Original Article

Spectrum of Eye Disease in Diabetes (SPEED) in India: A prospective facility-based study. Report # 4. Glaucoma in people with type 2 diabetes mellitus

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Purpose: To estimate the proportion of people with type 2 diabetes mellitus (T2DM) and glaucoma in a facility-based cross-sectional observational study in India. **Methods:** All people received a comprehensive eye examination. Glaucoma-specific examinations included applanation tonometry, optic disc and cup evaluation, and stereo biomicroscopy in all people; gonioscopy and visual field testing in glaucoma suspects. The International Society of Geographic and Epidemiologic Ophthalmology guidelines were used to diagnose and classify glaucoma. **Results:** The study recruited 11,182 people (average age: 58.2 ± 10.6; range 39–96 years). Glaucoma was diagnosed in 4.9% (n = 547) people. About 76.8% (n = 420) of those with glaucoma had bilateral disease, and 98.7% (n = 540) were >40 years. Among people with bilateral disease, 94.5% (n = 397) had primary glaucoma – open angle in 59.3% (n = 228) and angle closure in 40.2% (n = 169). Diabetes duration was ≤10 years in 71.5% (n = 300) people. On linear regression, the following were associated with glaucoma: advancing age [compared with <40 years age group; odds ratio [OR] in 50-60 year age group: 1.36 [95% confidence interval (CI): 1.01–1.8], P < 0.035); >60 years age group (OR: 2.05, 95% CI: 1.57–2.67; P < 0.001), and diabetic neuropathy (OR: 2.62, 95% CI: 1.35–5.10, P < 0.003). Glycemic control did not have significant association (P = 0.425). **Conclusion:** Presence of glaucoma in people with T2DM in this cohort was similar to the general population prevalence studies in India. Glaucoma was invariably bilateral. A comprehensive eye examination in people age 40 years and older with diabetes and/or glaucoma is beneficial.

Key words: Diabetes, diabetic retinopathy, glaucoma

Glaucoma is an important cause of blindness. In 2015, visual impairment secondary to glaucoma accounted for 8.49% (2.99%–15.66%) of the world's blindness.[1] The number of people with glaucoma is expected to increase from 64.3 million in 2013 to 76 million in 2020 and to 111.8 million by 2040.[2] The majority of adults with glaucoma live in Asia and Africa.[2] In 2013, the pooled overall glaucoma prevalence in Asia was 3.54%.[3] In a 2008 estimation, nearly 40 million of 309 million people age 40 years and above living in India were affected with glaucoma.[4] At around this age, lifestyle disease such as type 2 diabetes mellitus (T2DM) manifest, and findings from recent studies suggest a positive relationship of diabetes and glaucoma.[5-7] A recent systematic review and meta-analysis report significant increase in the odds of glaucoma in diabetes.[8] Reports from India on the prevalence of glaucoma in diabetics are limited, though a range of 2.5%–15.6% has been reported in the literature.[9] This communication is the analysis of the presence of glaucoma in people with T2DM reporting to the retina clinics (and subsequently referred to glaucoma clinics) in large referral centers participating in the Spectrum of Eye Disease in Diabetes (SPEED) study in India.

Methods

This multicenter, cross-sectional observational study recruited patients from 14 referral eye care facilities located in different zones of India. The ethics committee of each participating center approved the study. The study followed the tenets of the Declaration of Helsinki for human research. The details of the study are reported in Report #1.[10] In brief, patients with a known history of T2DM, confirmed by the in-house internist or people under treatment by an endocrinologist, presenting for the first time to the retinal clinic in each facility were included. A detailed pretested questionnaire was administered covering demographic data, current treatment, and medical history of systemic disorders. Previous eye diseases or eye

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treatment, and current ocular symptoms were included. A comprehensive eye examination included measurement of presenting vision (with spectacles, if available), subjective refraction, slit-lamp biomicroscopy, applanation tonometry, and gonioscopy in all glaucoma suspects (based on the slit-lamp and optic disc-cup examination before dilation of the pupil) and dilated (unless contraindicated) fundus examination using indirect ophthalmoscope. Patients suspected of having glaucoma were referred to the glaucoma specialist in the same eye care facility before dilation of pupil. In the glaucoma clinic, the intraocular pressure (IOP) was re-measured and gonioscopy re-performed; visual fields (Humphrey) were recorded when considered necessary by the glaucoma specialist.

