Original Article

Spectrum of Eye Disease in Diabetes (SPEED) in India: A prospective facility-based study. Report # 3. Retinal vascular occlusion in patients with type 2 diabetes mellitus

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Purpose: To determine the proportion of people with type 2 diabetes mellitus (T2DM) attending large eye care facilities across India who have retinal vascular occlusion (RVO). **Methods:** A 6-month descriptive, multicenter, observational hospital-based study of people was being presented to the 14 eye care facilities in India. The retina-specific component of comprehensive eye examination included stereoscopic biomicroscopy, binocular indirect ophthalmoscopy, and fundus fluorescein angiography, and optical coherence tomography was also available when needed. Data recording of the duration of diabetes, hypertension (HTN), stroke, and other variables was obtained from the medical history. The statistical analysis included frequencies, mean, and standard deviations for continuous variables. Odds ratio (OR) and multivariate analysis were undertaken to assess the associations between risk factors and RVO. **Results:** The study recruited 11,182 consecutive patients (22,364 eyes) with T2DM. About 59.0% (n = 6697) were male. The mean age was 58.2 ± 10.6 years. In this cohort, RVO was detected in 3.4% (n = 380) of patients; 67.6% (n = 257) of them had branch retinal vein occlusion (BRVO) and the remaining 32.4% (n = 123) had central retinal vein occlusion (CRVO). The frequency of unilateral BRVO (n = 220, 85.6%) and unilateral CRVO (n = 106, 86.18%) was much common. Unilateral RVO was more frequent (n = 326, 85.8%) than bilateral diseases (n = 54, 14.2%) (χ^2 = 126.95, P < 0.001). Ischemic CRVO was more common (n = 103, 73.6%) than nonischemic CRVO (n = 37, 26.4%). Macula-involving BRVO was found in 58.5% (n = 172) of cases, suggesting more than 50% of cases in RVO carries a risk of severe vision loss. The duration of diabetes apparently had no influence on the occurrence of RVO. On the multivariate analysis, a history of HTN [OR: 1.7; 95% confidence interval (CI): 1.3–2.1; P = 0.001) and stroke (OR: 5.1; 95% CI: 2.1–12.4; P < 0.001) was associated with RVO. **Conclusion:** RVO is a frequent finding in people with T2DM. History of stroke carries the highest risk followed by HTN. The management of people with T2DM and RVO must also include comanagement of all associated systemic conditions.

Key words: Retinal vascular occlusion, Spectrum of Eye Disease in Diabetes, type 2 diabetes mellitus

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Retinal vascular occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy (DR) and is an important cause of vision loss in people with diabetes mellitus (DM).[1-3] However, the pathogenesis of RVO is vaguely understood. This condition may be due to the combination of three systemic changes (Virchow's triad), which include hemodynamic changes (venous stasis), degenerative changes in the vessel wall, and blood hypercoagulability.[4] Systemic diseases such as hypertension (HTN) and dyslipidemia are the major risk factors for arteriolar thickening.[5,6] Other systemic risk factors include diabetes and smoking. Ophthalmic risk factors include glaucoma, hypermetropia, and ocular inflammatory disease.[7,8] Many studies have shown an inconsistent association of RVO with the above-mentioned risk factors.[9-14]

This study has estimated the proportion of people with type 2 diabetes mellitus (T2DM) recruited into the Spectrum of Eye Disease in Diabetes (SPEED) study across India, also who had RVO, and explored the systemic associations.

Methods

The SPEED study was a multicenter study that involved 14 eye care facilities in India. The details are described in report #

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1. In brief, the SPEED was a descriptive observational study of consecutive ophthalmic patients with T2DM presenting to the vitreoretinal service of participating eye care facilities which were widespread across India between the period of August 2016 and January 2017. Approval was obtained from the institutional ethics committee of each study center and the study was conducted as per the tenets of the Declaration of Helsinki on human research, after taking a written consent. The approvals from the individual ethics committee were submitted to the Indian Institute of Public Health (IIPH), Hyderabad. No patient or family was given any financial assistance in cash or kind.

The pretested questionnaire was administered to people who were included in the study. The data collection software and app base using Java were supplied to all participating centers on-line. Stata14SE for Windows (Stata Corp., TX, USA) was used for statistical analysis.

The study proforma included age, gender, type of DM and duration, history of other systemic risk factors [HTN, cardiovascular diseases (CVDs), and history of stroke], treatment for diabetes, and status of diabetes-related biochemical parameters including HbA1c levels on presentation to the retina service. Ocular evaluation consisted of comprehensive eye examination (measurement of distance and near-visual acuity using the Snellen's chart placed at 6 m, ocular motility, adnexal examination, slit-lamp examination of the anterior segment, and measurement of intraocular pressure with applanation tonometer, detailed slit-lamp biomicroscopy using 90D lens, and indirect ophthalmoscopy), and investigations such as fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) when needed were also done.

