

Contrast sensitivity and its determinants in people with diabetes: SN-DREAMS-II, Report No 6

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Abstract

Purpose To assess contrast sensitivity (CS) and to elucidate the factors associated with CS among subjects with type 2 diabetes in a cross-sectional population-based study.

Patients and methods Subjects were recruited from a follow-up cohort, Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular genetics Study (SN-DREAMS II). Of 958 subjects who were followed up in SN-DREAMS II, a subset of 653 subjects was included in the analysis. All subjects underwent a comprehensive eye examination, which included CS assessment using the Pelli–Robson chart. The cross-sectional association between CS and independent variables was assessed using stepwise linear regression analysis. A *P*-value of <0.05 was considered statistically significant.

Results The mean age of the study sample was 58.7 ± 9.41 (44–87) years. Mean CS of the study sample was 1.32 ± 0.20 (range: 0–1.65) log units. CS was negatively and significantly correlated with age, duration of diabetes, hemoglobin level, vibration perception threshold (VPT) value, albuminuria, best corrected visual acuity (BCVA), refractive error, total error score (TEM) of FM 100 hue test, and mean retinal sensitivity. In multiple regression analysis, after adjusting for all the related factors, CS was significantly associated with BCVA ($\beta = -0.575$; $P < 0.001$), VPT ($\beta = -0.003$; $P = 0.010$), severity of cataract ($\beta = -0.018$; $P = 0.032$), diabetic retinopathy ($\beta = -0.016$; $P = 0.019$), and age ($\beta = -0.002$; $P = 0.029$). These factors explained about 29.3% of the variation in CS.

Conclusion Among the factors evaluated, differences in BCVA were associated with the largest predicted differences in CS. This association of CS with visual acuity

highlights the important role of visual assessment in type 2 diabetes.

Eye (2017) 31, 460–466; doi:10.1038/eye.2016.252; published online 18 November 2016

Introduction

Retinopathy, the most frequent microvascular complication of diabetes, remains a leading cause of acquired blindness among working age adults.^{1,2} The prevalence of diabetic retinopathy (DR) is reported to be 18% among subjects with diabetes mellitus in the urban population in India.³ Earlier studies have shown that changes in the ganglion layer, inner retinal neurons, and peripheral network may be present in the asymptomatic stages of DR.^{4,5} There is evidence of thinning of the inner retina in patients with minimal retinopathy, caused primarily by a thinning of the ganglion cell layer in the pericentral area of the macula, and secondarily by thinning of the retinal nerve fiber layer more peripherally in the macula, because of axonal loss from the central ganglion cells.⁶

The characteristic ‘spatial tuning’ of ganglion cell receptive fields is reflected in peaked contrast sensitivity functions.⁷ The evaluation of contrast sensitivity in people with diabetes is important, as the reduction of contrast sensitivity can lead to difficulties in variety of tasks of daily living like stair descent, stair ascent, inserting a key in a lock, dialing a rotary telephone, face recognition and reading speed, and so on.^{8–11} Various studies have evaluated CS in diabetes with and without DR.^{12–18} Factors reportedly associated with abnormal CS in diabetes include age,^{12,13} visual acuity,¹⁴ duration of diabetes,¹³ glycosylated hemoglobin (HbA1c),¹⁴ and presence of DR.^{15,16} The reports are inconsistent as the studies varied in their methodology, that is, different techniques were

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Received: 22 January 2016
Accepted in revised form: 13 September 2016
Published online: 18 November 2016

used to assess the contrast sensitivity, study population was different as few studies included type 1 and others type 2 diabetes, few considered subjects without DR, and others with various stages of DR. And all the studies have not explored various systemic and ocular factors and their relation with the contrast sensitivity. The relationship between abnormal CS and vascular and metabolic abnormalities in diabetes has not been extensively studied in the Indian population.

The aim of the present study was to examine CS in a population-based cohort of subjects with type 2 diabetes and assess its correlation with systemic, biochemical, and ocular characteristics.

