

Prediction, by Retinal Location, of the Onset of Diabetic Edema in Patients with Nonproliferative Diabetic Retinopathy

Wendy W. Harrison,¹ Marcus A. Bearse Jr,¹ Marilyn E. Schneck,¹ Brian E. Wolff,¹ Nicholas P. Jewell,² Shirin Barez,¹ Andrew B. Mick,³ Bernard J. Dolan,³ and Anthony J. Adams¹

PURPOSE. To formulate a model to predict the location of the onset of diabetic retinal edema (DE) in adults with diabetic retinopathy (DR), at risk for DE.

METHODS. In all, 46 eyes from 23 patients with DR were included. Subjects were followed semiannually until DE developed or the study concluded. The presence or absence of DE within the central 45° at the final visit was the outcome measure, and data from the prior visit were used as baseline. A logistic regression model was formulated to assess the relationship between DE development and: multifocal electroretinogram (mfERG) implicit time (IT) Z-score, mfERG amplitude (Amp) Z-score, sex, diabetes duration, diabetes type, blood glucose, HbA1c, age, systolic (SBP) and diastolic blood pressure, and grade of retinopathy. A total of 35 retinal zones were constructed from the mfERG elements and each was graded for DE. Data from 52 control subjects were used to calculate the maximum IT and minimum Amp Z-scores for each zone. Receiver operating characteristic curves from a fivefold cross-validation were used to determine the model's predictive properties.

RESULTS. Edema developed in 5.2% of all retinal zones and in 35% of the eyes. The mfERG Amp, mfERG IT, SBP, and sex were together predictive of edema onset. Combined, these factors produce a model that has 84% sensitivity and 76% specificity.

CONCLUSIONS. Together mfERG, SBP, and sex are good predictors of local edema in patients with DR. The model is a useful tool for assessing risk for edema development and a candidate measure to evaluate novel therapeutics directed at DE. (*Invest Ophthalmol Vis Sci.* 2011;52:6825–6831) DOI:10.1167/iovs.11-7533

Diabetes is the leading cause of preventable blindness in the United States among adults ranging in age from 21 to 74 years.¹ Among these patients, a primary cause of vision loss

is macular edema, caused from leaking of fluid out of the retinal vessels into the tissue.^{2–4} Edema can occur at any stage of diabetic retinopathy and can have devastating visual consequences. Thus, predicting and preventing macular edema in “at-risk” individuals constitute an important clinical research and patient care goal. Presently, the standard-of-care treatment for macular edema is focal laser, which involves using tiny laser burns in the macular area to inhibit the spread of fluid in the retina. This treatment does not restore lost vision but can reduce further vision loss.⁵ Other treatments, such as injections of steroids and anti-vascular endothelial growth factor agents have been successful in some patients.^{6,7} More recent studies suggest that a combination of these treatments may be even more effective in reducing vision loss,⁸ but a preventative measure that is less invasive is still needed for these patients.

There have been a number of studies that have looked at factors associated with macular edema, with a particular interest in modifiable risk factors. Edema has been associated with a longer duration of diabetes, higher systolic and diastolic blood pressure, Latino and African American ethnicity, prior amputation, and increasing retinopathy severity.^{9,10} Some studies have used the multifocal electroretinogram (mfERG) to evaluate diabetic macular edema and its treatments.^{11,12}

The mfERG has been shown to be sensitive to changes in diabetes even quite early in the disease process.^{13,14} Thus these neural function measures might identify and predict more severe changes, such as retinal edema. The mfERG measures are affected by long-standing edema and increased foveal thickness. Studies have shown that the mfERG implicit time (IT) is prolonged and the mfERG amplitude (Amp) reduced with retinal edema.^{15,16} Furthermore, the mfERG has been shown to be not only a useful tool in evaluating the success of intravitreal injections for diabetes, but also predictive of the functional prognosis for the results after surgeries for diabetic eye disease.^{11,12,17}

We have previously developed multivariate models using the mfERG IT and other diabetes health measures to predict new local retinopathy development over 1 to 3 years in patients with diabetes mellitus both with, and without, nonproliferative diabetic retinopathy at baseline.^{18–22} Here we create a model using the mfERG IT and Amp to specifically predict potentially sight-threatening edema in patients with existing retinopathy. The ability to identify those patients at highest risk for vision loss within the following year could have widespread application in both clinical trials evaluating new treatments and in monitoring the care of patients with diabetic retinopathy.

From the ¹School of Optometry, Group in Vision Science and the ²Department of Statistics, Division of Biostatistics, University of California Berkeley, Berkeley, California; and the ³San Francisco Veterans Administration Medical Center, Eye Clinic, San Francisco, California.

