Original Article

Color vision abnormalities in type II diabetes: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study II report no 2

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Purpose: The purpose of this study is to assess color vision abnormalities in a cohort of subjects with type II diabetes and elucidate associated risk factors. **Methods:** Subjects were recruited from follow-up cohort of Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study I. Six hundred and seventy-three eyes of 343 subjects were included from this population-based study. All subjects underwent detailed ophthalmic evaluation, including the Farnsworth-Munsell 100 hue test. **Results:** The prevalence of impaired color vision (ICV) was 43% (CI: 39.2–46.7). Risk factors for ICV were higher heart rate (odds ratio [OR]: 1.043, [1.023–1.064]) and a higher intraocular pressure (IOP) (OR: 1.086, [1.012–1.165]). Subjects with clinically significant macular edema (CSME) had three times higher chance of having ICV. C1, C2, and C3 are the commonly found Early Treatment Diabetic Retinopathy Study (ETDRS) patterns. The moment of inertia method showed that the angle did not reveal any specific pattern of color vision defect. Although the major and minor radii were high in those with ICV, we did not observe polarity. Confusion index was high in subjects with ICV, indicating a severe color vision defect. **Conclusions:** The prevalence of ICV was 43% among subjects with type II diabetes. The most commonly observed patterns were increasing severities of the blue–yellow defect on ETDRS patterns, but no specific pattern was observed at the moment of inertia analysis. The presence of CSME, a higher heart rate, and IOP was significant risk factors for ICV. This functional impairment in color vision could significantly contribute to morbidity among subjects with diabetes.

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Despite effective treatment, diabetic retinopathy (DR) remains the leading cause of legal blindness and moderate visual impairment among the working age group.[1-4] Various studies have reported that patients with diabetes exhibit acquired impaired color vision (ICV), the inability to discriminate between hues.[5-8]

The Farnsworth-Munsell 100 (FM 100) hue test is a widely used panel test for evaluating color vision defects.[9,10] The moment of inertia method described by Vingrys and King-Smith[11] is a quantitative scoring method for panel tests. Previous studies, both clinic[6-8] and population based[5,8] have shown an association between ICV and diabetes, with or without retinopathy. However, further quantification of the ICV was not done. Of the few epidemiological studies from India on DR, none have looked at ICV in subjects with diabetes.[12,13] We previously reported the prevalence and the risk factors for ICV in subjects with diabetes but without DR.[14]

The aim of the present study was to assess color vision abnormalities using the FM 100 hue test, quantifying it based on classical and moment of inertia methods, and to assess associated risk factors in subjects with type II diabetes in both, the presence and in the absence of DR in a population-based study.

Methods

The Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS II) was a follow-up to SN-DREAMS I[13] conducted between 2007 and 2010. Of the 958 subjects followed in the study, 673 eyes of 343 subjects had undergone the FM 100 hue test. Exclusion criteria included a best-corrected visual acuity (BCVA) worse than 6/12 and unwillingness or inability to understand and perform the FM 100 hue test. The Ethics Committee and Institutional Review Board of Vision Research Foundation approved the study and written informed consent was obtained from all subjects in accordance with the Helsinki Declaration.

Demographic information and medical and ocular histories were obtained for all subjects, and all underwent a comprehensive eye examination. Lens opacity was graded

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by ophthalmologists, using the Lens Opacity Classification System (LOCS) III system.[15] After the pupils were dilated with tropicamide (1%) and phenylephrine hydrochloride (2.5%) drops (instilled twice, if necessary), each subject's eyes were examined with a slit lamp (SL-120; Carl Zeiss Meditec, Jena, Germany). Comparing each eye with the LOCS III standard photographs (mounted close to the slit lamp), the examiner identified specific lens opacities and assigned severity grades. The lens opacities were separated into four major groups according to the photographic standards as follows: nuclear opalescence (NO), nuclear color (NC), cortical cataract (CC), and posterior subcapsular cataract (PSC). Intergrader agreement was determined by having both graders assess the eyes of 50 patients recruited from the pilot study who had various grades of cataract. The grading agreements were as follows: NO (k = 0.87), NC (k = 0.83), CC (k = 0.89), and PSC (k = 0.81). The overall average grading agreement was high (k = 0.85). A significant NC was identified by the presence of an LOCS III score of >4 for NO or >4 for NC. Similarly, a significant CC was identified by an LOCS III score of >2 for CC, and a significant PSC was identified by an LOCS III score of >2 for PSC.[16,17]

