Diabetic Retinopathy Clinical Research Network

Temporal Variation in Optical Coherence Tomography Measurements of Retinal Thickening in Diabetic Macular Edema

Version 1.1

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CHAPTER 1.
INTRODUCTION

1.1 Background Information

Optical Coherence Tomography (OCT) is a noninvasive method for measuring the thickness of the central retina. It has become a standard tool in the management of patients with diabetic macular edema (DME).

OCT is a diagnostic imaging technique, which uses low-coherence interferometry to produce cross-sectional tomograms of the posterior segment eye structures. An 850 nm light source emits a probe beam of infrared light, which is split between the eye and a reference mirror at a known spatial location therefore producing two beams. Both beams are reflected back to a photo detector, the time of flight delay of light back scattered from different layers in the retina is determined, and thickness data are obtained. The OCT's internal computer acquires and processes the data to produce enhanced images. Retinal thickness is determined using many individual A-scans along each of six B-Scans. A computer algorithm is used to determine the inner and outer retinal boundaries for each scan.

The variability of retinal thickening during the day and the variability of OCT measurements in the study of macular edema is an area of considerable interest. A study by Frank et al [1] indicated that OCT retinal thickness measurements in DME vary according to time of day. In that study of 10 subjects, retinal thickness was measured at 8:00 am, 11:00 am, 2:00 pm, and 5:00 pm. There was a decline in the average macular thickness from 8:00 to 11:00 am and relatively little change thereafter. Only four of the 10 subjects had a consistent decrease in the thickening over the course of the day. The eyes with greater retinal thickening tended to show a greater decline over the day than did the eyes with less thickening. The magnitude of the decrease in retinal thickening appeared to be relatively small, although statistically significant. An earlier study by Sternberg et al [2] that employed psychovisual assessments noted that visual function due to macular edema may vary with time of day, generally worse in the morning, which supports the anatomic observations in the study by Frank, et al.

Since OCT is being used as an outcome measure in DME studies, it is important to have more information on its reproducibility as well as more information on the effect of the time of day on retinal thickening.

1.2 Synopsis of Protocol

This study is one of a series of studies being conducted by the Diabetic Retinopathy Clinical Research Network. The study will enroll approximately 100 subjects with DME in at least one eye at participating sites. Subjects will be selected so that there will be approximately 33 eyes with DME in the range of 225 to 300 microns (measured from the center subfield of the OCT3 retina map), 33 in the range of 300 to 450 microns, and 33 with >450 microns. Each subject will have two OCT measurements made on each eye every two hours from 8 am to 4 pm., with an additional measurement at 9 am. Measurements will be made by the same operator using the same OCT3 machine at each time point. The second measurement at each time point may be made by the same or a different operator. Two consecutive fast macular scans of acceptable quality will be submitted (center point thickness with standard deviation less than 10%).

CHAPTER 2.
STUDY PROTOCOL

2.1 Identifying Eligible Subjects and Obtaining Informed Consent

One-hundred subjects will be enrolled. Potential eligibility will be assessed as part of a routine-care examination. For subjects who are eligible for the study, the study protocol will be discussed with the patient by a study investigator and clinic coordinator. The subject will be given the Informed Consent Form to read and any questions will be answered by the site staff.

2.2 Subject Eligibility and Exclusion Criteria

2.2.1 Eligibility Criteria

1. Diagnosis of diabetes mellitus (type 1 or type 2).
   - Any one of the following will be considered sufficient evidence that diabetes is present:
     - *Current regular use of insulin for the treatment of diabetes*
     - *Current regular use of oral antihyperglycemia agents for the treatment of diabetes*
     - *Documented diabetes by ADA and/or WHO criteria (see Site Coordinator Manual)*
2. In at least one eye: (1) definite retinal thickening due to diabetic macular edema based on clinical exam involving the center of the macula, (2) OCT central subfield >=225 microns, and (3) pupil dilates to 5 mm or larger.
3. Able and willing to provide informed consent.

2.2.2 Exclusion Criteria

4. History of chronic renal failure requiring dialysis or kidney transplant.
5. Congestive heart failure currently under treatment.
6. Blood pressure >180/110 (systolic above 180 OR diastolic above 110).

2.3 OCT Procedures

The OCT images will be obtained by a certified operator using the same OCT3 system. The same operator will obtain the OCT images once at each time point. The second measurement at each time point may be made by the same operator or a different operator (*this will allow for assessment of both intra-observer and inter-observer variability*).

The DRCRnet Photography and OCT Procedures Manual details the procedures involved in obtaining the OCT and submitting the images to the Fundus Photograph Reading Center.

The pupils will be dilated about 30 minutes prior to the initial OCT with the drops routinely used by the site. Prior to each OCT, pupil size will be assessed with a light; when pupil constriction occurs to a diameter of <5 mm, additional dilating drops will be placed in the eyes.

