Original Article

Does myopia decrease the risk of diabetic retinopathy in both type-1 and type-2 diabetes mellitus?

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Purpose: To study the relationship between the severity of myopia and the severity of diabetic retinopathy (DR) in individuals with type 1 or type 2 diabetes mellitus (DM). **Methods:** This retrospective study was conducted using data from electronic medical records from a multicentric eyecare network located in various geographic regions of India. Individuals with type 1 or type 2 DM were classified according to their refractive status. Severe nonproliferative DR (NPDR), PDR, or presence of clinically significant macular edema (CSME) with any type of DR was considered as vision-threatening diabetic retinopathy (VTDR). **Results:** A total of 472 individuals with type-1 DM (mean age 41 ± 10 years) and 9341 individuals with type-2 DM (52 ± 9 years) were enrolled. Individuals with a hyperopic refractive error had a significant positive association with the diagnosis of VTDR (odds ratio (OR) 1.26; 95%CI 1.04–1.51, P = 0.01) and moderate nonproliferative DR (OR 1.27; 95%CI 1.02–1.59, P = 0.03) in type-2 DM; however, no significant association was found in type-1 DM. After adjusting for age, gender, anisometropia, and duration of diabetes, the presence of high myopia (< - 6 D) reduced the risk of VTDR in type 2 DM (OR 0.18; 95% CI 0.04–0.77, P = 0.02), but no association was found in type 1 DM. Mild and moderate myopia had no significant association with any forms of DR in both type-1 and type-2 DM. **Conclusion:** Hyperopic refractive error was found to increase the risk of VTDR in persons with type 2 DM. High-myopic refractive error is protective for VTDR in type 2 DM, but not in type-1 DM.

Key words: Diabetes mellitus, diabetic retinopathy, myopia, myopia progression, type-1 DM

Diabetic retinopathy (DR) is one of the primary causes of visual impairment in India and Worldwide, occurring in both type-1 and type-2 diabetes mellitus (DM).[1] The prevalence of DR in individuals with type-2 DM was found to be 18% and 10%, respectively in urban and rural populations of southern India,[2] which is less than that in China (Beijing Eye Study, 37%),[3] Australia BMES (Blue Mountain Eye Study, 32%),[4] and the USA (40%).[5] In contrast, the prevalence of DR in individuals with young onset type-1 diabetes (age between 10 and 25 years at diagnosis) was 53% in the Indian population,[6] which was in the same range as that of several countries like Norway (61%)[7] and Portugal (54%).[8] Previous epidemiological studies had identified that the risk for developing DR increases with longer duration of diabetes (>15 years), poor glycemic control (HbA1c >7%), and higher systolic blood pressure (per 10 mm of Hg).[9-13] It was also indicated that ocular factors such as myopia,[14,15] intraocular pressure,[16] and posterior vitreous detachment (PVD)[17,18] were also associated with the occurrence of DR. Depending upon the severity of DR, several clinical features such as microaneurysms, intraretinal hemorrhages,

hard exudates, macular edema, and foveal avascular zone abnormalities, cotton-wool spots, venous bleeding, and intraretinal microvascular abnormalities have been identified to be associated with DR.[19] The findings reported by Sankara Nethralaya-Diabetic Retinopathy Epidemiological and Molecular Genetic Study (SN-DREAMS, report 18) indicated the higher prevalence of astigmatism (47%) and hyperopia (40%) compared to myopia (20%) in individual with type-2 DM.[20] In individuals with type-2 DM, myopic refractive errors were associated with poor glycemic control, and those with hyperopic refractive error were found to have low plasma glucose (both acute and chronic) and known diabetes status.[20,21] A similar observation was noted in individuals with type-1 DM.[22]

The hypothesis that myopia is a protective factor for DR is not recent, having possibly been first reported by Jain *et al.*[23] There has been strong evidence on the association of myopia and decreased risk of DR in adult population.[14,15,24-32] Recent meta-analysis by Fu *et al.*[15] that included six population-based and five clinic-based studies and Wang *et al.*[14] that included six population-based and three clinic-based studies examined the association between axial length, refractive error and DR,

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reported that the longer eye length of the myopic eye and the greater the degree of myopic refractive errors reduced the risk of developing DR. However, few population-based studies such as the Beijing Eye study[33] and SN-DREAMS report[34] reported no significant association between myopia and DR. Likewise, Jee *et al.*[35] reported no significant association of myopia and hyperopia with the presence of DR in an adult population of more than 40 years old.

