Journal of Preventive Medicine and Public Health
July 2011, Vol. 44, No. 4, 157-166
This article is available at http://jpmph.org/.

doi: 10.3961/jpmph.2011.44.4.157
pISSN 1975-8375
eISSN 2233-4521

Original Article

Intraocular Pressure and Its Determinants in Subjects With Type 2 Diabetes Mellitus in India

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Objectives: This study was conducted to show the intraocular pressure (IOP) distribution and the factors affecting IOP in subjects with type 2 diabetes mellitus (DM) in India.
Methods: We measured the anthropometric and biochemical parameters for confirmed type 2 DM patients. A comprehensive ocular examination was performed for 1377 subjects aged > 40 years and residing in Chennai.
Results: A significant difference in IOP (mean ± standard deviation) was found between men and women (14.6±2.9 and 15.0±2.8 mmHg, p = 0.005).
A significantly elevated IOP was observed among smokers, subjects with systemic hypertension and women with clinically significant macular edema (CSME). After a univariate analysis, factors associated significantly with higher IOP were elevated systolic blood pressure, elevated resting pulse rate and thicker central corneal thickness (CCT). In women, elevated glycosylated hemoglobin was associated with a higher IOP. After adjusting for all variables, the elevated resting pulse rate and CCT were found to be associated with a higher IOP.
Conclusions: Systemic hypertension, smoking, pulse rate and CCT were associated with elevated intraocular pressure in type 2 DM. Women with type 2 DM, especially those with CSME, were more prone to have an elevated IOP.

Key words: Type 2 diabetes mellitus, Intraocular pressure, Central corneal thickness, Risk factors
J Prev Med Public Health 2011;44(4):157-166

INTRODUCTION

The range of intraocular pressure (IOP), among the general population, varies from 8-22 mmHg [1]. This variation can be explained by the numerous factors affecting IOP. Previous studies have shown that the factors associated with elevated IOP include smoking [2], older age [3], gender [2,3], blood pressure [2-4] family history of glaucoma [2,3], pulse rate [2,3], diabetes (elevated glycosylated hemoglobin) [2,3], myopia [5], alcohol usage [2], race (African) [4], nuclear sclerosis [3,5], body mass index (BMI) [2-4] and iris color [5].

Subjects with type 2 diabetes mellitus (DM) have an increased risk of developing open angle glaucoma [6]. It is important to study the distribution and effect of the factors affecting IOP among subjects with DM in India, as there are few population-based studies regarding the same [7]. Based on the procedure used and the population chosen, the distribution of intraocular pressure among type 2 DM varied from 14.86 to 21.5 mmHg [2,3,7-18].

However, these studies did not have standardized procedures like goldmann applanation tonometer (GAT) and fundus photography based standardized retinopathy grading. The aim of this study is to describe the IOP distribution and the factors affecting IOP in subjects with type 2 DM. It also elucidates the gender-specific influence of these factors on the IOP.

METHODS

Sankara Nethralaya - Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN- DREAMS 1) is a population-based, cross-sectional, study to estimate the prevalence and risk factors of diabetes and diabetic retinopathy in the South-Indian population. The detail methodology and study design of SN-DREAMS 1 is given elsewhere [19].

The study population was selected by multistage, systematic random sampling based on the socio-economic status, which made the sample a true

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Received : 27 October 2010, Accepted : 24 March 2011

representation of subjects with type 2 DM in India. Out of the 5999 individuals, aged ≥ 40 , enumerated from the general population, 1816 subjects had diabetes (known 1349 and provisional 469); 1563 (86.1%) subjects came for further evaluation at the base hospital and of these, 138 subjects with no diabetes and 11 subjects with ungradable retinal photographs were excluded. Apart from this, 30 subjects having IOP ≥ 22 mmHg, three glaucoma suspects and four subjects under anti-glaucoma medication (one of them being ocular hypertensive) were excluded from the study. Finally, we had 1377 subjects for this study. Known diabetics and provisional diabetics were selected in accordance with the ADA criterion [20]. Known diabetes is when diabetes is diagnosed by a medical practitioner, or the patient uses hypoglycemic medication, either oral or insulin or both and provisional diabetes is when the condition is diagnosed in a new asymptomatic individual with a first fasting blood glucose level ≥110 mg/dL (Accutrend alpha). The right eye was chosen for analysis, alternatively the eye without any history of ocular surgery was selected for analysis.