Raised IOP measuring more than 21 mmHg on applanation tonometry, optic disc changes such as focal notch, neuroretinal thinning, vertical cup–disc ratio (VCDR) more than 0.5, based on population-based norms for India,[11] nerve fiber layer splinter hemorrhage at disc margin, and corroborating visual field changes were the basis for glaucoma diagnosis. By the gonioscopic findings, they were categorized into open- or narrow-angle glaucoma. They were further classified into primary and secondary glaucoma depending on the etiology. The International Society of Geographic and Epidemiologic Ophthalmology (ISGEO)[12] classification was used by all participating eye care centers. In brief, the ISGEO definition of glaucoma is based on the structural (VCDR) and functional (specific visual field) defects. ISGEO has proposed three levels of diagnosis certainty: Category 1 – optic disc abnormalities (VCDR >97.5th percentile in the normal population) and visual field defect compatible with glaucoma; Category 2 when the visual field test could not be performed satisfactorily – a severely damaged optic disc (VCDR >99.5th percentile of the normal population); and Category 3 when the optic disc could not be examined because of media opacity (and, hence, no field test was also possible), IOP exceeding the 99.5th percentile of the normal population, or evidence of previous glaucoma filtering surgery.

Diabetes status was defined as per the Indian Council of Medical Research (ICMR) guidelines.[13] A person was considered diabetic when the recent plasma glucose level was >126 mg/dL, and 2-h post-load glucose and random glucose was >200 mg/dL and HbA1c >6.5%. Hypertension was defined as per the Indian standards: normal when blood pressure was less than 130/85 mmHg and hypertensive when the blood pressure was more than 140/90 mmHg.[14] Diabetic neuropathy was defined as the presence of symptoms and/or signs of peripheral nerve dysfunction after excluding some of the common causes (vitamin B12 deficiency, alcohol-related neuropathy, etc.) by the in-house internists.[15]

Data collection software and app-base using Java were supplied to all participating centers on-line. Pooled data from the participating centers were analyzed using Stata14SE for Windows (Stata Corp., TX, USA). Descriptive statistics were used to summarize the cohort. The mean and standard deviation for continuous variables and percentage for categorical variables were determined. The median and interquartile range were used to report nonparametric data. The normality of the data was tested by Kolmogorov–Smirnov test. If the normality was rejected, then nonparametric test was used. Analysis of the trend was performed using Chi-square test. Univariate and multivariate logistic regression analyses were undertaken to identify risk factors for glaucoma. To evaluate the effects of several factors associated with the risk for glaucoma simultaneously, discrete logistic regression analysis was performed using age, gender, diabetes duration, association of hypertension, cardiovascular disease, neuropathy and stroke as independent variables with glaucoma as the dependent variable. A *P* value of <0.05 was considered statistically significant.

Results

The study recruited 11,182 people with T2DM in 14 eye care facilities covering all zones of India, and their demographic details are listed in Report #1. In brief, 59.2% of the people in the study were men and their mean age was 58.2 ± 10.6 years (range 19–96 years). All people suspected as having glaucoma in the retina clinic (based on the IOP and VCDR) were referred to a glaucoma specialist on the same day in the same eye care facility; all of them attended the glaucoma service the same day.

Glaucoma was detected in 4.89% (*n* = 547) of people; two-third (*n* = 342) of them were men; 98.7% (*n* = 540) were above 40 years age, and 60.3% (*n* = 330) were older than 60 years of age. About 76.8% (*n* = 420) of those with glaucoma had bilateral disease. The types of glaucoma were as follows: primary open-angle glaucoma (POAG) in 54.3% (*n* = 228/420) of people, primary angle-closure glaucoma (PACG) in 40.2% (*n* = 169/420) of people, and secondary glaucoma in 5.5% (23/420) of people [Table 1]. The VCDR, which was recorded in 449 people with glaucoma, was 0.6 or more in 64.6% (*n* = 290) of people. The distribution of glaucoma by duration of diabetes [Table 2] did not show any specific pattern. In this study, 21.7% (*n* = 119/547) of people with glaucoma had diabetic retinopathy; almost equal numbers had nonproliferative (NPDR, 66/119 people) and proliferative diabetic retinopathy (PDR, 53/119) [Table 3].