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Corresponding author: Wendy W. Harrison, Midwestern University, Arizona College of Optometry, 19555 N 59th Avenue, Glendale, AZ 85308; wharri@midwestern.edu.

METHODS

Patients

Twenty-seven adult patients with diabetes completed the study. Four patients with type 2 diabetes were excluded from the analysis at the end of the study. Reasons for exclusion were outlined at the start of the study and were as follows: one patient was excluded due to poor mfERG fixation at baseline (resulting in a template-scaling measure, statfit, over 0.8), one patient developed a visually significant cataract requiring surgery, and two patients developed proliferative diabetic retinopathy, with blood obscuring the retinal tissue in the final fundus photos and needing laser photocoagulation. This left 23 patients that were included in the final analysis and both eyes of each patient were used. All patients ranged in age from 25 to 65 years, with a mean age of 47.4 ± 12.1 years. There were 10 patients with type 1 diabetes and 13 with type 2 diabetes. In addition, 52 healthy nondiabetic controls with an age range of 20 to 65 years (mean age, 43.1 ± 14.7 years) participated. Their data, newly obtained for this study, were used for normalization and to create Z-scores and local waveform templates for the mfERG analysis. At baseline, all patients and controls had 20/25 or better acuity, refractive errors between +4.00D and -6.50D, and all patients with diabetes had varying levels of nonproliferative diabetic retinopathy in at least one eye. All patients with media opacities, retinal edema in the central 45° at baseline, or prior laser treatment anywhere in the retina were excluded from the study; patient demographic data are shown in Table 1. All participants provided written informed consent and the procedures were in compliance with the Declaration of Helsinki and the University of California Berkeley Committee for Protection of Human Subjects.

Study Timeline and Testing Procedures

All patients with diabetes were followed semiannually over time until the study concluded or edema developed. Recruitment was continuous and the average time in the study was 2 years, with a range of 0.5 to 4 years. This was a new cohort of patients whose data were not included in any of our previous work. The last study visit was used as the outcome and the previous full study visit was used as the baseline for prediction.

Every year, each study subject would undergo a full study visit, which included a full medical history; random blood glucose reading (One Touch Ultra; Lifescan, Milpitas, CA) and glycated hemoglobin test for hemoglobin A1c (HbA1c; A1c At Home Test Kit; FlexSite Diagnostics, Palm City, FL); dilated fundus examination, with photos covering the central 50° (Carl Zeiss Meditec, Dublin, CA); an optical coherence tomography (Stratus OCT3 and also Cirrus OCT for all visits after 11/2008; Carl Zeiss Meditec), blood pressure reading (left arm seated on automatic blood pressure cuff; Omron Model HEM-773, Bannockburn, IL); and mfERG (VERIS software; Electro-Diagnostic Imaging, Inc., Redwood City, CA). In between full study visits, at a 6-month follow-up visit, all measures were repeated except the mfERG. There was no difference in the average time between the baseline and the outcome visit for patients who developed or did not develop edema. Patients who developed edema had an average study time between baseline and outcome of 9.0 ± 2.9 months. Patients who did not develop edema had a study time of 10.3 ± 2.9 months.

Patients who developed edema anywhere in the central 45° at any visit were asked to return within 2 weeks for a fluorescein angiogram (FA) to confirm the location and extent of the edema. All but two of the patients returned for the additional testing. The FA was graded in detailed fashion for the location of retinal edema and grade of overall retinopathy by a retinal specialist masked to the mfERG and all other results. The fundus photos, which were available to the retinal specialist as macular stereo photos, were graded in the same manner. Combinations of the results of the FA, photos, and OCTs were used to determine the exact location of edema. Patients with clinically significant macular edema (CSME) were referred to their ophthalmologist for evaluation and any necessary treatment.

mfERG Recordings

Subjects were dilated to at least 7 mm with 1% tropicamide and 2.5% phenylephrine. A bipolar contact lens electrode (Burian-Allen Electrodes, LKC Technologies, Gaithersburg, MD) was used for recording. A ground electrode was placed on the left earlobe of each patient and the other eye, which was not currently being recorded, was occluded. An mfERG system (VERIS 5.2; EDI, Redwood City, CA) was used with a scaled 103 hexagon display. A 75-Hz cathode ray tube display that subtended 45° on the retina was used. The unit had an eye-camera-refractor display that allowed subjects to self-adjust the screen to best focus to correct for their refractive error. This display also allowed us to monitor subjects' pupil position in real time. The monitor was calibrated regularly to ensure high-quality recordings. Pre-amplifier filters were set to 10 to 100 Hz and retinal signals were amplified 100,000 times. The contrast of the stimulus display was set to near 100% with the light elements at 200 cd/m² and the dark elements at <2 cd/m². When processing the waveforms, 17% spatial averaging was used with a single iteration of artifact removal.