DR was graded clinically using Klein's classification (Modified Early Treatment Diabetic Retinopathy Study (ETDRS) scales).[18] Retinal photographs were obtained after pupillary dilatation using Carl Zeiss FF 450 Plus IR Fundus Camera; all patients underwent 45°, 4-field stereoscopic digital photography (posterior pole, nasal, superior, and inferior). For those with any evidence of retinopathy, additional 30°, 7-field stereo digital pairs were obtained. All photographs were graded by two independent observers in a masked fashion; grading agreement was high (k = 0.83). None of the subjects had diabetic papillopathy.

Color discrimination was assessed monocularly with the FM 100 hue test, under the FM 100 hue viewing booth lighting condition developed by Zahiruddin *et al*.,[19] at a distance of 30 cm with near correction. The results were analyzed using web-based scoring software designed by Torok. The outcome parameter of the FM 100 hue test was total error score (TES) calculated based on the classical method. The parameters based on moment of inertia method[12] were as follows:

- Major and minor radius were derived from the color difference vectors plotted based on the cap arrangement by the individual subject
- Angle identifies the primary axis of color confusion
- Selectivity index (S-index) quantifies the amount of polarity or lack of randomness in a cap arrangement, calculated from the ratio of major and minor radii
- Confusion index (C-index) quantifies the degree of color loss relative to a perfect arrangement of caps and was derived by dividing the length of subject's maximum radius by the maximum radius obtained for a perfect arrangement of caps
- TES was calculated from the major and minor radii by obtaining the square root of their sum of squares.

Subjects were said to have ICV if the TES based on the classical method fell outside the 95th percentile for age, as published by Verriest *et al*.,[10] for monocular testing without previous binocular experience and normal otherwise. The critical values of TES for various age groups at 95% levels of confidence reported by Verriest *et al*.[10] are presented in Table 1.

Table 1: Age-related normal values of total error scores reported by Verriest *et al*.

Age (years)	Normal values (TES)
40-44	142
45-49	164
50-54	189
55-59	213
60-64	234
65-69	256
70-74	281
>75	317

TES: Total error score

Distribution of various ETDRS patterns of hue discrimination impairment was also analyzed.[20]

Statistical analysis

Statistical analyses were performed using the statistical software SPSS for Windows, ver. 15.0 (SPSS Science, Chicago, IL, USA). Normality of distribution was assessed using the Kolmogorov–Smirnov test. The results were expressed as mean ± standard deviation if the variables were continuous and as percentages if categorical. Student's t-test for comparing continuous variables and the Chi-square test for comparing proportions among groups were also used. A Mann–Whitney U-test was used to analyze the differences between variables that did not follow a normal distribution. Risk factors were assessed by multiple logistic regression. $P < 0.05$ was considered statistically significant.

Results

The mean age of the study subjects was 57.16 ± 8.55 years (range: 44–86 years). The gender-adjusted prevalence of ICV was 43% (confidence interval [CI]: 39.2–46.7) among type II diabetics in the total sample. Gender-adjusted prevalence of ICV among subjects with diabetes with no DR and those with DR was 42.7% (CI: 38.4–47) and 43.4% (CI: 35.9–50.9), respectively. Of the 26 subjects with ICV and cataract, 17 (6.7%) had CC, and nine (3.6%) had PSC. Table 2 presents a summary of various clinical and ophthalmic factors among subjects with type II diabetes with and without ICV. The proportion of men was significantly higher in those with no ICV (P = 0.017), and the proportion of women was higher in those with ICV (P = 0.017). Heart rate was marginally significantly higher in those with ICV (77.94 ± 10.02 ICV vs. 76.26 ± 9.54 no ICV; $P < 0.001$). Other systemic factors such as duration of diabetes, glycosylated hemoglobin, and systolic and diastolic blood pressure and serum lipids showed no association with the prevalence of ICV. Significant ocular factors were reduced BCVA (0.06 ± 0.11 ICV vs. 0.03 ± 0.09 no ICV; P = 0.003), the presence of PSC (3.6% ICV vs. 0.9% no ICV; P = 0.034), higher intraocular pressure (IOP) (14.51 ± 2.54 ICV vs. 14.06 ± 2.51 no ICV; P = 0.011) and a history of cataract surgery (no cataract surgery ICV 89% vs. cataract surgery ICV 11%; P = 0.012). Refractive error did not differ significantly between the groups (P = 0.568). The presence of DR was not associated with ICV, but the presence of clinically significant macular edema (CSME) (5.7% ICV vs. 1.5% no ICV; P = 0.003) and