OCT will be performed on first the right eye and then the left eye at 8 am, 9 am, 10 am, 12 noon, 2 pm, and 4 pm within a 30 minute window at each time point. The noon measurements should preferably be obtained prior to the patient eating lunch.

At each time point, two OCT measurements will be made on each eye. The right eye is scanned first, and then the left eye is scanned. Each scan must be evaluated to be of adequate quality for submission, according to the study procedures. If scan quality is judged substandard by the operator, then the scan will be repeated until a good quality scan is obtained. The patient will be

asked to stand up briefly, and then the second scans will be performed on each eye (with repetition to achieve good quality as needed). All scans, including those with poor quality, will be submitted to the Reading Center.

2.4 Other Procedures

Historical information will be collected, including demographics, prior treatment for diabetic retinopathy, and medications. In addition to the OCTs, the following procedures will be performed:

1. Refraction and E-ETDRS visual acuity in each eye using the DRCRnet procedures (see Visual Acuity/Refraction Procedures Manual) at 8 a.m., 12 noon, and 4 p.m. (only the sphere is required to be rechecked for the 12 noon and 4 p.m. refractions).

2. Fundus photos of each eye (3-fields).
   - *If photos were obtained within prior month and no treatment for DME has been performed since, photos do not need to be repeated.*

3. Height and weight.

4. Blood glucose checked by the subject using his/her own home glucose meter or the site's meter at 8 am, 12 noon (preferably prior to patient eating lunch), and 4 pm.

5. Blood pressure at 8 am, 12 noon (preferably prior to patient eating lunch), and 4 pm.

The patient's most recent HbA1c measurement (within past 3 months) will be recorded, or an HbA1c test will be performed that day and recorded as part of usual care (if the HbA1c measurement can not be performed on the study day, it should be obtained within 3 weeks).

2.5 Risks and Benefits

The procedures in this study are part of daily ophthalmologic practice in the United States and pose no additional known risks. Dilating eye drops will be used as part of the exam and may be repeated during the day. There is a small risk of inducing a narrow-angle glaucoma attack from the pupil dilation. However, all subjects will have had prior pupil dilation usually on multiple occasions and therefore the risk is extremely small. Fundus photography carries no known risk, although the camera flash may cause temporary discomfort for the patient. OCT carries no known risk.

The subject is not expected to receive benefit from study participation.

2.6 Patient Reimbursement

The study will provide $200 to each patient. Payment will be made by the study Coordinating Center, which will be provided the subject's contact information for this purpose.

2.7 General Considerations

The study is being conducted in compliance with the policies described in the DRCRnet Policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

The DRCRnet Procedures Manuals (Visual Acuity/Refraction Procedures Manual, Photography and OCT Procedures Manual, and Site Procedures Manual) provide details of the examination procedures.

There is no restriction on the number of patients to be enrolled by a site.

CHAPTER 3.
STATISTICAL CONSIDERATIONS

The approach to sample size estimation and the general statistical analysis plan are summarized below and will be detailed in a separate Statistical Analysis Plan.

3.1 Sample Size Estimation

The primary analysis involves determining how often there is a diurnal change in retinal thickening measured on OCT, defined as a change of at least 25%. The analysis will determine the proportion of eyes in which measurements made at 8am and 4pm exhibit a potentially meaningful relative change (defined in section 3.2.1) in retinal thickening.

The table below provides the sample sizes for a range of proportions and confidence interval widths.

Sample Size

	Proportion of Eyes with Potentially Meaningful Relative Change					
Half-Width of Confidence Interval	**.02**	**.05**	**.10**	**.15**	**.20**	**.25**
.05	31	73	139	196	246	289
.075	14	33	62	88	110	129
.10	8	19	35	49	62	73

It is postulated that 5-10% of eyes will have a decrease in retinal thickening of at least 25% during the day.

A convenience sample size of 100 subjects has been selected. In order to explore whether the frequency of diurnal change varies with the degree of retinal thickening, at least 33 eyes will be enrolled in each of the following three central subfield retinal thickness subgroups: 225-300 microns, 301-450 microns, >450 microns. The following table represents the half-width of a confidence interval for various proportions of eyes with potentially meaningful relative change for a sample size of 100 subjects (33 subjects in each subgroup).

Half-Width of Confidence Interval

	Proportion of Eyes with Potentially Meaningful Relative Change					
Sample Size	**.02**	**.05**	**.10**	**.15**	**.20**	**.25**
33	0.048	0.074	0.102	0.122	0.136	0.148
100	0.027	0.043	0.059	0.070	0.078	0.085

3.2 Analysis Plan

3.2.1 Diurnal Variation

The primary analysis will focus on determining the proportion of eyes with a potentially meaningful relative change in retinal thickening between 8am and 4pm. Therefore, a clinical definition for potentially meaningful relative change must be established. For purposes of this analysis, a 25%

relative change in the retinal thickening (not thickness) is deemed to be a potentially meaningful relative change between the two time points. A 25% relative change is larger than what would be expected by random variability. Change in retinal thickening is defined as [(retinal thickness at first time point – retinal thickness at second time point)/(retinal thickness at first time point – normal thickness)].