First-order kernel mfERG P1 IT and P1 Amp were measured with the template-scaling method.²³ The local templates were constructed from the mean local waveforms of the 52 control subjects. The template was then scaled in time and amplitude to match the subject's local waveform, by minimizing the least-square difference between the two. The program designates a measure of the goodness of fit for each waveform labeled a "statfit." A "statfit" over 0.8 indicates a poor fit and was a criterion for rejection, and one subject was rejected on this basis. Each local IT measure and Amp measure for the diabetic patients was converted to a Z-score using the local mean and SD of the 52 controls. For our instrumentation, an mfERG IT Z-score on average is equal to 0.9 ms and an mfERG Amp Z-score is equal to 0.19 μV.

To be spatially conservative, 35 retinal zones, containing two or three neighboring hexagons, were constructed from the 103 mfERG stimulus elements. For each zone a maximum IT Z-score and a minimum Amp Z-score were assigned, selecting from the Z-scores of the mfERG for hexagons in that zone. All fundus photographs and FAs were graded in a detailed and masked fashion for the presence or absence of edema, and the degree of retinopathy on a clinical scale (none, mild, moderate, severe). The mfERG array was overlaid onto the digital photographs to match the location of edema with the mfERG zones (Fig. 1).

Statistical Analysis

Logistic regression²⁴ was performed to examine associations between development of diabetic edema and 11 baseline risk factors. These

TABLE 1. Baseline Patient Demographic Data

| Group | Number of Patients | Sex M:F | Type 1:2 | Age (y) | Duration (y) | Blood Glucose (mg/dL) | HbA1c (%) | Blood Pressure SBP/DBP (mm Hg) | Degree of Retinopathy (Clinical Scale)* |
|----------|--------------------|---------|----------|-------------|--------------|-----------------------|-----------|--------------------------------|---|
| Diabetes | n = 23 | 12:11 | 10:13 | 47.4 ± 12.1 | 16.5 ± 8.5 | 172.5 ± 79.7 | 9.3 ± 1.9 | 128.9/78.8 ± 25.8/11.9 | 3, 18, 17, 6 |
| Controls | n = 52 | 23:29 | N/A | 43.1 ± 14.7 | N/A | 105.6 ± 22.3 | N/A | 113.4/70.3 ± 17.5/9.7 | N/A |

* Levels on a clinical scale: None, Mild, Moderate, Severe. N/A, not applicable.