The study was approved by the Institutional Review Board and a written informed consent was obtained from the subjects as per the Helsinki Declaration. Subjects with provisional diabetes were confirmed to be having diabetes by re-estimating fasting blood glucose by enzymatic assay based glucose oxidation method (Accutrend alpha) [20]. The biochemical analyses done using the Merck Micro Lab 120, semi automated analyzer included total serum cholesterol (CHOD-POD method), high-density lipoproteins (after protein precipitation CHOD-POD method), serum triglycerides (CHOD-POD), hemoglobin (calorimetric hemoglobinometer), packed cell volume (capillary method) and the glycosylated hemoglobin fraction (Bio-Rad DiaSTAT HbA1c Reagent Kit).

Anthropometric measurements, including weight, height, waist and hip, were obtained using standardized techniques. The blood pressure was recorded, in the sitting position, in the right arm, to the nearest 2 mmHg using the mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken, five minutes apart, and their mean, was taken as the blood pressure. Microalbuminuria was estimated using the first morning urine sample, by a semi-quantitative procedure (Clintek 50 Bayer Urine Analyzer) in which the subjects were considered to have microalbuminuria, if the albumin creatinine ratio (ACR) was between 30 and 299 mg/g [21]. Diabetic neuropathy was assessed by measuring the vibration perception threshold (VPT) using a sensitometer by a single

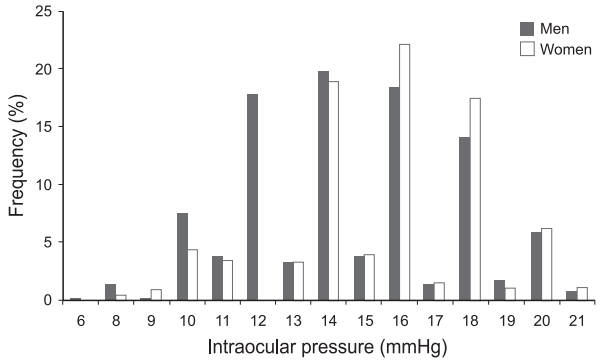

Figure 1. Distribution of intraocular pressure in subjects with type 2 diabetes mellitus.

observer with a biothesiometer probe placed perpendicular to the distal plantar surface of the great toe in both legs. The mean VPT measure of the three readings of both legs was considered for the analysis. The presence of diabetic neuropathy was considered if the VPT value was >20 V [22].

After the initial phases of sampling, diabetes confirmation, biochemical and anthropometric examination, a comprehensive ophthalmic examination was conducted at a dedicated facility created in the base hospital in a pre-determined specific order - starting from the subject's medical and ophthalmic condition to recording the presenting and the best-corrected distance visual acuity using the modified ETDRS chart (Light House Low Vision Products, New York, NY, USA). For those who could not read the English alphabet, the Landolt's ring was shown. The pinhole visual acuity was assessed for those having visual acuity less than 4/4 (LogMAR 0.0). An objective refraction was performed with a streak retinoscope (Beta 200, Heine, Germany) and was followed by subjective refraction. The corneal endothelial status was assessed with the corneal specular microspcopy, the corneal thickness was measured using the Corneal Pachymeter (Alcon ultrasound pachymeter) after which the slit lamp examination was performed (Zeiss SL 130). The peripheral anterior chamber depth was assessed as per the van Herick grading [23] and the iris was examined for neovascularization. The IOP in both the eyes were measured using Goldmann applanation tonometer (Zeiss AT 030 Applanation Tonometer, Carl Zeiss, Jena, Germany), using 0.05% proparacaine eyedrops as topical anaesthesia and 2% fluorescein to stain the tear film [24]. The IOP in the right eye was measured first and taken for analysis (Intra correlation coefficient 0.84 between the eyes), with only one reliable measurement recorded for each. The instrument was calibrated on the first working day of

Table 1. Distribution of Intraocular pressure in various subgroups among subjects with type 2 diabetes mellitus