The proportion of people with glaucoma who had systemic diseases (reported by all participants in the SPEED study, Report

Table 1: Type of glaucoma in people with type 2 diabetes mellitus

	Unilateral glaucoma *n*=889 eyes (*n*, %)	Bilateral *n*=420 people (*n*, %)
POAG	455 (51.2%)	228 (54.3%)
PACG	356 (40.0%)	169 (40.2%)
Secondary glaucoma	78 (8.8%)	23 (5.5%)

POAG: Primary open-angle glaucoma; PACG: Primary angle-closure glaucoma

Table 2: Distribution of glaucoma against the duration of diabetes

Duration of diabetes	Unilateral *n*=889 (*n*, %)	Bilateral *n*=420 (*n*, %)
<5 years	402 (45.21)	192 (45.71)
6-10 years	222 (24.97)	107 (25.48)
11-15 years	110 (12.37)	51 (12.14)
>16 years	155 (17.45)	70 (16.67)
Total	889	420

1) was as follows: 4.9% had hypertension (n = 271/5,500), 4.5% had cardiovascular disease (30/672), and 5.7% had stroke (3/52). Increasing age and coexisting neuropathy were associated with glaucoma. Compared with people less than 40 years of age, the odds of glaucoma in the 50- to 60-year age group was 1.36 [95% confidence interval (CI): 1.01–1.8; $P < 0.035$) and for people age 60 years or older it was 2.05 [95% CI: 1.57–2.67; $P < 0.001$). The odds of glaucoma in people with neuropathy was 2.62 (95% CI: 1.35–5.10, $P < 0.003$). Glycemic control was not associated with glaucoma ($P = 0.425$).

Discussion

In this study, 1 in 20 (4.9%) people with T2DM had glaucoma. The diagnosis and classification of glaucoma used both structural and functional changes in glaucomatous optic neuropathy, using population-based norms for India.[16] Of

the three characteristics, that is, VCDR, IOP, and visual fields, the former two (VCDR and IOP) were more often used in this study to diagnose glaucoma. The configuration of the angle on gonioscopy was used to classify glaucoma (incidentally, the configuration of the optic disc in the Indian eyes is no different than the Caucasian eyes).[16]

Despite the fact that this study was a clinic-based study, the proportion of people with glaucoma was similar to the prevalence reported in two population-based studies in the United States, the Blue Mountain Eye Study and the Los Angeles Latino Eye Study.[17,18] But it was lower than a hospital-based study in Maharashtra, India.[19] In this study, there was a male predominance ($P = 0.007$), but this could be biased as it was a hospital-based study and we suspect that many female patients possibly did not report to the retina clinic. A similar trend was noted in one of the studies from Oman.[20] The prevalence is reported to be higher in African and American diabetic females than the male counterparts.[21,22]

The overall proportion of people with glaucoma in this study (4.89%) lies within the range of prevalence data from population-based studies in India of participants age 30–50 years,[23-31] that is, POAG 1.62%–3.51% and PACG 0.71%–7.24%. POAG was more common than PACG. Advancing age is a well-recognized risk factor for glaucoma.[4,30] In our cohort, 98.7% of the people were older than 40 years and the age-adjusted linear regression analysis showed a significant association [Table 4]. Furthermore, as the glaucoma prevalence in this study among the patients with or without PDR did not differ, the co-occurrence of diabetes and glaucoma may be independent of each other, reflecting a similar age of onset.[32-34] Simultaneous screening for diabetic retinopathy and

Table 3: Stage of diabetic retinopathy among people with glaucoma (n=119)

Diabetic retinopathy stage		Glaucoma
No diabetic retinopathy		423
Nonproliferative diabetic retinopathy, n=66 (55.5%)	Mild	29 (43.93)
	Moderate	28 (42.42)
	Severe	9 (13.63)
Proliferative diabetic retinopathy, n=53 (44.5%)	NVE	46 (86.79)
	TRD	1 (1.88)
	VH	6 (11.32)