To date, previous studies only included adult-onset type-2 DM to evaluate the association of myopia and decreased risk of DR, leaving a gap in the literature about the association of myopia or the different grades of myopia with the decreased risk of DR in people with younger-onset diabetes. Therefore, the influence of myopia (mild, moderate, and high) on the occurrence of DR in persons with type-1 DM remained unknown.

Based on a large data set of individuals with diabetes from a muticentric eyecare network institutes situated in the eastern and southern geographical regions of India, the present study aims to investigate the association between the severity of myopia and the severity of DR in people with type-1 or type-2 DM.

Methods

This retrospective study was carried out using data from four tertiary eye care network institutes located in different geographic regions of India. The study was approved by the Institutional Ethics Review Board (LEC 09-17-094), and it follows the principles of the Helsinki Declaration. All individuals provided a general informed consent to the use of data for the research purposes at the time of registration for their eye examination. For children under 18 years, the parent/guardian provided the consent.

The required data of individuals who visited one of the tertiary eye care centers located in different geographical locations of India (Bhubaneswar, Vijayawada, Visakhapatnam, Hyderabad) between January 2016 to December 2016 for ophthalmic consultation, was extracted from the eyeSmart electronic medical records (EMR) database of the institute. In all, 80,000 individuals aged 6–90 years were diagnosed with diabetes and were on treatment for the disease. The extracted variables from EMR included age, gender, type, and degree of refractive error (based on the spherical equivalent value), best-corrected visual acuity (BCVA), posterior segment findings, ocular diagnosis, type of DM, duration of DM, onset of DM, diagnosis of DR, and clinically significant macular edema (CSME). The medical records of individuals with any missing data for the required variables and the presence of one of the other ocular conditions (cataract [with any form or degree], amblyopia, aphakic, psuedophakic, postrefractive surgeries, keratoconus, silicone oil insertion, and pterygium) that could influence the refractive error were not included in the analyses, which lead to a final sample of 9813 individuals with either type-1 or type-2 DM. Among 9831 individuals with DM, there were 472 individuals with type-1 DM (4.8%), and 9341 individuals with type-2 DM (95%) who met the inclusion criteria and whose refractive error and DR diagnosis indicated the association of myopia in varying degrees with DR.

By following the UK practical classification guidelines for diabetes based on age at which DM was diagnosed and the

dependency on insulin,[36] individuals were categorized into two groups, namely, type-1 DM and type-2 DM. The patients whose date of DM detection was less than 35 years and who were dependent on insulin (continual) from the onset of diabetes to 6 months of duration were categorized as type-1 DM. The patients whose date of DM detection was greater than 35 years and who were either insulin dependent (noncontinual) or noninsulin dependent, from the onset of DM to 6 months of duration were categorized as type-2 DM. In addition to this, based on date of DM detection, i.e., after 35 years of age or before 35 years of age, and in combination with the usage of insulin, i.e., continual or noncontinual insulin treatment, they were also pooled to type-1 DM and type-2 DM groups, respectively.

The objective refraction and subjective refraction were performed by skilled optometrists for each individual to determine the best refractive correction. The spherical equivalent refraction (SER) error based on subjective refraction was defined as the sum of the spherical power and half the cylindrical power. Myopia was defined as the SER less than -0.50 diopters (D). Based on the degree of myopia, myopic subgroups were categorized as mild (< -0.50 to -3.00 D), moderate (< -3.00 to -6.00D), or high myopia (< -6.00D). Hyperopia was defined as a SER being more than + 0.50D. Emmetropia was defined as SER from -0.50 to + 0.50 D. Anisometropia is defined as the difference in the SER between two eyes of ≥ 0.50 D. The BCVA was estimated under normal room illumination with the standard logarithm of the minimal angle of resolution visual acuity charts. DR was classified based on international clinical DR and macular edema severity scale.[37] The Severe nonproliferative DR (NPDR), proliferative diabetic retinopathy (PDR), and presence of CSME with any type of DR was considered as vision threatening DR (VTDR).