Patients and methods

Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS II) was a follow-up study of SN-DREAMS I.¹⁹ Among the 958 subjects followed in SN-DREAMS II, 653 subjects who have undergone contrast sensitivity test were included for the current analysis. Contrast sensitivity was not assessed in 146 subjects as they were illiterate. The study was approved by the organization's Institutional Review Board, and informed consent was obtained from the subjects in accordance with the Declaration of Helsinki. One eye of each subject was analyzed. If the subject did not have DR in either eye, the right eye was selected; if DR changes were seen in one eye, that eye was included; and if both eyes had evidence of DR, the eye with more severe DR grade was considered for analysis.

Demographic data and detailed medical and ocular history were obtained from each subject. The various factors included in the current study were further classified as demographic factors and systemic factors, such as duration of diabetes, HbA1c level, hypertension, hemoglobin, nephropathy, neuropathy, and lipid profile (serum total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein). Ocular parameters included are BCVA, refractive error, color vision, cataract status, DR status, central retinal thickness (CRT), photoreceptor layer thickness, and mean retinal sensitivity.

Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or a history of using antihypertensive medications. Biochemical investigations (total serum cholesterol, high-density lipoproteins, serum triglycerides, hemoglobin, and HbA1c) were conducted at the base hospital in a fasting state. The low-density lipoprotein was calculated using the modified Friedewald formula for the Indian population.²⁰ Glycemic control was categorized as normal (HbA1c $< 5.6\%$), good to fair (HbA1c 5.6–8.0%), or poor (HbA1c $> 8.1\%$).²¹ Anemia was defined as a hemoglobin concentration of < 13 g/dl in men or < 12 g/dl in

women.²² The patient was considered normoalbuminuric if albumin creatinine ratio (ACR) was < 0 mg/g, microalbuminuric if the ACR was between 30 and 300 mg/g, and macroalbuminuric if the ACR was above 300 mg/g.²³ Diabetic nephropathy was defined as present if the ACR is ≥ 30 mg/g.

Quantitative assessment of vibration perception threshold (VPT) is a widely applied tool in the screening for diabetic sensory neuropathy, particularly in epidemiological studies. Diabetic neuropathy was assessed by measuring VPT using a sensitometer (Sensitometer-VPT, Dhansai Laboratory, Mumbai, India). The VPT was measured by a single observer by placing a biothesiometer probe perpendicular to the distal plantar surface of the great toe of both legs. The VPT was measured at a voltage level when patient felt the first vibration sensation. The mean VPT measure of three readings for each leg was considered for the analysis. Diabetic neuropathy was considered present if the VPT value was > 20 V.²⁴

All subjects underwent a comprehensive ophthalmic examination. Contrast sensitivity was assessed using a Pelli-Robson chart²⁵ at 100 cd/m² measured at 1 m distance with the best corrected refractive error based on the subjective refraction performed on the same day. The logarithmic CS value of the last triplet of which at least two letters are correctly seen is marked as the result. Color discrimination was assessed using the Farnsworth-Munsell 100 (FM 100) hue test under viewing booth illuminated designed by Zahiruddin *et al*,²⁶ and the total error score (TES) was calculated. Lens opacity was graded according to the Lens Opacity Classification System (LOCS) III.²⁷ Cataract was graded as 'no cataract = 0, NC = 1, CC = 2, PSC = 3, Mixed = 4'. DR was graded clinically using Klein's classification (Modified Early Treatment Diabetic Retinopathy Study scales).²⁸ Severity of DR was coded as 'no DR = 0, mild non-proliferative diabetic retinopathy (NPDR) = 1, moderate NPDR = 2, severe NPDR = 3, proliferative DR = 4, clinically significant macular edema = 5' for the purpose of analysis. After pupillary dilatation retinal photographs were obtained with the Carl Zeiss FF 450 Plus IR Fundus Camera; all patients underwent 45°, 4-field stereoscopic digital photography (posterior, nasal, superior, and inferior poles). For those who showed evidence of any retinopathy, additional 30°, 7-field stereo digital pairs were obtained. All photographs were graded by two independent observers in a masked fashion; the grading agreement was high ($k = 0.83$).