Table 2: Summary of clinical and ophthalmic factors in those with and without color vision impairment in Type II diabetes

Risk factors	*n*=673	No ICV, *n* (%) 390 (57.9)	ICV, *n* (%) 283 (42.1)	*P*
Demographic and systemic risk factors				
Gender				
Men	402	248 (63.6)	154 (54.4)	0.017
Women	271	142 (36.4)	129 (45.6)	
Duration of diabetes	-	9.69±6.49	8.86±5.61	0.094
HbA1c	-	7.33±1.79	7.55±1.69	0.062
Systolic BP	-	132.67±19.22	132.96±20.11	0.800
Diastolic BP	-	77.42±9.34	77.23±10.46	0.608
Heart rate		76.26±9.54	77.94±10.02	<0.001
Serum total cholesterol	587	169.42±45.24	173.99±43.59	0.187
Serum HDL	587	37.91±10.58	36.43±9.13	0.104
Serum triglycerides	584	123.90±91.10	130.41±102.01	0.567
Ocular risk factors				
Visual acuity (logMAR)	673	0.03±0.09	0.06±0.11	0.003
Refractive error (spherical equivalent)		0.47±1.76	0.50±2.17	0.568
Intraocular pressure		14.06±2.51	14.51±2.54	0.011
Presence of cataract (LOCS III grade)				
None	511	289 (90.3)	222 (88.1)	0.394
Any	61	31 (9.7)	30 (11.9)	
Monotype				
NC	1	1 (0.3)	0 (0.0)	1.000
CC	36	19 (5.9)	17 (6.7)	0.518
PSC	12	3 (0.9)	9 (3.6)	0.034
Mixed				
NC + CC	6	4 (1.3)	2 (0.8)	1.000
NC + PSC	2	0	2 (0.8)	1.000
CC + PSC	0			
NC + CC + PSC	4	4 (1.3)	0	1.000
Cataract surgery				
No	572	320 (82.1)	252 (89.0)	0.012
Yes	101	70 (17.9)	31 (11.0)	
Diabetic retinopathy				
No DR	506	295 (75.9)	211 (74.6)	0.748
Any DR	145	89 (22.8)	56 (19.7)	0.334
Mild DR	61	42 (10.8)	19 (6.7)	0.070
Moderate DR	60	35 (9.0)	25 (8.8)	0.950
Severe NPDR	7	5 (1.3)	2 (0.7)	0.705
PDR	17	7 (1.8)	10 (3.5)	0.156
Presence of CSME	22	6 (1.5)	16 (5.7)	0.003
STDR	46	18 (4.6)	28 (9.9)	0.007

LogMAR: Logarithm of the minimum angle of resolution, LOCS: Lens Opacity Classification System, HBA1c: Glycosylated hemoglobin, ICV: Impaired of color vision, BP: Blood pressure, HDL: High density lipoprotein, NC: Nuclear color, CC: Cortical cataract, PSC: Posterior sub capsular cataract, DR: Diabetic retinopathy, NPDR: Nonproliferative diabetic retinopathy, PDR: Proliferative DR, CSME: Clinically significant macular edema, STDR: Sight threatening diabetic retinopathy; Continuous variables were assessed by Mann-Whitney U-test

sight-threatening DR (includes severe nonproliferative DR [NPDR], proliferative DR, and CSME) (9.9% ICV vs. 4.6% no ICV; $P = 0.007$) was significant factors associated with ICV.

Table 3 presents multiple logistic regression analysis of risk factors for the presence of ICV in the study population. After adjusting for other significantly associated factors, it was shown that higher heart rate (odds ratio [OR]: 1.043, [1.023–1.064]) and a higher IOP (OR: 1.086, [1.012–1.165]) were associated with ICV. Subjects with CSME were three times more likely to have ICV (OR: 3.41 [1.19–9.72]).