Statistical analyses were performed using Microsoft Excel (2016 version) and IBM SPSS Statistical Software 21.0.0 (SPSS, Inc., Chicago, IL). The results were indicated in the mean values of the standard deviation, if the data were continuous variable, and as a percentage, for a categorical variable. The Chi-square test was used to compare proportions between groups, and the student *t*-test and analysis of variance for comparing the continuous variable. There was no significant difference in the mean subjective refraction of the right and left eye ($P < 0.05$). Therefore, the right eye alone was considered for the refractive condition analysis in the two diabetic groups. For both univariate and multivariate analysis, a P value of <0.05 was considered significant. Multivariate logistic regressions were performed with severity of DR (mild NPDR, moderate NPDR, and VTDR) as the dependent variable to analyze the relationship of hyperopia, and subgroups of myopia (mild, moderate, high), with severity of DR (emmetropes were considered as control group). The logistic regression model was adjusted for age, gender, anisometropia, and duration of diabetes.

Results

In both the categories, i.e., individuals with type-1 or type-2 DM, there was a greater proportion of individuals with DR from Hyderabad (N = 133/233, 57% vs. 731/1530, 48%), followed by Bhubaneswar (N = 69/233, 30% vs. 523/1530, 34.1%), Visakhapatnam (11/233, 5% vs. 107/1530, 7%), and Vijayawada (20/233, 8.5% vs 169/1530, 11%). Males numbered

higher than did females among the individuals with type-1 DM ($N = 309$; 65%) or type-2 DM ($N = 6038$; 64%). The mean age and SER in type-1 DM group were 41 ± 10 years (range from 6 to 69 years), and -0.56 ± 2.10 D (ranged from + 8.50 to -16.50 D), respectively; the corresponding values for individuals with type-2 DM were 52 ± 9 years (age range from 13 to 90 years) and 0.22 ± 1.92 D (SER range from 12 to -23.25 D), respectively. The frequency of DR in individuals with type-1 DM (49.4%) is significantly greater compared to individuals with type-2 DM (16.4%), $P < 0.05$.

Table 1 shows the univariate analysis of age, duration of diabetes (in years), and onset of diabetes (in years) in different refractive error group under the category of type-1 and type-2 DM. In general, individuals with myopic refractive error were significantly younger ($P < 0.005$) compared to emmetropes and hyperopes in both diabetic groups. In individual with type-1 DM, the duration of diabetes ranged between 11 and 18 years, and onset of diabetes ranged from 24 to 29 years of age. The duration of diabetes ranged 5–7 years, and onset of diabetes ranged 42–48 years in individuals with type-2 DM.

Distribution of refractive error in individuals with type 1 or type 2 diabetes

Fig. 1 shows the distribution of refractive errors in individuals with different grades of DR in both DM categories. The frequency of VTDR in myopic subgroups significantly decreased with increasing severity of myopia in both type-1 (mild vs moderate vs high: 39% vs 15% vs 11%, $P = 0.01$), and type-2 (7% vs 5% vs 2%, $P = 0.02$) in both DM groups. The percentage of individuals with VTDR and hyperopic refractive error was significantly greater in both type-1 (43%, $P < 0.001$) and type-2 DM groups (9%, $P = 0.001$) in vision-threatening DR compared to the nonvision threatening DR group.

Using multivariate logistic regression, the relationship between refractive errors and the presence of mild NPDR, moderate NPDR, and VTDR was evaluated in persons with type-1 or type-2 DM [Table 2]. After adjusting for age, gender, anisometropia and duration of diabetes, the regression model showed that individuals with hyperopic refractive error had a significant positive association with the diagnosis of VTDR (OR 1.26; 95%CI 1.04–1.51, $P = 0.01$) and moderate NPDR (OR 1.27; 95%CI 1.02–1.59, $P = 0.03$) in type-2 DM; however, no significant association was found in type-1 DM. High-myopic refractive error reduced the risk of developing VTDR in individuals with type-2 DM (OR 0.18; 95% CI 0.04–0.77), and the association was found to be significant ($P = 0.02$). We found no significant association between mild/moderate myopic refractive error and any forms of DR in type-2 DM. Moreover, no significant association was found between myopic subgroups (mild, moderate, high) and any form of DR in individuals with type-1 DM.

Discussion

Using retrospective study design, the current study aimed to investigate the association of myopia and different degrees of myopia with DR in individuals with type-1 or type-2 DM. In the type 2 DM groups, eyes with hyperopic refractive error were at higher risk of developing moderate NPDR and VTDR as compared to emmetropes. The findings indicated that high myopia (< -6 D) reduced the risk of developing in VTDR in individuals with type-2 DM, but not in type-1 DM.