The primary diurnal variation analysis will involve construction of a 95% confidence interval on the proportion of eyes that demonstrate a potentially meaningful change in retinal thickening (relative change >= 25%) between 8am and 4pm. Only eyes with 8am retinal thickness >=250 microns will be included in the primary analysis.

If any cases of a potentially meaningful change are found, then theses cases will be characterized and the data will be explored to try to identify factors that are associated with the occurrence of a diurnal change. Factors to be assessed will include: age, gender, ethnicity/race, type of diabetes, blood pressure, amount of retinal thickening, prior focal laser treatment for DME, level of retinopathy, visual acuity, body mass index, hours patient was in bed the previous night, presence of COPD, presence of sleep apnea, medication including diuretics, blood glucose change from 8am to 12 noon, and HbA1c.

For eyes with a potentially meaningful change between 8am and 4pm, exploratory analysis will present the distribution of the magnitude of change, time point of first 25% change (clinical definition of meaningful change according to this analysis plan), and the time points of the maximum change. It is anticipated that a small proportion of the eyes will exhibit a potentially meaningful change from 8am to 4pm. Since the proportion is expected to be small, exploratory analysis will be conducted on an individual eye level.

For each eye with a relative change in retinal thickening from 8am to 4pm of at least 25%, a secondary analysis will sequentially compare each subsequent time point to 4pm beginning with 2pm to determine if and when equivalence between two time points is met. If equivalence is met the next time point will be tested to determine if equivalence is sustained. The process will continue until two time points are not equivalent.

3.2.2 Reproducibility

Multiple OCT measurements are being obtained on each eye at each time point to assess reproducibility. The primary aim of the reproducibility analysis is to estimate the variance (or standard deviation) of an observed OCT measurement in order to determine the magnitude of observed change in OCT measurements required to have reasonable certainty that the change is real and not due to the variability of the measurements. Only repeated measurements taken by the same operator will be included in this analysis. This will reduce the additional source of variation associated with different operators. The reproducibility analysis will allow the construction of a confidence interval around the true retinal thickness measured on OCT for each eye and the estimation of a confidence interval around a change between two measurements.

There is speculation that the variance of the OCT measurements will depend on the thickness of the retina. Therefore, additional reproducibility analysis will be conduced separately for each retinal thickness subgroup: (225 to 300 microns, 301 to 450 microns, and >450 microns).

To assess inter-observer variability, the standard deviation will be estimated as the square root of the mean square error from a least squares model with OCT central thickness as the independent variable and subject, time, and subject-time interaction as the fixed effect dependent variables.

Since several subjects will have two eyes in the study, a fixed eye effect nested within subject effect and the nested effect and time interaction will be explored.

The standard deviation of the difference between two measurements will be computed as the square root of two, times the standard error of measurement obtained above.

Bland-Altman plots graphing the differences in measurements against the measurement means will also be presented.

Additional analysis will estimate the intra-class correlation between the two measurements from the same observer.

Tabulations on the distribution of the amount of difference will also be presented.

This reproducibility technique will be repeated on all eyes with 8am thickness < 225.

The analysis for inter-observer reproducibility will mimic the analysis for the intra-observer reproducibility. The inter-observer analysis will include measurements at time points that were obtained by two different observers.

3.2.2.1 Estimate for Standard Deviation of Change

As described above, the estimated margin of error between two measurements on the same eye at the same time point will be reported as sqrt(2)*1.96*(Estimated standard deviation). The table below represents the magnitude of the ratio between the true margin of error and the estimated margin of error.

In estimating the confidence interval for the estimate of the standard deviation for change, the following assumptions have been made:

- Total Sample Size: N = 100 patients, 200 eyes
- 20% of patients will have two study eyes.
- All eyes measured twice at 6 time points
- 80% of the duplicate measurements made by the same observer, 20% made be different observers.

Confidence Interval for σ/S

Inter-Observer		**Intra-Observer**	
Study Eyes (N= 576 pairs)	**Nonstudy Eyes (N= 384 pairs)**	**Study Eyes (N= 144 pairs)**	**Nonstudy Eyes (N= 96 pairs)**
(0.95, 1.06) The estimate of the SEM will be within 5% less and 6% more than the true value.	(0.93, 1.08) The estimate of the SEM will be within 7% less and 8% more than the true value.	(0.90, 1.13) The estimate of the SEM will be within 10% less and 13% more than the true value.	(0.88, 1.16) The estimate of the SEM will be within 12% less and 16% more than the true value.

REFERENCES

1. Frank RN, Schulz L, Abe K, Iezzi R. Temporal Variation in Diabetic Macular Edema Measured by Optical Coherence Tomography. American Academy of Ophthalmology 2004; 111:211-17.
2. Sternberg PJ, Fitzke F, Finkelstein D. Cyclic Macular Edema. Am J Ophthalmol 1982; 94:664-9.