A Novel Color Vision Test for Detection of Diabetic Macular Edema

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PURPOSE. To determine the sensitivity of the Seoul National University (SNU) computerized color vision test for detecting diabetic macular edema.

METHODS. From May to September 2003, a total of 73 eyes of 73 patients with diabetes mellitus were examined using the SNU computerized color vision test and optical coherence tomography (OCT). Color deficiency was quantified as the total error score on the SNU test and as error scores for each of four color quadrants corresponding to yellows (Q1), greens (Q2), blues (Q3), and reds (Q4). SNU error scores were assessed as a function of OCT foveal thickness and total macular volume (TMV).

RESULTS. The error scores in Q1, Q2, Q3, and Q4 measured by the SNU color vision test increased with foveal thickness (P < 0.05), whereas they were not correlated with TMV. Total error scores, the summation of Q1 and Q3, the summation of Q2 and Q4, and blue-yellow (B-Y) error scores were significantly correlated with foveal thickness (P < 0.05), but not with TMV.

CONCLUSIONS. The observed correlation between SNU color test error scores and foveal thickness indicates that the SNU test may be useful for detection and monitoring of diabetic macular edema.

Keywords: color vision, diabetic macular edema, optical coherence tomography, foveal thickness

Diabetic macular edema is a major cause of visual loss in diabetic patients.1 Although there have been significant advances in the treatment of diabetic macular edema, for patients to obtain the maximum benefit from treatment, it is necessary to develop a screening test to enable early diagnosis of diabetic macular edema. Early detection of diabetic macular edema is important because effective treatments, such as intravitreal anti-VEGF injection, have been emerging, and long-standing macular edema causes irreversible vision loss.2 Macular edema is not easy to detect through routine ophthalmological examination.3 Fluorescein angiography (FAG) carries the risk of allergic reaction to fluorescein and the required setup is not always available.4 Optical coherence tomography (OCT) is a relatively new noninvasive and noncontact transpupillary imaging technology that is used to visualize and measure anatomical layers of the retina and optic disc.5–7 OCT is not always available, although it is very sensitive for detection of macular edema8 and it is expensive.9 Thus, it could be very useful to study the association between color vision and macular thickness and volume. Color vision testing can be a very good screening test because it is easy and fast.10 Tritan (blue-yellow [B-Y]) color vision has been reported to be reduced in diabetic patients.11,12 Defective color vision in diabetic patients has been described to be associated with severity of diabetic retinopathy and macular edema.13–17 Several studies have reported decreased B-Y hue discrimination in diabetic patients on the Farnsworth-Munsell 100 hue test17–19; however, the test takes a long time to complete and is hard to perform.1,11,12 Recently, we quantified and classified color vision abnormality using the Seoul National University (SNU) Computerized Color Test.20,21 The SNU color vision test uses pseudoisochromatic plates displayed on a computer monitor to measure the degree of red, green, blue, and yellow color vision abnormality. In addition, the SNU color vision test is fast and easy to perform. In our previous study, the SNU color vision test has been reported to be useful in classification of congenital color vision defect20 and in discrimination between congenital color vision defect and acquired color vision defect with high sensitivity and high specificity.22 The SNU color vision test revealed that the total error scores increased depending on the severity of diabetic retinopathy.21 The incidence of diabetic macular edema increases as diabetic retinopathy progresses.23 Thus, in this study, we evaluated the efficacy of our color vision test to screen for diabetic macular edema by analyzing the relationships between the degree of color vision abnormality and macular thickness or volume as measured by OCT.

METHODS

The protocol and informed consent forms were approved by individual sites’ institutional review boards and adhered to the
tenets of the Declaration of Helsinki. Participants in the study had diabetes mellitus. Diabetes was diagnosed according to the American Diabetes Association and/or World Health Organization criteria.