Retinal vein occlusion, when present, was classified into either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Based on the location and FFA characteristics, the BRVO was further classified into BRVO major and BRVO macula. The CRVOs were classified into ischemic or nonischemic CRVO. The diagnosis was separately made for the right and left eyes.

The status of the diabetes was determined based on the Indian Council of Medical Research (ICMR) guidelines.[15] We defined a good control of DM when the recent plasma glucose level was as follows: fasting: <110 mg/dL, 2-h post-load glucose <140 mg/dL, and HbA1c < 5.7%. We defined a person as diabetic when the recent plasma glucose level was >126 mg/dL, 2-h post-load glucose >200 mg/dL, random >200 mg/dL, and HbA1c >6.5%. HTN was defined (as per the Indian standards) as normal when the blood pressure was less than 130/85 mmHg and hypertensive when the blood pressure was more than 140/90 mmHg.[16] Stroke was defined as per the World Health Organization (WHO) standards by three criteria[17]: (1) in which an area of brain is transiently or permanently affected by ischemia or bleeding or (2) in which one or more brain blood vessels are primarily involved in a pathological process, or (3) a combination of these conditions.

Statistical analysis was performed using Stata14SE software for the Windows (Stata Corp, TX, USA) and the analysis was performed using Chi-square test. Univariate and multivariate logistic regression analyses were undertaken to identify the risk. To evaluate the effects of the systemic association, discrete logistic regression analysis was performed using the association of HTN and CVD, with stroke as an independent variable along with the RVO as the dependent variable. A P value of <0.05 was considered statistically significant.

Results

The study was conducted among all patients with T2DM who attended vitreoretina department with various eye complains in 14 different eye care facilities spread across different geographical locations of India. The study period was from August 2016 to January 2017. A total of 11,182 consecutive patients (22,364 eyes) suffering from T2DM were recruited for the study. All the cases fulfilled the inclusion criteria of the study.

In this cohort, a total of 380 (3.4%) subjects had RVO (both BRVO and CRVO together) and the remaining subjects had other vitreoretinal diseases. About 59.0% (n = 6597) of participants were male. The mean age of the patients was 58.2 ± 10.6 years. The duration of diabetes varied from ≥5 to ≥16 years.

BRVO was found in 294 eyes of 257 patients (67.6% of all RVO) and 37 patients (14.4%) of them had bilateral involvement. CRVO was found in 140 eyes of 123 patients (32.4% of all RVO) and 17 patients (13.8%) had bilateral involvement. The ratio between BRVO and CRVO in the diabetic population was found to be 2:1. Altogether, unilateral RVO is more common ($\chi^2 = 126.95$, $P < 0.001$) [Table 1]. Among the unilateral group, right eye involvement was marginally more than the left eye.

About 58.5% (n = 172) of eyes of BRVO had macula involvement, where superior temporal retinal vein or tributary branch vein was affected. Around 41.5% of eyes (n = 122) had BRVO in one of the four major venules without macular involvement. Macula-involving BRVO was found to be more common than nonmacula-involving BRVO. Ischemic CRVO (n = 103) was found 2.8 times more than the nonischemic CRVO (n = 37) [Table 2].

The maximum frequency of BRVO was within 5 years of detection of DM (n = 151, 34.4%), and thereafter the frequency is more or less the same in each 5 years interval up to more than 16 years of diabetic age, whereas CRVO was less in the group of patients who were within 6–10 years of diabetic age. In other age groups, the frequency distribution was similar [Table 3].

RVO is more common in patients with uncontrolled and poorly controlled diabetes (n = 208, 72.5%) [Table 4]. On the multivariate analysis, a history of HTN (57.2% of subjects) [odds ratio (OR): 1.7; 95% confidence interval (CI): 1.3–2.1; P = 0.001] and stroke (OR: 5.1; 95% CI: 2.1–12.4; $P < 0.001$) was significantly associated with RVO [Table 5].