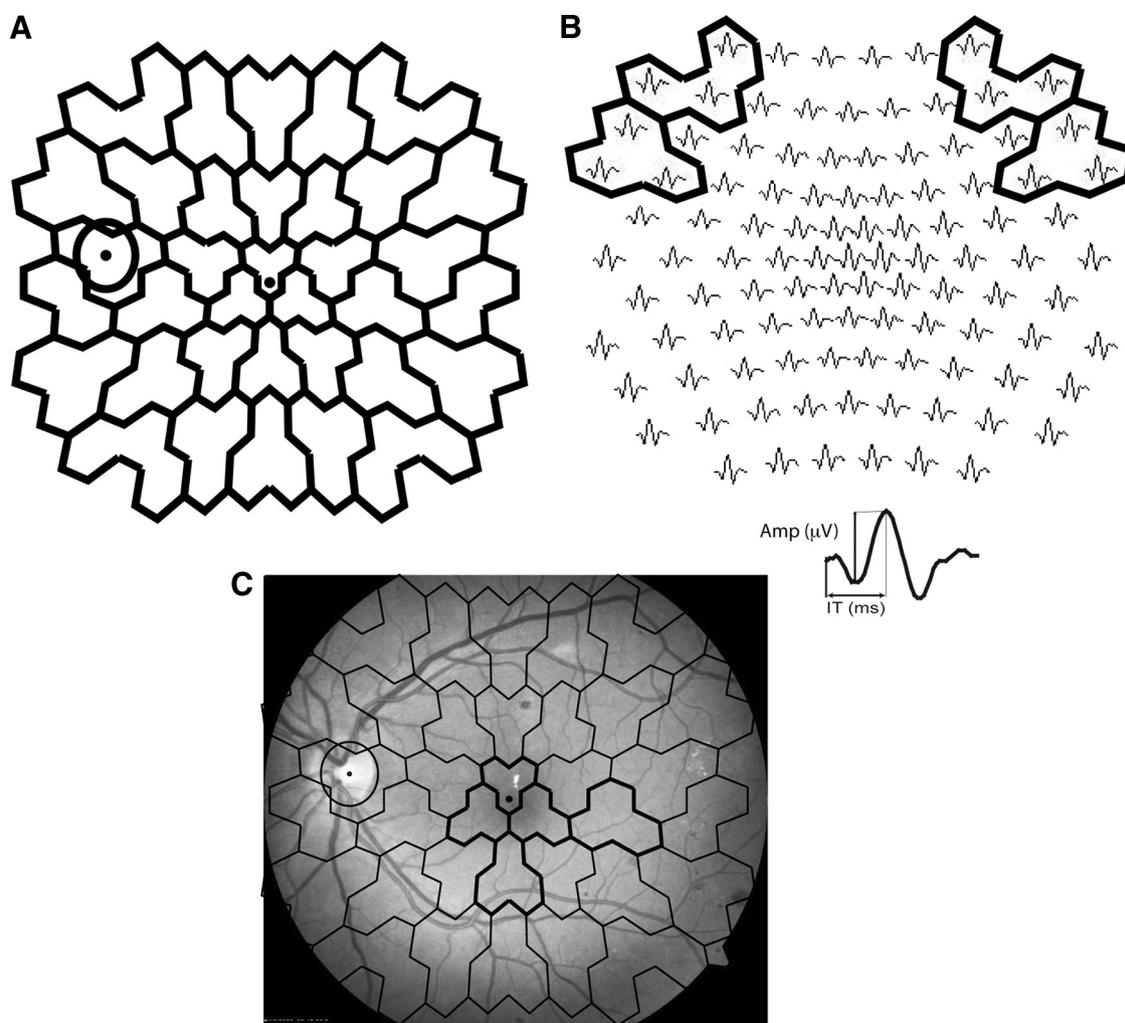


FIGURE 1. (A) The 35 retinal zones that were constructed. (B) The maximum mfERG IT Z-score and minimum mfERG Amp Z-score were assigned to the entire zone. The *inset* indicates how mfERG IT and Amp are measured. (C) The zones were overlaid on the fundus photographs to mark the location of the edema. Locations with edema in this type 1 diabetic patient are highlighted in bold.

factors were measured at the last full study visit (within 1 year before the outcome) for the individuals who developed edema, and also at the last full visit for patients who did not develop edema. The baseline measures included in the modeling process are mfERG IT Z-score, mfERG Amp Z-score, diabetes duration, diabetes type, sex, blood glucose level, HbA1c, systolic blood pressure, diastolic blood pressure, age, and degree of retinopathy.

The univariate relationship between edema and degree of retinopathy was also examined at the time of the outcome measurements (follow-up), as well as the relationship between edema and change in retinopathy status. These were not included in the model but were evaluated separately as individual associations.

Since correlations likely exist in this data structure between both the mfERG measures in different zones within an eye of any one subject, and between eyes of the same subject, model coefficients were estimated with generalized estimating equations (GEEs). GEEs allow coefficient estimates to account for covariance between zones in the same subject, but assume independence across subjects.²⁵ As in previous models by our group,^{20,22} observations from a single subject were combined into a single cluster to permit correlations across eyes. Robust variances were used for inference to accommodate for any differences between the true and assumed covariance structures.

For the logistic regression analysis, we followed the steps of a standard stepwise forward regression. We first performed a univariate analysis of all 11 risk factors and determined which factors were most

likely to be predictive. Second, possible confounders and interaction terms were evaluated. Finally, two models were created. The first model used only mfERG measures to predict edema (labeled as mfERG only model [model 1]), thereby ignoring all other factors. The second model evaluated the mfERG IT and mfERG Amp along with the additional 9 risk factors to create the best multivariate predictive model using all the data available (labeled as multivariate model [model 2]). All logistic regressions used an independent correlation structure with robust estimates for inference as previously noted.

Receiver operating characteristic (ROC) curves were constructed from probabilities of new edema development calculated from the models.²⁶ The data were then randomly divided into five subsets and a fivefold cross-validation procedure was used to validate each model's results. Each of the five subsets was used to validate a model created by combining the other four subsets of data. The validations were averaged to determine the generalized predictive properties of each model.^{27,28}

RESULTS

Edema Development and Location

Edema developed in 16 of the 46 eyes (35%), 10 of the 23 patients (43%), and 83 of the 1610 retinal zones (5.2%). Of the

patients who developed edema, 7 had type 2 diabetes and 3 had type 1 diabetes.