Fig. 1 shows the distribution of 13 ETDRS patterns of hue discrimination impairment in our study sample. The most common were C3 (28.7%), C2 (19%), and C1 (12.1%). Most of our subjects were found to have a blue–yellow color defect.

Table 3: Multiple logistic regression model for risk factors for impairment of color vision in the study population

Risk factors	Adjusted	
	OR (95% CI)	*P*
Gender		
Men	1	
Women	1.40 (0.975-2.01)	0.067
PSC	2.24 (0.766-6.55)	0.141
Heart rate	1.043 (1.023-1.064)	<0.001
IOP	1.086 (1.012-1.165)	0.022
Diabetic retinopathy		
No DR	1	
Mild DR	0.72 (0.38-1.36)	0.252
Moderate DR	0.81 (0.44-1.51)	0.361
Severe NPDR	0.00 (0.00-0.00)	0.999
PDR	2.19 (0.70-6.80)	0.161
Presence of CSME	3.41 (1.19-9.72)	0.030
Visual acuity (logMAR)	2.68 (0.36-19.86)	0.335

Cataract surgery and PSC were collinear, so cataract surgery was automatically removed by the model. PSC: Posterior subcapsular cataract, IOP: Intraocular pressure, DR: Diabetic retinopathy, NPDR: Nonproliferative diabetic retinopathy, CSME: Clinically significant macular edema, LogMAR: Logarithm of the minimum angle of resolution, OR: Odds ratio, CI: Confidence interval, PDR: Proliferative DR

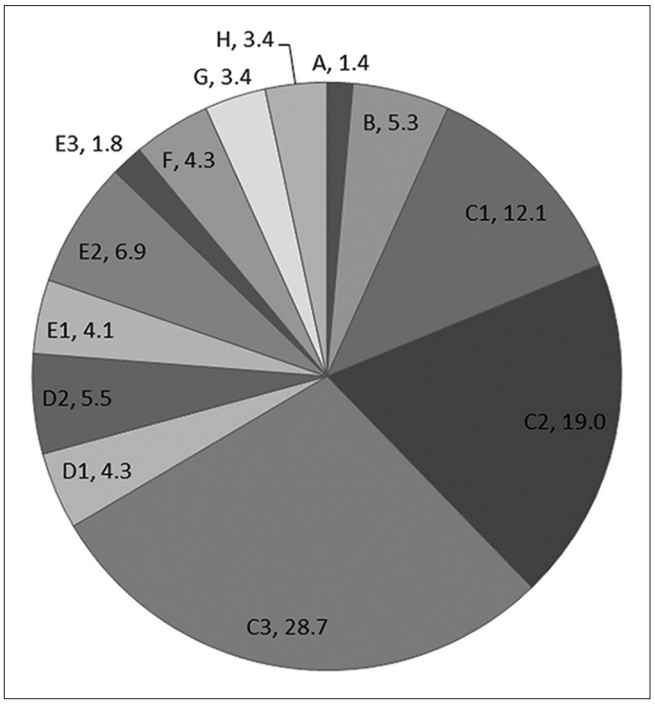

Figure 1: Distribution of Early Treatment Diabetic Retinopathy Study patterns of hue discrimination impairment

Table 4 shows color vision characteristics based on the moment of inertia method in our sample. The angle of maximum radius was similar in all groups. Because of the random nature of cap placement, our sample did not show any specific trend (protanope, deuteranope, and tritanopia defects) of color vision defects. There was a statistically significant difference in angle between normal and abnormal color vision (69.7 ± 9.5 vs. 54.8 ± 3.9, $P = 0.039$) in severe NPDR. Both major and minor radii were high in those subjects with ICV in all subgroups; however, we did not observe polarity (S-index was not statistically significant between normal and abnormal ICV groups). However, in subjects with no DR, there was a statistically significant difference in the S-index between the normal and abnormal color vision groups (1.5 ± 0.3 and 1.6 ± 0.3, respectively). Table 3 also shows a higher C-index in subjects with abnormal color vision in all subgroups, suggesting a severe color vision defect. This table also shows moment of inertia analysis for the C1, C2, and C3 ETDRS patterns of hue discrimination impairment and these three patterns showed increasing radii, S- and C-index from C1 to C3.