Mean retinal sensitivity was assessed using MP1 microperimeter (Nidek Technologies, Padova, Italy); CRT and photoreceptor layer thickness (PRL) were assessed using spectral domain optical coherence tomography (Copernicus, Poland).

Statistical analysis

Statistical analyses were performed using the statistical software SPSS for Windows, ver.15.0 (SPSS Science, Chicago, IL, USA). Duration of diabetes for newly diagnosed subjects with diabetes was considered as 0. Contrast sensitivity was represented as mean ±SD. Both unadjusted and adjusted linear regression was performed for the variables with contrast sensitivity as a dependent variable. Stepwise linear regression was used for selection of variables for the multivariate model. The linearity assumption for variables included in the model as continuous factors was checked by visual inspection of scatter plots. A *P*-value of <0.05 was considered statistically significant.

Results

The mean age of the study sample was 58.7 ± 9.41 (44–87) years and 384 of the subjects (58.8%) were male. Mean duration of diabetes mellitus was 8.94 ± 6.24 (0–37) years and mean logMAR visual acuity of the study sample was 0.063 ± 0.14 (–0.10–1.3) log units. Mean CS of the study sample was 1.32 ± 0.20 (0–1.65) log units. Table 1 shows the distribution of CS among the demographic and systemic factors. CS was significantly reduced among the older age groups (*P* < 0.001). CS was noted to be significantly lower among subjects with a duration of diabetes of more than 5 years (1.30 ± 0.20 vs 1.36 ± 0.19; *P* < 0.001), subjects with anemia (1.29 ± 0.20 vs 1.34 ± 0.20; *P* = 0.002), those with neuropathy (1.26 ± 0.21 vs 1.34 ± 0.19; *P* < 0.001), those who were taking insulin (1.27 ± 0.16 vs 1.33 ± 0.20; *P* = 0.047), and those with poor glycemic control (*P* = 0.002).

Table 2 shows the distribution of CS among the ocular parameters. CS was significantly reduced in those with visual acuity worse than 0.00 logMAR (1.22 ± 0.22 vs 1.37 ± 0.17; *P* < 0.001), those with refractive error (1.30 ± 0.21 vs 1.35 ± 0.18; *P* = 0.003), and those with an abnormal color vision TES > 100 (1.31 ± 0.19 vs 1.36 ± 0.14; *P* = 0.047). Other ocular factors associated with a significantly reduced CS were the presence of cataract (*P* < 0.001), presence of DR (*P* = 0.003), and presence of sight-threatening DR (1.20 ± 0.20 vs 1.30 ± 0.19; *P* = 0.007).

Factors associated with reduced CS in univariate analysis were increased age ($\beta = -0.007$, *P* < 0.001), increased duration of diabetes ($\beta = -0.004$, *P* = 0.002), increased VPT score, that is, diabetic neuropathy ($\beta = -0.007$, *P* < 0.001), use of insulin ($\beta = -0.06$, *P* = 0.047), poor BCVA ($\beta = -0.695$, *P* < 0.001), increased severity of DR ($\beta = -0.029$, *P* < 0.001), presence of cataract ($\beta = -0.065$, *P* < 0.001), history of cataract surgery ($\beta = -0.079$, *P* < 0.001), and increased TES on the FM 100 ($\beta = -0.001$, *P* < 0.001). An increase in mean retinal sensitivity ($\beta = 0.021$, *P* < 0.001) and an increase in hemoglobin ($\beta = 0.012$, *P* = 0.002) were associated with increased CS.