The edema tended to form in the temporal or central macula, qualifying as CSME and potentially threatening sight. Overall, 11 of the 16 eyes (69%) that developed edema qualified as clinically significant. Edema was found in the two zones just temporal and inferotemporal to the central fovea (Fig. 2), in 10 of the 16 (63%) eyes that developed edema.

Relationship of Edema and Degree of Retinopathy

Edema development was found to be associated with the degree of retinopathy at the follow-up visit, at the time the edema was clinically visible ($P < 0.0001$). However, degree of retinopathy at baseline was not predictive of future edema ($P = 0.19$). Given this result, we also examined change in retinopathy status between the two visits and its relationship to edema development. Although there was a trend toward worsening retinopathy being associated with edema development, in our sample it was not a significant association ($P = 0.06$). Eleven of the 46 eyes had retinopathy that worsened between the two study visits and about half (5) of these eyes developed edema. Two eyes had improvements in their retinopathy from baseline to the outcome visit. Neither of these eyes developed edema. The remaining 33 eyes had no changes in the overall amount of retinopathy as determined by clinical fundus grading. Of the unchanged eyes, 11 developed edema and 22 did not.

Predictive Model Creation

Univariate Analysis of Risk Factors. First we evaluated the individual predictive properties of each potential risk factor in univariate models. The mfERG Amp Z-score was found to be the most significant univariate factor for the prediction of edema. Other factors that were significant ($P < 0.05$) were mfERG IT Z-score and age (Table 2). This means that each of these factors could independently predict edema development. Thus, edema development was associated with delayed IT, decreased Amp, and older age. There were five baseline factors that were categorized as marginally predictive of edema, with a value of $P < 0.2$. These were degree of retinopathy, SBP, type of diabetes, sex, and duration of diabetes. These factors were added first in the stepwise regression. The rest of

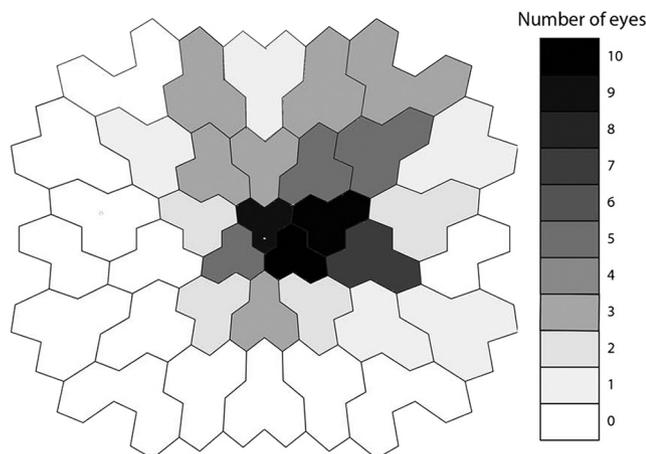


FIGURE 2. Retinal distribution of new edema development. Colors on the grayscale represent the number of eyes that developed edema in a particular zone when all eyes were displayed as left eyes. The darkest zones are the locations where the greatest number of patients developed new edema.

TABLE 2. Significant Univariate Coefficients for the Prediction of Edema

| Variable | Coefficient | P Value | Odds Ratio [95% CI (range)] |
|---------------------|-------------|---------|-----------------------------|
| mfERG IT, Z-scores | 0.435 | 0.005 | 1.55 (1.14–2.09) |
| mfERG AMP, Z-scores | −0.851 | 0.001 | 2.34 (1.41–3.90) |
| Age, years | 0.090 | 0.026 | 1.09 (1.01–1.18) |

the factors were not independently predictive, but were still evaluated for inclusion in the multivariate model discussed later.

Location-Specific Prediction of Edema Using Only mfERG IT and mfERG Amp. Given that both mfERG measures were highly predictive in the univariate analysis, we were interested in how well the mfERG alone could predict future edema. First, the potential confounding of mfERG IT and Amp by the other risk factors was examined. No factors were found to confound in this model. Additionally, no interaction was found between mfERG IT and mfERG Amp. In the model (shown in the following equation), p is the probability of developing edema in a zone within 1 year. The model—mfERG only model (model 1)—which uses only mfERG IT Z-score and mfERG Amp Z-score, was highly significant for the prediction of edema.

$$\log[p/(1-p)] = -3.79 + 0.37 (\text{IT Z-score}) - 0.88 (\text{Amp Z-score})$$

The coefficients here yield odds ratios that can be interpreted as approximate relative risks. For increasing mfERG IT, the odds ratio is 1.44 (95% confidence interval [CI], 1.05–2.11) and, for decreasing mfERG Amp, the odds ratio is 2.41 (95% CI, 1.30–3.86). This means, for example, that for every unit increase in mfERG IT Z-score the odds of developing edema increase by 44%, when the amplitude is held constant.