Discussion

The association of DM with RVO has been studied worldwide. This is the first study in India where data were collected from 14 different cities covering the entire country and a standard diagnostic criterion was adopted. DR is the important and blinding complication of DM in the adult population. RVO and DR share certain common clinical ophthalmoscopic findings in the ocular fundus. In retinal vein occlusion, the venules of the

Table 1: Clinical profile of RVO in diabetic population

Category	No. of subjects	No. of eyes	No. of subjects Both eyes' involvement (*n*, %)	No. of subjects One eye involvement (*n*, %)	Right eye (*n*, %)	Left eye (*n*, %)
BRVO	257 (67.6%)	294	37 (14.40%)	220 (85.60%)	125 (48.64%)	95 (36.96%)
CRVO	123 (32.4%)	140	17 (13.82%)	106 (86.18%)	53 (43.09%)	53 (43.09%)
Total	380	434	54	326	178	148

RVO: Retinal vascular occlusion; BRVO: branch retinal vein occlusion; CRVO: Central retinal vein occlusion, Total number of patients with T2DM with VR complaints screened=11,182 (22,364 eyes); total number of RVO detected, *n*=380 (434 eyes); male: *n*=6697 (59%); female: *n*=4562 (41%); average age=58.2±10.6 years; BRVO: CRVO=2:1

Table 2: Vision-threatening RVO in diabetic population

BRVO, no. of eyes (*n*, %)			CRVO, no. of eyes (*n*, %)		
Macula involved	Macula not involved	Total	Ischemic	Nonischemic	Total
172 (58.5%)	122 (41.5%)	294	103 (73.6%)	37 (26.4%)	140

RVO: Retinal vascular occlusion; BRVO: branch retinal vein occlusion; CRVO: Central retinal vein occlusion, About 58.5% of BRVO and 73.6% of CRVO presented with severe vision loss; as all the centers were tertiary eye care center, the RVO cases were not fresh cases

Table 3: Duration of diabetes in people with retinal vascular occlusions

Diabetes duration	Right eye		Left eye		Both eyes	
	Patients	%	Patients	%	Patients	%
≤5 years	69	38.3	54	35.8	14	25.9
6-10 years	45	25	38	25.2	8	14.8
>11-15 years	32	17.8	31	20.5	17	31.5
>16 years	34	18.9	28	18.5	15	27.8
Total	180	100	151	100.0	54	100

Table 4: Status of diabetes control at presentation in people with retinal vascular occlusions

Control of diabetes	Right eye		Left eye		Both eyes	
	Patients	%	Patients	%	Patients	%
Well-controlled	40	22.2	39	25.8	8	14.8
Some control	67	37.2	57	37.8	28	51.8
Not controlled	46	25.6	36	23.8	15	27.8
No data	27	15	19	12.6	3	5.6
Total	180	100	151	100	54	100

retina are dilated and tortuous and there are cotton wool spots with retinal edema. CRVO occurs at the disc,[18] whereas BRVO occurs at the arteriovenous crossing site.[19] RVO is further subdivided into ischemic and nonischemic types.

Epidemiological and other studies documented various findings regarding the association of RVO and DM. Shahsuvaryan and Melkonyan[20] and others[9,11,14,21] reported positive association between RVO and DM. In a pooled data analysis of different cohorts, Cugati *et al.*[22] described RVO as a risk factor for cardiovascular mortality in the diabetic population of 43–69 years of age group. Mohamed *et al.*[23] and Ehters and Fekrat[24] found that only 5% of RVO had a systemic association with diabetes. In a meta-analysis of public health data (Brno, Czech Republic), Kolar[25] found that DM and some other systemic factors such as HTN, high-density lipoprotein, and PAD are strong risk factors for RVO. The authors also concluded that pathogenesis of CRVO and BRVO is multifactorial and ill-understood till date.

Hayreh *et al.*[13] and others[14,26-28] documented that uncontrolled DM in the male gender and older age increases the risk of RVO. Beaver Dam Study[9] similarly documented strong association between BRVO and DM (OR: 2, 43; 95% CI: 1.04–5.70) and HTN (OR: 542; 95% CI: 2.18–3.47). Stem *et al.*[28] in a longitudinal study conducted among 1,300 clinic-based patients in the United States found an association between CRVO and end-organ damage from DM [hazard ratio (HR) = 1.53; 95% CI: 1.28–1.84] along with other systemic risk factors. Several studies have also shown that uncontrolled DM in male gender and older age increases the risk of RVO in them.[13,14,26,27]

Klen *et al.*[26] and others[29-31] could not find any constant relationship between DM and RVO. The Eye Disease Case-control Study Group[7] documented that DM in a diverse group of patients in the United States did not increase the risk of CRVO, but HTN alone increases the risk of CRVO in 66% of subjects. However, DM, HTN, and HLD together increase the risk of developing CRVO in 58% of subjects in comparison to those who do not have the above three systemic conditions together.

