shown for the Abnormality Associations

Subject Group	IT vs. Thinness	IT vs. Thickness	AMP vs. Thinness	AMP vs. Thickness
Control	0.99	0.99	0.99	0.99
Type 1	0.99	0.53	0.62	0.66
Type 2	0.09	0.16	0.11	0.10

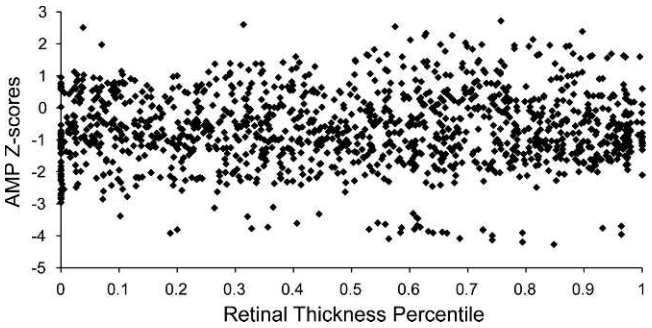

Figure 5. Association between retinal thickness and mfERG AMP in the Type 2 group.

relationship between full retinal thickness abnormalities and neuroretinal dysfunction.

It appears that, in both Type 1 and Type 2 diabetes without retinopathy, full retinal thickness measurements and mfERG findings are not identifying similar aspects of retinal changes. The two measures differ in their capabilities to identify significant early retinal changes, as diabetes affects structure and function. Perhaps the most important conclusion from these results is that the mfERG and OCT measurements of full retinal thickness cannot be treated as surrogates of each other in the evaluation of retinal changes produced by diabetes, at least before the onset of diabetic retinopathy.

In our study, Type 2 patients have worse mfERG retinal function as compared with Type 1 patients, although their duration of diabetes is approximately half the duration of diabetes of Type 1 patients and their glucose control assessed by HbA1c is similar. This finding is in agreement with other studies done in our laboratory.[15,28] Type 1 and Type 2 diabetes have very different presentations and the two diseases affect vascular and neural health with different time courses and natural histories. The reasons for the retinal function differences we observed between the Type 1 and Type 2 groups, therefore, could be related to differences in the pathophysiologies and comorbidities of the two diseases.

To our knowledge, our study is the first to quantitatively analyze the potential associations between local retinal thickness changes assessed by OCT and local functional changes assessed by mfERG in patients with diabetes and no retinopathy. Previous studies performed to correlate visual acuity and retinal thickness in diabetes have provided mixed results. Some have found significant correlation,[29] and some found weak association.[30] Most of the previous studies have examined eyes with advanced stages of retinopathy, and insensitive psychophysical vision measures, such as visual acuity, have been used as a measure of retinal function. To date, no other study has examined local retinal structure-function relationships in early diabetes before signs of diabetic retinopathy can be seen clinically.

Apart from the selection criteria for patients, the main difference between this study and the other studies is the method used to analyze retinal thickness. In our study, we used a coregistration technique to overlay topographic structural and functional maps of the retina that facilitate the local evaluation of 37 different locations in the central 20° of the retina. This allowed us to verify our results in multiple small sectors of retina.

The primary limitation of our study was the relatively small number of patients in the Type 1 subject group. In addition, because this was a cross-sectional study, the results of a similar study focused on patients with more advanced, clinical stages of diabetic retinopathy might yield different results. Despite these potential limitations, we have observed that local functional changes are not associated with local retinal thickness changes in patients with diabetes without retinopathy. The fact that we are using full retinal thickness as a measure of structural health cannot be overlooked. This is a potential weakness of the study. It is possible that studying individual retinal layers and different aspects of OCT scan (apart from total retinal thickness) may reveal some more interesting and more subtle properties of the disease. The possibility of finding associations between individual retinal layer thickness changes and mfERG function cannot be denied and will be the focus of our future study. A recent study found a strong correlation between specific retinal layer thickness (not full thickness) and visual acuity in late stages of diabetic retinopathy.[31]

New knowledge and understanding of local structure-function relationships will help create effective therapies that could save vision at an earlier or even subclinical stage of diabetic eye disease and revolutionize care of diabetic retinopathy. We are planning in the future to use segmentation techniques to examine potential relationships between the mfERG and the thickness of different retinal layers in early diabetes.

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