Cross-Validation. A fivefold cross-validation was used to estimate the validity and general accuracy of the mfERG only model. It yielded the five sets of coefficients (Table 3) whose average was 0.37 for mfERG IT Z-score, −0.88 for mfERG Amp Z-score, the same as the coefficients in the mfERG model before cross-validation. Each of these five models yielded an ROC curve, which had a range of sensitivities and specificities from 68 to 83% (Fig. 3). The average accuracy of these ROC curves indicates that this mfERG only model has a cross-validated sensitivity and specificity of 72%.

Multivariate Model Using mfERG and Other Factors to Predict Local Edema. A stepwise forward regression was used to examine other measured factors to see whether they improved the model. Two additional factors, SBP and sex, were found to be significant at a $P < 0.05$ level and improved the model and its predictive abilities.

The selected multivariate model (model 2) is

TABLE 3. Fivefold Cross-Validation for mfERG Only Model (Model 1)

| Fivefold Model Number | IT Z-Score Coefficient | Amplitude Z-Score Coefficient | Sensitivity (%) | Specificity (%) |
|-----------------------|------------------------|-------------------------------|-----------------|-----------------|
| 1 | 0.406 | −0.863 | 68 | 68 |
| 2 | 0.357 | −0.873 | 74 | 74 |
| 3 | 0.371 | −0.835 | 83 | 83 |
| 4 | 0.352 | −0.883 | 68 | 68 |
| 5 | 0.376 | −0.948 | 68 | 68 |
| Average | 0.372 ± 0.02 | -0.880 ± 0.04 | 72.2 ± 6.6 | 72.2 ± 6.6 |

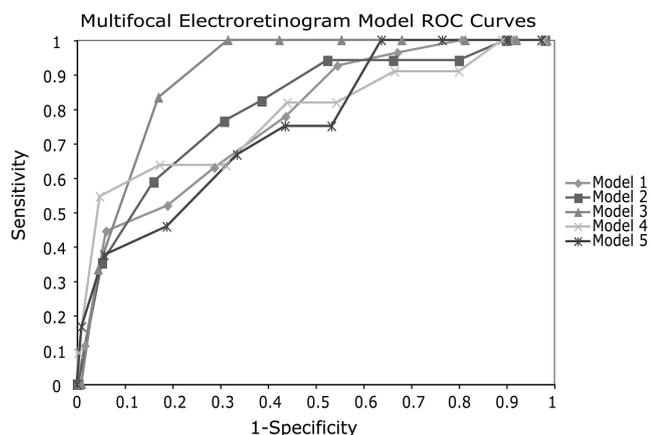


FIGURE 3. Five ROC curves from the fivefold cross-validation of mfERG only model (model 1). Each symbol represents a curve constructed from one fifth of the data using coefficients modeled from the other four fifths of the data.

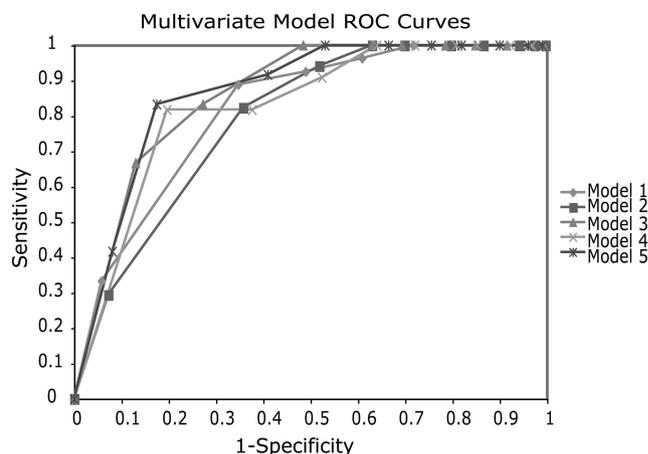


FIGURE 4. Five ROC curves from the fivefold cross-validation of the selected multivariate predictive model (model 2). Each symbol represents a curve constructed from one fifth of the data using coefficients modeled from the other four fifths of the data.

$$\log[p/(1 - p)] = -5.39 + 0.37(\text{IT Z-score}) - 0.87(\text{Amp Z-score}) + 0.017(\text{SBP}) - 1.93(\text{Sex})$$