Table 1 Contrast sensitivity by demographic and systemic factors

Variables	n	Contrast sensitivity mean ± SD	P-value
Mean contrast sensitivity (log units)	653	1.32 ± 0.20	NA
Age (years)			
40–49	128	1.40 ± 0.19	< 0.001
50–59	255	1.36 ± 0.17	
60–69	181	1.27 ± 0.21	
≥ 70	89	1.20 ± 0.20	
Gender			
Men	384	1.31 ± 0.20	0.256
Women	269	1.33 ± 0.20	
Duration of diabetes			
≤ 5 years	250	1.36 ± 0.19	< 0.001
> 5 years	403	1.30 ± 0.20	
HbA1c (%)			
Normal (<5.6)	71	1.32 ± 0.17	0.029
Good to fair (5.6–8.0)	402	1.34 ± 0.18	
Poor (≥8.1)	180	1.29 ± 0.24	
Hypertension			
Absent	331	1.33 ± 0.19	0.108
Present	322	1.31 ± 0.20	
Anemia			
Absent	455	1.34 ± 0.20	0.002
Present	198	1.29 ± 0.20	
Nephropathy			
Absent	470	1.34 ± 0.18	0.051
Present	160	1.29 ± 0.25	
Neuropathy			
Absent	482	1.34 ± 0.19	< 0.001
Present	171	1.26 ± 0.21	
Lipid profile			
Serum total cholesterol (mg/dl)			
< 200	538	1.33 ± 0.20	0.246
≥ 200	115	1.30 ± 0.21	
Serum triglycerides (mg/dl)			
< 150	521	1.32 ± 0.20	0.772
≥ 150	132	1.32 ± 0.20	
Serum high-density lipoprotein (mg/dl)			
≥ 60	33	1.30 ± 0.25	0.348
< 60	620	1.32 ± 0.20	
Serum low-density lipoprotein (mg/dl)			
< 100	318	1.33 ± 0.18	0.289
≥ 100	335	1.31 ± 0.21	
Treatment			
Non insulin	606	1.33 ± 0.20	0.047
Insulin	47	1.27 ± 0.16	

Bold values indicate significant *P*-values.

Table 3 summarizes the coefficients when analyzed in a multiple linear regression model and quantifies the relationship between CS and the variables. With a 0.1 log unit worsening of BCVA, CS is reduced by 0.575 units. With an increase in VPT score and cataract severity on LOCS III, CS is decreased by 0.003 and 0.018 log units. We also found that a 1 grade increase in DR was associated with an average of 0.016 units decrease in CS. With every 1 year increase in age, CS is reduced by 0.002 units.

Following model predicts the CS based on both systemic and ocular parameters.

Predicted CS = 1.594 + (-0.575) BCVA + (-0.003) VPT score + (-0.018) cataract grading by LOCS III + (-0.016) stage of DR + (-0.002) age.

Discussion

In this population-based study we report that CS was significantly reduced in the presence of DR. The mean CS in our subjects with diabetes was 1.32 ± 0.20 log units, which was $< 1.44 \pm 0.05$ log units reported by Stavrou *et al*¹⁸. The difference could be because of the larger sample size in our study and that they included only subjects with early DR, whereas our study included subjects with various stages of DR, as well as subjects with diabetes but without DR. Mantyjarvi *et al*²⁹ reported normal CS ranged from 1.68 to 1.84 log units in healthy individuals, which was high compared with our diabetic sample. We found an inverse association between CS and severity of DR consistent with previous reports.^{15,16} However, these studies had several limitations, including the lack of adjustment of the various factors affecting CS, lack of demonstration of an established association among the risk factors and the CS. To the best of our knowledge this is the first study to assess various risk factors for CS in a population-based study in south India. The prevalence of DR in the study sample was 20.9%, and diabetic macular edema among subjects with DR was 16%. Prevalence of neuropathy was 26% and that of nephropathy was 25.39%. Among the diabetic microangiopathies, DR and neuropathy were associated with CS, which was consistent with earlier reports.^{15,16,18}