Jeganathan *et al.*[32] compiled different studies and found a constant but varied association of DM and RVO. The Eye Disease Case-control Study Group[7] implicated HTN as a risk factor for BRVO in 50% of cases. Lam *et al.*[33] also could not find any association between DM and BRVO. Zhou *et al.*[4] and Rehak and Rehak[34] described only HTN as risk factor for RVO. In the Beijing eye study[4] (population-based longitudinal study), no risk association was found between DM and BRVO.

Singapore Malay Eye Study[35] recorded HTN as a risk factor for RVO rather than DM. The study also documented a lower prevalence of RVO in the Asian population than Caucasians as found in the Blue Mountains Eye Study.[9] However, Dodson *et al.*[12] described Asians are at higher risk for RVO than Caucasians in the diabetic population. Stem *et al.*[28] found a higher risk of CRVO in the African American general population but did not comment about the association between DM and RVO. So it is apparent that epidemiological and other studies could not establish a definite relationship between DM and RVO.

About 3.4% of the patients with diabetes with vitreoretinal problems of the present cohort had RVO. This is higher than in the population-based prevalence studies such as Blue Mountain Eye Study, the Framingham Eye Study,[27] and

Table 5: Association between systemic diseases and retinal vascular occlusion: univariate and multivariate analyses, and age- and sex-adjusted analysis

Systemic disease		Retinal vein occlusion			Univariate analysis				Multivariate analysis			
		Yes	No	Total	OR	95% CI	χ^2	*P*	OR	95% CI	χ^2	*P*
Hypertension	No	106	5660	5416	1			1	1			
	Yes	171	5245	5766	1.9	1.5-2.4	25.4	<0.001	1.7	1.3-2.1	17.78	0.001
	Total	277	10,905	11,182								
CVD	No	252	10,277	10,529	1				1.0			
	Yes	25	628	653	1.4	0.9-2.1	2.48	0.115	1.3	0.8-2.0	1.48	0.056
	Total	277	10,905	11,182								
Stroke	No	271	10,862	11133					1			
	Yes	6	43	49	5.3	2.2-12.7	17.6	<0.001	5.1	2.1-12.4	15.67	<0.001
	Total	277	10,905	11,182								

OR: Odds ratio: CI: Confidence interval; CVD: Cardiovascular disease

Beaver Dam Eye Study[26] where the prevalence of RVO was 1.6%, 0.15%, and 0.8%, respectively. Unlike other studies, this study was a facility-based study and almost 50% of RVO cases had a visual impairment. Opportunistic screenings explain the proportionally higher prevalence of RVO in the diabetic population in the study. All the recruited patients self-reported in the eye care facilities for treatment of their eye complaints. It probably reflects the eye-care-seeking behavior of the population. In this study, unilateral RVO was more frequent than bilateral disease (326/54 eyes) and it was statistically significant (χ^2 = 126.95, $P < 0.001$). BRVO was more frequent than CRVO which does not differ from other reports. More than half of the BRVO patients had a risk of developing vision loss due to macular edema. In diabetic population, ischemic CRVO was 2–8 times more in comparison to nonischemic group suggesting risk of vision loss.

We observed that uncontrolled or poorly controlled DM was related to RVO and not merely the duration of DM. We also report a strong association of HTN and CVD with RVO in the Indian population. On the multivariate analysis, a history of HTN (OR: 1.7; 95% CI: 1.3–2.1; $P = 0.001$) and stroke (OR: 5.1; 95% CI: 2.1–12.4; $P < 0.001$) was associated with RVO. Many investigators as described earlier also implicated HTN and CVD as important risk factors for RVO in the diabetic population.

The limitation of this study was that it was an opportunistic hospital-based screening among the patients who attended in VR department, and hence it did not estimate the prevalence of RVO in the population. We did not collect renal function or hematocrit data. This study did not measure anthropometry, particularly body mass index which is also associated with RVO.[12] Despite the odds, the strength of the study was that it was the first pan India study and used a uniform protocol.

Conclusion

This facility-based opportunistic study provides summary data on the occurrence and risk factors of RVO disease among people with T2DM in India. Though the patient pool was from different parts of the country, yet it did not represent the entire population in general. The study documented that vascular retinopathy was the second most common vascular lesion in people with diabetes and which occurred more often in uncontrolled diabetes. About 3.4% of the vitreoretinal problems in patients with diabetes are due to RVO. Stroke, HTN, and CVDs are important systemic association and HTN and stroke were significant risk factors. For prevention and holistic management of retinal vascular disease in people with diabetes, attention to the systemic condition is important.

SPEED study participating clinical facility organizations and investigators

1. Aravind Eye Hospital, Madurai (Dr. Kim Ramasamy, MD)
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Conflicts of interest

There are no conflicts of interest.

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