In this model *p* is again the probability of developing edema in a given zone within 1 year. The coefficients give an odds ratio for mfERG IT Z-score of 1.44 (95% CI, 1.13–1.84), an odds ratio of 2.38 for decreasing mfERG Amp Z-score (95% CI, 1.55–4.48), an odds ratio for blood pressure of 1.02 (95% CI, 1.00–1.04) per mm Hg change, and 6.89 for sex (95% CI, 2.32–20.09), all interpreted when holding all the other included factors constant. These can also be interpreted as approximate relative risks. In this model the coefficients for amplitude and sex are negative terms. This means that, as mfERG Amp decreases, the risk of edema increases. The negative sex term means that males were more than six times more likely to develop edema than females in a given local retinal area.

Cross-Validation. A fivefold cross-validation was also used to estimate the validity and general accuracy of this model. There are five sets of coefficients (Table 4) whose average was 0.37 for mfERG IT, -0.87 for mfERG Amp, 0.017 for blood pressure, and -1.93 for sex. Each of these five models yielded an ROC curve, which had a range of sensitivities from 82 to 88% and a range of specificities from 65 to 84% (Fig. 4). The average accuracy of these ROC curves indicates that the final model has a cross-validated sensitivity of 84.4% and a specificity of 75.8%.

DISCUSSION

We have created a multivariate model for the prediction of diabetic retinal edema onset in an at-risk patient group. This model shows that mfERG Amp, mfERG IT, SBP, and sex are

collectively predictive of edema onset at specific retinal locations within 1 year. The model has high sensitivity (84%) and high specificity (76%).

Previously, we developed multivariate models to look at prediction of retinopathy in patients with diabetes, both with and without retinopathy. In those models we showed that the mfERG IT is highly predictive of new retinopathy in patients with early-stage retinal complications.^{18,20–22} Most recently we reported that the mfERG IT has predictive capabilities for impending diabetic retinopathy in eyes that have had no prior retinopathy.²² In the present study we used the mfERG technique to successfully predict more serious vision-impacting edema onset in the retina. It is known from prior work that the mfERG implicit time is affected by previous retinopathy and presence of hard exudates in an eye,^{13,29} and that the mfERG is also able to differentiate between different kinds of retinopathy.^{13,30} In our study, most of the patients had abnormal mfERGs from their diabetes-induced retinal changes. Importantly, our model was able to predict, with good sensitivity, the retinal areas about to undergo the more serious vision-threatening retinal onset of edema.

With further analysis of the sensitivity and specificity of the multivariate model (model 2), we found that in the zones around the regions where the edema developed, the model produced a number of false positives (regions that were predicted to develop edema but did not). This indicates that the neural dysfunction seen in our study may extend beyond the region where the fundoscopic changes are seen. In fact, this difference between the area of neural dysfunction and the observed fundus changes decreases the specificity of the model (76%). This is in agreement with the work reported by Greenstein et al.,¹⁵ who also found that the mfERG changes

TABLE 4. Fivefold Cross-Validation for Multivariate Model (Model 2)

| Fivefold Model Number | IT Z-Score Coefficient | Amplitude Z-Score Coefficient | SBP Coefficient | Sex Coefficient | Sensitivity (%) | Specificity (%) |
|-----------------------|------------------------|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| 1 | 0.419 | -0.837 | 0.017 | -1.95 | 88 | 74 |
| 2 | 0.353 | -0.873 | 0.018 | -2.00 | 82 | 65 |
| 3 | 0.387 | -0.837 | 0.017 | -2.07 | 84 | 76 |
| 4 | 0.332 | -0.896 | 0.018 | -2.02 | 83 | 80 |
| 5 | 0.364 | -0.914 | 0.013 | -1.60 | 85 | 84 |
| Average | 0.371 ± 0.03 | -0.871 ± 0.03 | 0.017 ± 0.002 | -1.93 ± 0.17 | 84.4 ± 2.1 | 75.8 ± 6.4 |

extend beyond the areas where edema is present. Consequently, it is plausible that the specificity could be considerably higher if we had averaged the mfERG responses of the eye and used that in this model rather than the 35 separate zones. However, such an approach sacrifices the ability to predict the specific retinal sites for the impending edema, a feature of our modeling results. Also, the resulting relatively small sample size would be less than ideal for such an analysis.