Frisen³⁰ reported that visual acuity is unaffected until 55% of all neuroretinal channels are affected. It has been well documented that contrast sensitivity may be compromised despite normal visual acuity among subjects with diabetes but no retinopathy.¹⁸ Vision in the low-contrast domain is as important as that in high-contrast domain. There are various tasks done by subjects with diabetes where they require good contrast sensitivity, one such task is checking of urine or blood sugar level. Few patients use contrast differences as the clue when lowered color discrimination disturbs the reading of the test results. As the contrast sensitivity and

Table 2 Distribution of contrast sensitivity among various ocular factors

Variables	n	Contrast sensitivity mean \pm SD	P-value
BCVA			
Normal (0.00 logMAR or better)	449	1.37 \pm 0.17	<0.001
Abnormal (worse than 0.00 logMAR)	202	1.22 \pm 0.22	
Refractive error (spherical equivalent)			
Absent (-0.5 to +0.5 D)	236	1.35 \pm 0.18	0.003
Present (< -0.50 and > 0.50)	417	1.30 \pm 0.21	
Color vision (FM 100-TEs)			
≤ 100	51	1.36 \pm 0.14	0.047
> 100	144	1.31 \pm 0.19	
Lens status			
No cataract	474	1.36 \pm 0.18	<0.001
Any Cataract	84	1.19 \pm 0.24	
Pseudophakic	95	1.25 \pm 0.20	
Cataract			
NC	8	1.14 \pm 0.31	0.028
CC	42	1.26 \pm 0.22	
PSC	11	1.17 \pm 0.11	
Mixed	23	1.08 \pm 0.24	
Diabetic retinopathy			
No DR	516	1.33 \pm 0.20	0.003
Mild NPDR	55	1.33 \pm 0.20	
Moderate NPDR	47	1.27 \pm 0.18	
Severe NPDR	5	1.20 \pm 0.18	
PDR	8	1.21 \pm 0.15	
CSME	22	1.20 \pm 0.23	
Any DR			
Absent	516	1.33 \pm 0.20	0.003
Present	137	1.28 \pm 0.20	
STDR			
Absent	102	1.30 \pm 0.19	0.007
Present	35	1.20 \pm 0.20	
Central retinal thickness (1 mm area) (μm)			
≤ 190	261	1.35 \pm 0.16	0.864
> 190	237	1.34 \pm 0.19	
Photoreceptor layer thickness (μm)			
≤ 65.5	365	1.34 \pm 0.18	0.953
> 65.5	174	1.34 \pm 0.20	
Mean retinal sensitivity (dB)			
< 18.26	200	1.33 \pm 0.21	0.052
≥ 18.26	14	1.45 \pm 0.21	

Abbreviations: BCVA, best corrected visual acuity; CC, cortical cataract; CSME, clinically significant macular edema; DR, diabetic retinopathy; NC, nuclear cataract; NPDR, non-proliferative DR; PDR, proliferative DR; PSC, posterior sub-capsular cataract; STDR, sight-threatening DR; TES, total error score. Bold values indicate significant P-values.

Table 3 Multivariate linear association between contrast sensitivity and all variables

Risk factors	Adjusted			SE	P-value
	Coefficient (β)	95% CI			
		Lower bound	Upper bound		
Constant	1.594	1.489	1.698	0.053	<0.001
BCVA	-0.575	-0.705	-0.445	0.066	<0.001
VPT	-0.003	-0.006	-0.001	0.001	0.010
Severity of cataract	-0.018	-0.034	-0.002	0.008	0.032
DR stages ^a	-0.016	-0.029	-0.003	0.007	0.019
Age	-0.002	-0.004	0.000	0.001	0.029

Abbreviations: BCVA, best corrected visual acuity; DR, diabetic retinopathy; VPT, vibration perception threshold. ^aDR stages were stratified as no DR, mild NPDR, moderate NPDR, severe NPDR, PDR, and CSME. The variables adjusted are age, duration of diabetes, hemoglobin, VPT, nephropathy, insulin intake, BCVA, DR stages, cataract status, FM 100-TES, mean retinal sensitivity, and refractive error. Bold values indicate significant P-values.

color vision are slowly impaired, subjects are unaware of their inability. Periodic evaluation of visual function even in the absence of retinopathy helps in early detection and management of the progression of disease.