Briefly, these criteria include oral glucose tolerance test or fasting plasma glucose of 126 mg/dL or higher, or classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose of 200 mg/dL or higher, or glycated hemoglobin (HbA1c) threshold of 6.5% or higher. Exclusion criteria were cataract, glaucoma, uveitis, epiretinal membrane, tractional retinal detachment, age-related macular degeneration, other ocular surgical history, refractive errors exceeding 6.50 spherical diopters or 3.00 cylindrical diopters and visual acuity less than 20/40. Best-corrected visual acuity was measured with the Snellen chart adjusted for a 6.1 m viewing distance for each patient according to a standard protocol and was converted to logarithm of the minimal angle of resolution (logMAR) visual acuity. Participants were tested with the SNU color vision test and underwent OCT. OCT scans were obtained from both eyes of these subjects at six time points between 8 AM and 4 PM by a certified operator using the Stratus OCT system (Carl Zeiss Meditec, Inc., Dublin, CA). Only the right eye of each patient with diabetes mellitus was used for this study.

SNU Color Vision Test

The program used in the development of the computerized hue test was Matlab 6.0 (MathWorks, Natick, MA), an application program for multimedia production. The software provided various colors and enabled these to be edited together with the sound information in a Microsoft Windows environment. On-screen instructions were given. The computer display specifications included a graphic card with a resolution greater than 75 Hz and color temperature of approximately 9000 to 9700 K, corresponding to daylight color. Matlab 6.0 (MathWorks) can express 360 hues, 100 lightness differences, and 100 saturation differences. The SNU color vision test is a pseudoisochromatic test comprising 80 plates of 4 pictures. The pictures are composed of dots and take the form of a cross, circle, triangle, or blank. HSV color space coordinates were used. Each plate has a fixed lightness, but varying saturation and hue. The values for saturation vary between 5% and 50% (5%, 10%, 20%, 30%, 40%, and 50%), whereas those for hue vary between 0° and 330° (0°, 30°, 45°, 60°, 75°, 90°, 120°, 150°, 180°, 210°, 225°, 240°, 255°, 270°, 300°, and 330°), and there are three fixed values for lightness (35%, 50%, and 65%; Fig. 1). The lightness of each color is adjusted to prevent subjects with defective color vision from discriminating between pictures by light and dark. The subjects identify the test picture by selecting the one picture from a choice of four that corresponds to the test picture. The screens are displayed in random order. On completion of the test, the error score and test results are calculated and displayed, and a graph of the results is produced (Fig. 2). The SNU color vision test system can perform all of the result calculations and analysis as well as displaying and printing the test results.

During the SNU color vision test, the examinee sat comfortably at a 60-cm distance (arm’s length) from the monitor screen. The screen was standardized at 90% contrast and 80% brightness in a bright room without direct sunlight, and the test time was limited to 2 minutes for each of the 80 plates. It takes 10 minutes to administer. In all tests, the examinee was informed about the test procedure by an examiner and then performed the test. The total error score was defined as the sum of all error scores. Previous studies have shown that individuals with normal color vision typically...
To quantify type and severity of color vision defect, the color circle of hues used on the SNU test were divided into four quadrants (Q1–Q4) corresponding to different colors; Q1: yellowish hues 30–90, Q2: greenish hues 120–180, Q3: bluish hues 210–270, and Q4: reddish hues: 300–0; see Fig. 2). Error scores were computed for individual quadrants (Q1–Q4), the sum of Q1 and Q3, the sum of Q2 and Q4, and as a B-Y error score defined as the sum of error scores at hues 45, 60, 75 (yellows), and 225, 240, and 255 (blues).