Table 1: Association of refractive error with diabetic retinopathy in individuals with type-1 or type-2 diabetes mellitus using univariate analysis

Variables	Type 1 DM						P	Type 2 DM						P
	Emmetropia	Hyperopia	Mild-myopia	Moderate-Myopia	High Myopia			Emmetropia	Hyperopia	Mild-myopia	Moderate-Myopia	High Myopia		
n	217	81	139	26	9			3705	3862	1415	240	119		
Age (years)	41.7±9.8	48.3±10.7	38.4±9.4	35.6±10.5	37.8±11.2		0.01	48.7±8.6	55.7±7.6	49.2±10.4	49.9±12.2	48.3±9.5		0.04
Male, n (%)	148	50	90	17	4		0.001	2509	2357	958	138	76		0.001
	(68.2)	(61.7)	(64.7)	(65.4)	(44.4)			(67.7)	(61)	(67.7)	(57.5)	(63.8)		
Duration of DM (years)	12.5±7.7	18.8±8.4	11.6±6.5	11.5±5.5	10.8±8.2		0.02	5.6±5.2	7.3±6.3	5.8±5.3	6.0±5.9	5.7±4.9		0.03
Onset of DM (years)	29.1±6.6	29.5±6.5	26.7±7.6	24.1±9.2	27.0±7.4		0.04	43.0±8.0	48.3±8.1	43.3±10.0	43.8±12.1	42.6±9.9		0.03

The data represents the mean (standard deviation) and number (%) for the continuous variable "years"
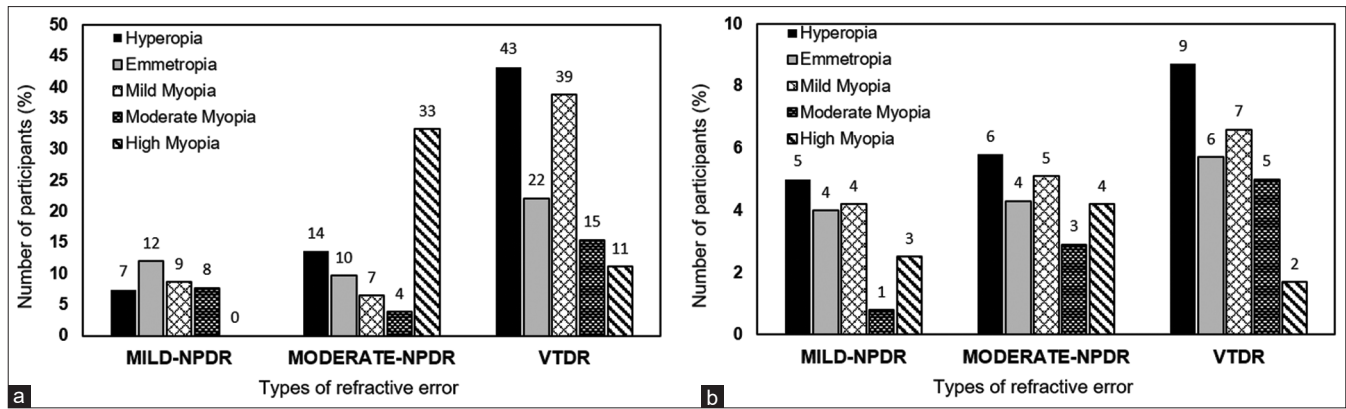
Figure 1: Distribution of refractive errors in individuals with type-1 diabetes mellitus (a) and type-2 diabetes mellitus (b). *NPDR (Nonproliferative diabetic retinopathy); VTDR (Vision-threatening diabetic retinopathy)

Table 2: Association of refractive error with diabetic retinopathy in individuals with type-1 or type-2 diabetes mellitus using Multivariate Logistic Regression

Refractive error	Adjusted odds ratio (95% CI)					
	Type 1 DM			Type 2 DM		
	NPDR - Mild	NPDR - Moderate	VTDR	NPDR - Mild	NPDR - Moderate	VTDR
Emmetropia	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hypermetropia	0.58 (0.18-1.86)	1.44 (0.61-3.43)	1.43 (0.78-2.63)	1.20 (0.94-1.52)	1.27 (1.02-1.59)	1.26 (1.04-1.51)
Mild myopia	1.20 (0.55-2.59)	1.27 (0.52-3.06)	1.58 (0.95-2.63)	0.87 (0.63-1.21)	0.88 (0.65-1.19)	0.83 (0.64-1.07)
Moderate myopia	0.91 (0.18-4.43)	0.52 (0.06-4.31)	0.60 (0.18-1.93)	0.24 (0.06-1.01)	0.65 (0.30-1.42)	0.58 (0.31-1.09)
High Myopia	-	6.90 (1.17-40.56)	0.37 (0.04-3.30)	0.49 (0.11-2.02)	0.52 (0.16-1.69)	0.18 (0.04-0.77)

No significant association was found between mild/moderate myopic groups and any forms of DR in both type-1 and type-2 DM.