Age is an established risk factor for reduced contrast sensitivity,^{12,13} and this association was confirmed in our current study. The Salisbury Eye Evaluation (SEE) study evaluated the relations among various measures of visual function in older population and reported a strong relationship between contrast sensitivity and age.³¹ It has been reported that reduced contrast sensitivity is related to both optical and neural factors.¹² Anemia has been reported to be associated with the development and progression of both micro- and macrovascular complications of diabetes.³² CS was positively correlated with hemoglobin levels in the present study. This may be due to the retinal vascular and visual defects caused by localized retinal tissue hypoxia in subjects with diabetes.^{33,34} Studies have reported that hyperoxia significantly improved mean contrast sensitivity in subjects with diabetes.³⁵ VPT values showed a significant negative correlation with CS ($r = -0.238, P < 0.001$), which was in contrast to the study done by Moaven-Shahidi A *et al*,³⁶ who reported that CS did not vary between subjects with and without neuropathy.

A statistically significant inverse correlation was found between CS and logMAR visual acuity ($\beta = -0.575, P < 0.001$), consistent with the results reported by Misra *et al*¹⁴ ($\beta = -0.427, P < 0.001$). The presence of cataract was significantly associated with reduced CS; consistent with the earlier reports.³⁷⁻³⁹ Studies reported that nuclear and cortical cataracts influence median and high-frequency

CS; whereas PSC impacted low-frequency CS.⁴⁰⁻⁴² In our study, in contrast, cataract types influenced CS at 1 cpd, which is a measure of from the Pelli-Robson test.

Mean retinal sensitivity was positively correlated with CS, but it showed no association on multiple regression after adjusting for all variables. No correlation was found between CS and CRT or PRL in this study. This could be explained by the early impact of diabetes on the inner retina,⁴³ even though outer retina is also involved. Both histopathologic and imaging studies have reported that diabetes causes apoptosis of ganglion cells and their dysfunction is primarily responsible for the abnormal CS.^{6,43-45} Assessment of inner retinal thickness and function of ganglion cells would have added more value for this study.

Presence of DR was significantly associated with abnormal CS, as reported by previous studies using various techniques. Using an oscilloscope to generate gratings, Howes *et al*³⁷ found a systematic decrease in CS with severity of background DR. They also reported that background retinopathy produced abnormal CS at low and medium frequencies. In contrast, Sokol *et al*¹⁶ reported that no specific spatial frequency is selectively affected in DR. With a 1-step increase in severity of DR, CS was reduced significantly by 0.016 units. The disturbance of visual function may be linked to vascular damage and thus correlated to the degree of retinopathy.

The regression model explains about 29.3% of the variation in CS. The main purpose of the model was to explore the relative importance of ocular and systemic factors for the assessment of CS in type 2 diabetes sample. In conclusion, contrast sensitivity is impaired in DR. The changes in contrast sensitivity are related to both ocular and systemic characteristics in type 2 diabetes and not alone on severity of DR, as is clear from our study about various systemic and ocular risk factors associated with CS in subjects with diabetes. This is important as the reduction of contrast is associated with impaired performance of tasks in domains of mobility, activities of daily life, and visually intensive tasks.

Summary

What was known before

- Contrast sensitivity was affected among subjects with diabetic retinopathy.
- Ocular factors related to contrast sensitivity are reported.

What this study adds

- We assessed factors affecting contrast sensitivity among diabetic subjects in a population-based cohort.
- Changes in contrast sensitivity are related to both ocular and systemic characteristics.
- Contrast sensitivity was associated with VA, neuropathy, cataract, diabetic retinopathy and age.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The study was supported by Jamshejji Tata trust, Mumbai.

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