Optical Coherence Tomography

The OCT measurements were performed in a dim room after pupil dilatation with tropicamide (50 mg/10 mL) drops. The pupils were dilated to at least 5-mm diameter before measurements commenced. The OCT examination was analyzed with version 4.1 software (Carl Zeiss Meditec, Inc.). Macular measurements were performed in accordance with the Early Treatment of Diabetic Retinopathy Study (ETDRS) macular mapping protocol. This consists of six individual line scans regularly arranged in a radial pattern with a default scan length of 6 mm. Each line scan was composed of 128 individual A-scans, so that a 6-mm diameter macular area was sampled at 768 separate points. An internal-fixation target was used in all scans, with the location of each scan on the retina monitored using an infrared-sensitive video camera. Scans were performed using default axial length (24.46 mm) and refractive errors for consistency with usual clinical practice. The patients were asked to fixate on an internal target and the operator centered the macular scans on the foveal pit. The scans were accepted if free of artifacts (boundary errors and decentration), and if complete cross-sectional images were seen for all individual line scans. Retinal thickness was automatically determined by the instrument software as the distance between the internal limiting membrane and the RPE. Total macular volume (TMV) was automatically calculated by the software. Foveal thickness was measured by the software at the cutting point of the six individual line scans.

Statistics

Correlations were analyzed using Spearman’s rank correlation coefficient. Statistical significance was based on two-tailed statistical analyses, and probability values less than 0.05 were considered statistically significant. Snellen visual acuity was analyzed using logMAR. To assess test sensitivity and specificity, receiver operating characteristic curves (ROCs) were constructed. The area under the ROC curve (AUC) was used to compute SNU test sensitivity and specificity (SPSS 15.0 for Windows; SPSS, Inc., Chicago, IL). A two-sample t-test assuming unequal variances was performed to compare the patients with macular edema with the patient without macular edema.

RESULTS

Data were analyzed from a total of 73 eyes of 73 patients (29 men and 44 women). The mean age was 59.18 ± 10.48 years. Average logMAR visual acuity was −0.05 ± 0.12, average foveal thickness was 203.20 ± 32.29 μm, and average macular volume was 7.21 ± 0.71 mm³. The mean total error score was 20.95 ± 13.89. Thirty eyes had no diabetic retinopathy. Of the rest, mild nonproliferative diabetic retinopathy (NPDR) was seen in 16 eyes, moderate NPDR in 14 eyes, and severe NPDR in 9 eyes; proliferative diabetic retinopathy (PDR) was found in 5 eyes. Eleven eyes of patients (15.07%) showed visible macular edema confirmed by fluorescein angiography or fundus biomicroscopy.
The error scores were significantly different over the four quadrants (repeated measures ANOVA, $F_{3,237} = 45.24, P < 0.01$). Post hoc paired $t$-tests indicated that Q1 error scores (yellow) were higher than Q3 (blue; $P < 0.02$), Q3 (blue) were higher than Q2 (green; $P < 0.01$), and Q2 (green) were higher than Q4 (red; $P < 0.01$). The sum of Q1 and Q3 error scores increased as foveal thickness increases.

**Color Vision Defect by SNU Color Vision Test**

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Total error scores were not significantly associated with LogMAR visual acuity was not correlated with foveal thickness (P = 0.094, r = −0.205, Spearman correlation test). The error scores in Q1, Q2, Q3, and Q4 measured by the SNU color vision test increased with foveal thickness (P = 0.010, 0.002, 0.001, and 0.003, respectively; Figs. 3A-D). The sums of Q1 and Q3 and the sums of Q2 and Q4 showed a positive correlation with foveal thickness (P = 0.002 and 0.001, respectively; Figs. 3E, 3F). B-Y error scores and total error scores were positively correlated with foveal thickness (P = 0.001 and 0.006, respectively; Figs. 3G, 3H).

**Color Vision and Total Macular Volume**

LogMAR visual acuity was not correlated with TMV (P = 0.372, r = −0.111, Spearman correlation test). There was a significant association between TMV groups and foveal thickness groups (P = 0.000); however, the error scores in Q1, Q2, Q3, and Q4 measured by the SNU color vision test did not show any correlation with TMV (P = 0.235, 0.145, 0.188, and 0.288, respectively; Figs. 4A-D). The sums of Q1 and Q3 and the sums of Q2 and Q4 did not show any positive correlation with TMV (P = 0.231 and 0.138, respectively; Figs. 4E, 4F). B-Y error scores were positively correlated with TMV (P = 0.006; Fig. 4G). Total error scores were not significantly associated with TMV (P = 0.14; Fig. 4H).