Discussion

This population-based study found that the prevalence of ICV in subjects with type II diabetes was 42%; in subjects with diabetes but no retinopathy, the prevalence of ICV was 41.6%; and in subjects with retinopathy, it was 43%. Various studies reported that patients with DR exhibit deterioration in the ability to discriminate between hues.[6,21-23] Green *et al*.[6] reported a lower prevalence of ICV in subjects with diabetes with no retinopathy (24%) and a higher prevalence in subjects with retinopathy (40%). Similarly, Trick *et al*.[22] also reported the prevalence of ICV among diabetics with no retinopathy as 5.4% and among those with retinopathy as 10%. The difference in the prevalence rates of ICV across other studies and our study can probably be attributed to differences in color vision test methodology and analysis, as well as to differences in grading DR.

In the current study, we observed that a higher heart rate, a higher IOP, and the presence of CSME were associated with ICV. In our previous report on ICV in subjects with diabetes with no DR,[14] we observed that a higher heart rate and a higher IOP were associated with ICV. Nevertheless, heart rate is only 1.68 mmHg higher in those with ICV compared to those with no ICV. In addition, the IOP is still in the normal range in both the groups. Therefore, the clinical significance of this observation is not well understood and needs further evaluation. There was no significant association between refractive error and ICV in our study.

Although on univariate analysis, we found that women were at a higher risk of developing ICV than men, when adjusting for potential confounding factors on multiple logistic regression analysis, there were no significant gender differences. The previous studies did not observe any gender difference.[5,6,11,21,24] Eisner and Toomey[25] showed evidence suggesting that the estrogenic response affects the color naming of short-wavelength test stimuli presented on 580-nm backgrounds. Both types of estrogen receptor (ERα and ERβ) are present within the human retina;[26] but the roles of estrogen receptors for visual processing remain unknown.

With increasing age, yellow chromophores continuously accumulate inside the lens in nuclear cataract,[27] reducing the transmission of blue light to the retina, and resulting in blue-yellow color vision defects. Normal age-related color vision changes and those found in diabetic patients are predominantly seen in the blue–yellow color vision axis.

Table 4: Color vision characteristics based on moment of inertia method

Factors	CVI	*n*	Mean±SD					
			Angle	Major radius	Minor radius	TES	Selectivity index	Confusion index
Over all subjects	Normal	390	62.4±12.4	5.4±1.4	3.5±0.7	6.4±1.5	1.5±0.3	2.1±0.5
	Abnormal	283	63.4±14.0	8.6±1.7**	5.5±1.4**	10.2±2.1**	1.6±0.3*	3.4±0.7**
No DR	Normal	295	61.5±12.8	5.3±1.4	3.5±0.7	6.4±1.5	1.5±0.3	2.1±0.6
	Abnormal	211	62.2±13.6	8.5±1.8**	5.4±1.4**	10.1±2.1**	1.6±0.3*	3.4±0.7**
Any DR	Normal	95	65.2±10.9	5.4±1.4	3.5±0.6	6.4±1.5	1.5±0.3	2.1±0.5
	Abnormal	72	66.9±14.9	8.6±1.6**	5.7±1.5**	10.4±2.0**	1.5±0.2	3.4±0.7**
Mild DR	Normal	42	63.3±10.6	5.3±1.4	3.5±0.7	6.3±1.4	1.5±0.2	2.1±0.5
	Abnormal	19	62.7±17.3	8.6±1.7**	5.6±1.3**	10.3±1.9**	1.5±0.2	3.3±0.8**
Moderate DR	Normal	35	63.9±11.7	5.4±1.6	3.4±0.62	6.5±1.6	1.6±0.3	2.2±0.6
	Abnormal	25	63.0±14.9	8.6±1.7**	5.7±1.9**	10.3±2.5**	1.6±0.2	3.4±0.7**
Severe NPDR	Normal	5	69.7±9.5	5.7±0.6	3.7±0.6	6.8±0.8	1.5±0.1	2.3±0.2
	Abnormal	2	54.8±3.9*	8.6±1.5	5.6±0.3*	10.2±1.4	1.5±0.2	3.4±0.6
PDR	Normal	7	73.5±6.3	5.2±0.4	3.4±0.2	6.2±0.4	1.5±0.1	2.0±0.2
	Abnormal	10	78.5±6.0	9.5±0.9**	6.1±0.7**	11.3±1.1**	1.6±0.2	3.8±0.6**
CSME	Normal	6	72.8±11.2	6.2±1.8	3.7±0.8	7.2±1.9	1.6±0.2	2.4±0.7
	Abnormal	16	72.3±11.1	8.3±1.5*	5.5±1.3*	10.0±1.9*	1.5±0.2	3.2±0.7
C1	Normal	89	64.9±12.5	4.8±0.9	3.2±0.5	5.8±1.0	1.5±0.4	1.9±0.8
	Abnormal	19	65.3±7.6	6.8±0.9**	4.4±0.5**	8.1±0.9**	1.5±0.2	2.7±0.4**
C2	Normal	81	64.9±12.9	5.6±1.2	3.6±0.6	6.6±1.3	1.5±0.2	2.2±0.5
	Abnormal	39	65.6±16.5	7.7±1.1**	4.9±0.6**	9.1±1.1**	1.6±0.2	3.0±0.4**
C3	Normal	74	61.9±13.9	6.4±1.3	4.0±0.7	7.6±1.3	1.6±0.3	2.5±0.6
	Abnormal	92	61.8±14.3	8.7±1.7**	5.4±1.2**	10.3±1.8**	1.6±0.3	3.4±0.7**