NVE: New vessels elsewhere; TRD: Traction retinal detachment; VH: Vitreous hemorrhage

Table 4: Logistic regression analysis of the variables with glaucoma as dependent variable

Risk factors for glaucoma		Univariate		Multivariate	
		Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Sex	Female	1		1	
	Male	1.16 (1.0-1.38)	0.105	1.18 (0.98-1.14)	0.077
Age	<40 years	1		1	
	40-50 years	1.36 (1.01-1.8)	0.035*	1.42 (1.05-1.9)	0.020*
	>60 years	2.05 (1.57-2.67)	<0.001*	2.22 (1.69-2.92)	<0.001*
Diabetes control	Well-controlled	1		1	
	Not controlled	1.11 (0.86-1.44)	0.435	1.11 (0.84-1.46)	0.452
	Some control	1.27 (1.0-1.62)	0.049*	1.39 (1.09-1.78)	0.007*
Neuropathy	No	1		1	
	Yes	2.62 (1.35-5.10)	0.003*	3.90 (1.86-8.16)	<0.001*
Hypertension	No	1		1	
	Yes	1.0 (0.84-1.18)	0.934	0.93 (0.78-1.11)	0.424
Cardiovascular disease	No	1		1	
	Yes	0.8 (0.6-1.2)	0.355	0.72 (0.48-1.09)	0.121
Stroke	No	1		1	
	Yes	1.3 (0.4-4.1)	0.689	1.23 (0.34-4.43)	0.749
Diabetes duration	<5 years	1		1	
	6-10 years	0.90 (0.72-1.10)	0.292	0.89 (0.71-1.10)	0.274
	11-15 years	0.79 (0.60-1.04)	0.097	0.75 (0.56-1.0)	0.051
	>16 years	1.01 (0.79-1.28)	0.957	0.89 (0.69-1.16)	0.387

CI: Confidence interval, Well-controlled - fasting plasma glucose (FPG) 80-110 mg/dL; some control - FPG 111-125 mg/dL; not controlled >125 mg/dL, *Significant

glaucoma may help prevent blindness associated with both these conditions. The inclusion of VCDR assessment, which can be done at the time of DR screening or during image grading, would be feasible, requiring minimal additional resources.

The duration of diabetes has been implicated as a risk for development of glaucoma.[19,35] Our study did show a moderate association on multivariate analysis when the duration of diabetes ranged from 11 to 15 years [Table 4]. Sustained hyperglycemic state may cause glycation of lipids, increase oxidative stress, promote cellular apoptosis, and cause ganglion cell loss. There is also growing evidence to suggest that elevated protein kinase C may cause abnormalities of matrix metalloprotease in the trabecular meshwork and impair the aqueous outflow.[36]

Limitations of this study

The retina specialists used IOP of 21 mmHg for primary referral to the glaucoma service; this might have erroneously excluded some people with normal tension glaucoma. Data were not collected to identify individuals with ocular hypertension or pseudo-exfoliation. Moreover, the data capturing software was not designed to gather parameters to the detail of picking the subtypes of secondary glaucoma, particularly neovascular glaucoma. The diagnosis of glaucoma was more clinical (optic disc–cup evaluation, IOP, and gonioscopy when performed) and visual fields were performed when glaucoma was suspected on other grounds, which may have led to the misclassification of glaucoma status. The risk of glaucoma at various stages of diabetes was not analyzed, though no difference in prevalence of glaucoma was noted in proliferative and nonproliferative stage of diabetic retinopathy. Because it was a hospital-based study of people with known diabetes, it is possible that people who did not know their diabetes status or did not have visual impairment did not report to the retina clinic.

The strength of the study lies in the large cohort recruited from all regions of the country and uniform diagnostic criteria (ISGEO) used by all participating eye care facilities.

Conclusion

In conclusion, glaucoma in people with diabetes is common and increases with increasing age, as in the general population. In most instances, the condition is bilateral, and open-angle glaucoma is more common than angle-closure glaucoma. A relatively high proportion of people age 40 years and above in India have one or both conditions and this must be borne in mind while screening for diabetic retinopathy or examining people with diabetes and/or glaucoma.

SPEED study participating clinical facility organizations and investigators

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Conflicts of interest

There are no conflicts of interest.

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