**Detecting the Presence of Macular Edema**

Error scores in the patients with diabetic macular edema were significantly higher compared with patients without diabetic macular edema in Q1 (P < 0.001; Fig. 5A), Q2 (P = 0.001; Fig. 5B), Q3 (P < 0.001; Fig. 5C), Q4 (P = 0.006; Fig. 5D), the sums of error scores of Q1 and Q3 (P < 0.001; Fig. 5E), the sums of error scores of Q2 and Q4 (P = 0.001; Fig. 5F), B-Y error scores (P < 0.001; Fig. 5G) and total error scores (P < 0.001; Fig. 5H).

In ROC curve analysis (Fig. 6), the AUC was 0.851 (95% confidence interval [CI], 0.725–0.976) for foveal thickness, 0.826 (0.653–1.000) for total macular volume, 0.849 (95% CI, 0.741–0.957) for the sum of Q1 and Q3, 0.792 (95% CI, 0.646–0.938) for the sum of Q2 and Q4, 0.822 (95% CI, 0.701–0.944) for B-Y error scores, and 0.817 (95% CI, 0.694–0.939) for total error scores. The sensitivity and specificity of the SNU color test to detect diabetic macular edema is shown in the Table.

**DISCUSSION**

In this study, we used the SNU color vision test to evaluate color vision defects in diabetic patients. The SNU color vision test is a pseudoisochromatic plate test and has several advantages. First, it is easier and quicker to administer than hue discrimination tests. It has been reported to take more than 10 minutes per eye for the Farnsworth-Munsell 100 hue test and 2 minutes for Lanthony Desaturated D-15. Second, unlike traditional pseudoisochromatic plate tests and hue discrimination tests, the SNU color vision test is not affected by illumination because the colors are viewed on a computer screen. Last, it can be used to evaluate B-Y vision abnormality because it includes many blue and yellow plates, which is not the case for other pseudoisochromatic plate tests. The SNU color vision test has been reported to be useful in acquired color vision defects and congenital color vision defects showing high sensitivity and high specificity.

The present study is the first to investigate the relationships between foveal thickness, TMV, and color vision. A significant
correlation was found between total SNU color vision test error scores and foveal thickness, but not TMV. A significant correlation was found between error scores in all quadrants and foveal thickness. The sums of Q1 and Q3 as well as the sums of Q2 and Q4 were correlated with foveal thickness. Although degree of severity of diabetic retinopathy is associated with color vision abnormality, macular edema may be a more likely cause of these abnormalities.

Tritan color vision (B-Y color vision) has been well known to be impaired in diabetic patients. Tritan color vision abnormality in diabetic patients has been explained by four mechanisms. First, S-cone sensitivity loss in diabetic patients has been shown to be correlated with both level of retinopathy and degree of macular edema. Second, short-wavelength visual evoked potential latency is delayed in diabetic patients. A change or deficit in the short-wavelength chromatic pathway that is responsible for B-Y color discrimination has been described. Third, macular edema reduces the transmission of light to the photoreceptors. This may affect the blue rather than the red-green mechanism as a result of the lower density and number of blue cones in the human fovea. A final possible explanation for the tritan color defect might be the oblique orientation of the S cone photoreceptors. In showing that, not only tritan color vision defects, but also protan and deutan defects are measureable with the SNU color vision test in patients with diabetic macular edema. Furthermore, protan and deutan color vision defects were correlated with foveal thickness, but not TMV. The computer-based SNU color vision test may be more sensitive to subtle protan- and deutan-acquired defects. The series of plates uses a combination of various saturations and three fixed lightness levels at each color direction, which may be contributory to the enhanced sensitivity at various color directions.