Our previous models have not included mfERG Amp Z-score as a predictive factor for diabetic change. We had not found it to be predictive of early retinal changes, probably because the measure can be variable, leading to insensitivity in prediction until more serious retinal changes are impending.^{13,19,21,31} However, given that previous work has shown that edema significantly changes mfERG amplitude,¹⁵ we chose to evaluate it as part of this model. We found decreased amplitudes in zones that developed subsequent edema. Furthermore, decreased amplitudes had the most significant *P*-value ($P < 0.0001$) of the four predictive factors in the multivariate model and a very high odds ratio. As a point of caution regarding this statement, it is important to note that the odds ratios for measures in the model cannot be compared with each other since they are dependent on different scales. The odds ratio for blood pressure, for example, is per mm Hg increase. More clinically meaningful differences in units of blood pressure (5–10 mm Hg) would necessarily carry a much larger odds ratio but the significance of the prediction would remain the same.

Studies of the prediction and evaluation of sight-threatening retinopathy and macular edema note the importance of blood pressure control in reducing the risk of vision loss from diabetes. Improved blood pressure control reduces the risk of retinopathy and macular edema.^{32,33} Furthermore, elevated blood pressure has been shown to increase the risk for retinopathy progression.^{34–36} The Wisconsin epidemiologic study of diabetic retinopathy (WESDR) found that higher blood pressure at baseline, even in the absence of clinical hypertension, increased the risk of future edema.³⁷ Our study and model are in agreement with these studies and reveal higher blood pressure at baseline, regardless of the presence of hypertension, is an important risk factor for developing edema.

Our multivariate model also reveals that male sex is associated with an increased risk of local diabetic retinal edema. In our laboratory, Ozawa et al.³⁸ found that there is a difference in the mfERG of diabetic males and females even before retinopathy develops, with females younger than 50 years having fewer neuroretinal defects than males of the same age. Several studies found that males have a higher risk for, or are more likely to have, diabetic retinopathy than females.^{39–42} However, we could find no other studies in the literature showing a direct association between male sex and diabetic edema. It is worth noting though that studies evaluating edema and retinopathy frequently controlled for sex, raising the possibility that those authors considered sex to be an important confounder in their studies.^{43,44}

Although retinal edema can occur at any stage of diabetic retinopathy, the severity of retinopathy increases the likelihood of edema and sight loss.^{9,10,45} In our study, when looking at the levels of retinopathy in patients at the time the outcome measures were made, we also found that patients with more severe retinopathy were more likely to have edema. Based on the previous work, we targeted patients with moderate retinopathy to increase the likelihood that patients would develop edema in the follow-up period. For the same reason, we selected patients with longer durations of diabetes (average duration of our patients was 16 ± 8.5 years). In effect, we truncated the range of durations of diabetes in our study population compared with our previous modeling studies. This

selection of patients may be the reason that duration, as a potential risk factor, was not significant in our study. We also did not find retinopathy level at baseline to be statistically related to future edema, despite other studies noting this trend.⁴⁶ Again, this may be due to our choice of patients with predominantly moderate retinopathy and to our relatively small sample size.

Here we have predicted which local retinal regions were at the highest risk for new edema. Evaluating new edema development also gave us an opportunity to examine which larger regions of the retina seemed to be most vulnerable to edema. We noted that most of the new edema occurred near the fovea and qualified as CSME. This is consistent with findings from the Early Treatment Diabetic Retinopathy Study; patients with edema within one-disc diameter of the macular center were more common there as well.⁴⁷ The WESDR study also looked at the incidence of macular edema in diabetic patients and found similar results.⁴⁶

We noted a nasal-temporal asymmetry in the location of new edema, with most edema occurring in the temporal retina. However, with only 16 eyes developing new edema, this may be idiosyncratic to our study. Perhaps relevant is the finding of Hudson et al.⁴⁸ who looked at blood flow in the macular region in patients with clinically significant edema and found that for patients with edema the blood flow temporally, but not nasally, was slower than the blood flow in control patients. So there may be a nasal-temporal asymmetry in edema development, but more studies with larger study groups are certainly needed to explore this.

In summary, mfERG Amp, mfERG IT, SBP, and sex are, collectively, predictive of future sight-threatening edema in at-risk diabetic patients with retinopathy. Furthermore, with use of the mfERG, the predictions are specific to retinal locations. The usefulness of inclusion of blood pressure in the model is consistent with previous findings that blood pressure is an important factor in the progression of diabetic eye disease.^{33,49} Our model also suggests that male sex is a risk factor for more severe changes in the eye beyond retinopathy. Clinically this indicates that male patients with higher SBP and mfERG abnormalities are at increased risk of edema onset compared with other patients with long durations of diabetes and nonproliferative diabetic retinopathy. Our study is an important step in the prediction of edema in the highest risk patient groups. It establishes all these measures as candidates for selecting patients for targeted studies looking at prevention of edema.

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