Statistical significance (*<0.05, **<0.001). SD: Standard deviation, CVI: Cortical visual impairment, TES: Total error score, DR: Diabetic retinopathy, NPDR: Nonproliferative DR, CSME: Clinically significant macular edema, PDR: Proliferative DR

Ventruba[28] reported that color vision was significantly improved in subjects who underwent cataract surgery. Nevertheless, in our study, the presence of PSC and negative history of cataract surgery did not show significant association with ICV after adjusting for potential confounding factors.

Studies have reported that the incidence of abnormal color discrimination correlates with the severity of retinopathy.[6,29] In our study, the presence of CSME was a significant risk factor for ICV, independent of the cataract status. It has been hypothesized that the formation of new vessels may not adequately supply oxygen for the metabolic needs of the photoreceptors, resulting in death of photoreceptors and hence affecting color vision. Ventruba *et al*. attributed abnormal color discrimination to a reduction in the transmission of light to the photoreceptors[28] and indicated that this might affect the blue rather than the red–green mechanism because of the lower density and number of blue cones in the fovea.[30]

Patients with type II diabetes showed both generalized errors of color discrimination and specific patterns of the same. Although the most commonly found ETDRS patterns were C1, C2, and C3, representing increasing severities of the blue–yellow defect, moment of inertia analysis failed to reveal any specific angle representing the tritan axis defect, and no polarity was revealed by the S-index. Because of the random nature of cap placement, our sample did not show any specific pattern defect; but the higher C-index in subjects with abnormal ICV in all subgroups suggests a severe color vision defect. In addition, the patterns C1 to C3 represent an increasing the severity of defect, as seen by the increasing C-index.

The results of our study do not have any therapeutic significance. It emphasizes the presence of functional visual loss in subjects with diabetes, which may not be visible on routine clinical examination.

Our study was a population-based study. Since our research questions were essentially intended to examine for color vision abnormalities in people with type II diabetes, we did not include women with gestational diabetes in the study. However, this is an interesting area of study that needs further exploration.

The limitation of our study being conducted in a specific diabetic population could not extrapolate the results to more general diabetic population as the sample size was calculated to estimate the prevalence of DR rather than for the ICV. In addition, the results of our study represent correlations alone and not causation. In addition, we did not examine ICV in age-matched controls. This could be a potential limitation of our study.

Conclusions

In summary, ICV was commonly observed among subjects with diabetes, both with and without retinopathy. The most commonly found patterns were increasing severities of the blue–yellow defect on ETDRS patterns, but no specific pattern was observed with moment of inertia analysis. Various risk factors for ICV were higher heart rate and IOP and the presence

CSME. The present study also shows that the ETDRS patterns C1-C3 represent increasing the levels of color vision defects, as confirmed by the moment of inertia method. The high prevalence of ICV among diabetics suggests a possible need for occupational counseling.

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Conflicts of interest

There are no conflicts of interest.

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