In this study, macular volume was correlated with B-Y error scores only (Fig. 4). B-Y error scores were significantly correlated with macular volume as well as foveal thickness. These results suggest that B-Y error scores could be more useful for detection of macular edema. Error scores measured by the SNU color test were higher in patients with macular edema compared with patients without macular edema (Fig. 5). The ROC curve showed that AUC of Q13 and B-Y error scores was large. The most commonly used global index of diagnostic accuracy is the AUC. We revealed the sensitivity and specificity of the SNU color vision test for detection of macular edema in the Table. This study included 11 eyes with diabetic macular edema (positive cases) and 62 eyes without macular edema (negative cases), which is a sufficient number for ROC analysis (MedCalc, version 12.7.4; MedCalc Software, Ostend, Belgium). The most commonly used global index of diagnostic accuracy is the AUC. Values of AUC close to 1.0 indicate that the marker has high diagnostic accuracy, and the larger the AUC, the better the overall diagnostic performance to correctly identify diseased and nondiseased patients. ROC analysis showed that the AUC of Q13 and B-Y error scores was large, exemplifying the high sensitivity and specificity of the SNU color test.

To eliminate the effect of visual acuity, our study criteria specified a visual acuity of 20/40 or better. This may have resulted in the exclusion of patients with severe ischemic maculopathy or severe macular edema. However, the point of this study was that the color vision abnormality can be a screening tool for diabetic macular edema even though the color vision abnormalities may be associated with visual acuity. In this study, we did not consider the macular perfusion state by fluorescent angiography and the shape of the edematous

<table>
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<tr>
<th>Cutoff Values, Error Scores</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
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<tr>
<td>Q1, yellowish hues</td>
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<tr>
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<td>Q3, bluish hues</td>
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<td>B-Y error scores</td>
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<td>Total error scores</td>
<td>&gt;27</td>
<td>66.7</td>
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Figure 6. Receiver operating characteristic curves for foveal thickness, total macular volume, B-Y error scores, the sum of error scores of quadrants I (Q1) and III (Q3), and the sum of quadrants II (Q2) and IV (Q4).
macula. There is a need for further studies in subjects to investigate color vision changes with fluorescent angiography and the shape of the edematous macula to determine the relationship between color vision and macular state.

OCT is a high-resolution technique that permits cross-sectional visualization of the retinal structure. OCT has been used for the detection and the analysis of clinically significant macular edema (CSME) with high sensitivity and high specificity. The resolution of OCT has been improved. In this study, we used time-domain OCT, which provided the axial resolution of 10 μm.

The limitations of this study are that it does not include patients with macular edema without diabetic retinopathy. In our previous study, the color vision defect depending on the severity of diabetic retinopathy was revealed. However, it is not clear whether the color vision defect in diabetic patients is due to diabetic macular edema, or due to abnormality of other visual pathways. In this study, we found that the color vision defects measured by the SNU color vision test are related to the macular edema. We could not perform the SNU color vision test repeatedly, because the test is time-consuming and requires high concentration, similar to the Farnsworth-Munsell 100 hue test. However, our previous studies have proven that the SNU color vision test is useful in a variety of clinical situations. This study does not include subjects without diabetes, which is another limitation of this study. However, our previous study showed the score errors in the healthy subjects were zero. In our previous study, the mean age of healthy subjects was 29 years (range, 19–36 years). Further study is necessary to investigate the influence of age on results of the color vision test. In this study, only diabetic patients were enrolled. In addition, we evaluated only the possibility of a novel color test as a screening test for detection of macular edema. The patients with visual acuity of better than 20/40 were enrolled.

This study represents a preliminary investigation of the feasibility of using a color vision test to screen for diabetic macular edema, by comparing the degree of color vision abnormality with macular thickness or volume measured by OCT. In conclusion, in diabetic patients, color vision error scores measured by the SNU test were correlated with foveal thickness and were significantly greater in patients with definite macular edema. The SNU color vision test promises to be useful for detecting and monitoring the progression of diabetic macular edema.

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References