The novelty in the current study was that this study individually examined the association of DR and myopia over the range of mild to high myopia in a large cohort of individuals with type-1 or type-2 DM. To date, there have been few studies investigating the association of myopia and the decreased risk of DR in type-1 DM. From a sample of 116 people with diabetes (*n* = 70 with type 1 DM, *n* = 46 with type 2 DM), Bazzazi *et al.*[32] examined the frequency of DR (proliferative/nonproliferative) in high-myopic eyes, reporting that DR was less frequent in high myopic eyes compared to the fellow eye (acting as controls) in both type-1 and type-2 DM groups. Likewise, Moss *et al.*[27] (the Wisconsin Epidemiological Study of Diabetic Retinopathy) reported that overall myopia was associated with decreased risk of progression to PDR in young-onset diabetes (OR, 0.40; 95% CI 0.18–0.86). However, we did not find significant association between myopic subgroups (mild, moderate, and high) and any forms of DR in individuals with type-1 DM.

Several population and clinic-based studies have high myopia as a protective factor for DR in adult-population (>40 years).[28,30,38] In 629 individuals with diabetes (over 40 years), Lim *et al.*[28] reported that all grades of myopia (mild, moderate, high) have a protective effect against DR (any DR, moderate DR, VTDR), particularly VTDR. However, in our study, we found that in individuals with type-2 diabetes (onset of diabetes >35 years of age), the protective effect of myopia against DR was not continuous over the range of degree of myopia, and only high myopia appear to have a protective influence against DR, particularly VTDR. In a cohort of Indians living in Singapore (40–84 years), the Singapore Indian Eye Study reported that myopic eyes were less likely to have DR (OR, 0.68; 95% CI, 0.46–0.98) compared to emmetropic eyes.[30] The findings from the current study indicated that the risk of VTDR in individuals in type-2 DM is likely to be reduced in high-myopic eyes, but not in mild and moderate myopic eyes.

It remains unclear whether it is the refractive component or the structural component, or both that have a protective influence against DR. In a population-based cohort study (1562 eyes), Man *et al.*[25] reported that it was only longer axial length that was associated with the lower incident of DR. Myopic eyes have longer axial length compared to emmetropes and hyperopes and increase in axial length corresponds to progression of myopia;[39] hence, high myopia may serve as a "surrogate" measure for longer axial length in the present study. In addition, we also found that hyperopic refractive error was significantly associated with increased risk of DR, which was consistent with the findings of the Beijing Eye Study 2006 (OR: 1.13; *P* = 0.08).[33]

Several mechanisms have been put forward explaining the protective nature of myopia against DR including: (a) reduced blood flow due to the narrowing of blood vessels (retinal arterioles and venules) in a longer myopic eye, thus preventing retinal capillary pressure and thereby proliferation,[38,40-42] (b) degenerative changes in myopic retina decreases retinal function and oxygen consumption, counteracting the

hypoxic changes in diabetes by reducing the production of inflammatory cells,[38] (c) presence of PVD in myopes to enhance oxygen diffusion through liquefied vitreous and reduced risk for neovascularization and PDR,[43] and (d) thinning of the peripheral retina which in turn reduces the amount of metabolic demand of the retina.[44] While these are all speculations at this stage, further studies are warranted to understand how retinal and choroidal morphology can explain the protective nature of high myopia on VTDR.

The strengths of this study are its assessment of how the presence of different types and grades of refractive error influence the occurrence of DR in both type-1 and type-2 DM, and its large, the population-based sample from different geographical regions of India (Hyderabad, Bhubaneswar, Visakhapatnam and Vijayawada). One limitation of this study was the unavailability of biometry data (such as axial length) and certain confounding variables such as HbA1c levels, systolic blood pressure, cholesterol, and triglyceride levels.

Conclusion

In conclusion, eyes with the high-myopic refractive error have reduced risk of developing VTDR in individuals with type-2 DM, but not in type-1 DM.

Conflicts of interest

There are no conflicts of interest.

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