Mean±SD

Risk factors	Over all (n=1377)			Men (n=731)			Women (n=646)		
	n	IOP (mmHg)	p	n	IOP (mmHg)	p	n	IOP (mmHg)	p
Mean IOP		14.8 ± 2.9			14.6 ± 2.9			15.0 ± 2.8	0.005
Demography									
Age (y)									
40 - 49	385	14.7 ± 2.7	0.69	210	14.4 ± 2.6	0.59	175	15.1 ± 2.8	0.94
50 - 59	494	14.9 ± 2.9		245	14.8 ± 3.1		249	15.1 ± 2.8	
60 - 69	342	14.7 ± 2.9		178	14.6 ± 3.0		164	14.9 ± 2.9	
70 +	156	14.7 ± 2.9		98	14.6 ± 3.1		58	15.0 ± 2.6	
Duration of diabetes (y)									
< 5	799	14.8 ± 2.8	0.51	403	14.7 ± 2.9	0.21	396	14.9 ± 2.7	0.49
≥ 5	578	14.7 ± 2.9		328	14.4 ± 2.9		250	15.1 ± 2.9	
Nuclear cataract									
Absent	1011	14.8 ± 0.438	0.44	550	14.6 ± 2.9	0.57	461	15.1 ± 2.8	0.69
Present	187	15.0 ± 0.439		93	14.8 ± 3.0		94	15.2 ± 2.1	
Alcohol history									
Absent	1074	14.9 ± 2.9	0.002	428	14.8 ± 2.9	0.06	646	15.0 ± 2.8	-
Present	303	14.4 ± 2.9		303	14.4 ± 2.9		0	-	
Refractive error									
Absent	511	14.8 ± 2.9	0.67	287	14.5 ± 3.0	0.64	224	15.0 ± 2.7	0.93
Present	866	14.8 ± 2.9		444	14.6 ± 2.9		422	15.0 ± 2.8	
Family history of glaucoma									
Absent	1371	14.8 ± 2.9	0.92	727	14.6 ± 2.9	0.50	224	15.0 ± 2.8	0.39
Present	6	14.5 ± 2.8		4	13.5 ± 3.0		422	16.5 ± 0.71	
Smoking status									
Non smoker	1106	14.3 ± 2.9	0.001	460	14.3 ± 2.9	0.021	646	15.0 ± 2.8	-
Smoker	271	14.9 ± 2.9		271	14.8 ± 2.9		0	-	
Insulin									
Non user of insulin	1310	14.8 ± 2.9	0.46	698	14.6 ± 2.9	0.42	612	15.0 ± 2.8	0.87
User of insulin	67	15.1 ± 3.1		33	15.0 ± 3.3		34	15.1 ± 3.0	
Anthropometry									
BMI									
Lean	87	14.2 ± 2.9	0.19	66	14.2 ± 2.9	0.50	21	14.1 ± 3.1	0.38
Normal	522	14.8 ± 3.0		365	14.7 ± 3.1		157	14.9 ± 2.9	
Overweight	562	14.9 ± 2.7		258	14.5 ± 2.8		304	15.2 ± 2.7	
Obese	206	14.9 ± 2.9		42	14.6 ± 2.8		164	14.9 ± 2.9	
Height (cm)									
≤ 156	586	15.0 ± 2.7	0.007	652	14.6 ± 2.9	0.95	619	15.1 ± 2.8	0.06
> 156	791	14.6 ± 2.9		79	14.6 ± 2.8		27	14.0 ± 3.0	
Weight (kg)									
< 57.5	410	14.7 ± 2.9	0.50	208	14.7 ± 3.1	0.08	163	14.8 ± 2.8	0.26
≥ 57.5	967	14.8 ± 2.9		523	14.6 ± 2.9		483	15.1 ± 2.8	
Axial length (mm)									
< 22.6	565	14.7 ± 2.9	0.25	257	14.3 ± 2.9	0.03	308	15.0 ± 2.7	0.97
≥ 22.6	786	14.9 ± 2.9		465	14.8 ± 2.9		321	15.1 ± 2.9	
Hypertension									
No	499	14.6 ± 2.9	0.03	300	14.4 ± 2.9	0.10	199	14.9 ± 2.8	0.33
Yes	878	14.9 ± 2.9		431	14.7 ± 2.9		447	15.1 ± 2.8	
Systolic BP (mmHg)									
< 130	401	14.4 ± 2.9	0.001	242	14.1 ± 2.8	0.003	159	14.8 ± 2.9	0.21
≥ 130	976	14.9 ± 2.9		489	14.8 ± 2.9		487	15.1 ± 2.8	
Diastolic BP (mmHg)									
< 80	429	14.7 ± 2.9	0.27	241	14.4 ± 2.9	0.17	188	15.0 ± 2.8	0.94
≥ 80	948	14.9 ± 2.9		490	14.7 ± 2.9		458	15.0 ± 2.8	
Biochemical									
Serum total cholesterol (mg/dL)									
< 200	883	14.7 ± 2.9	0.30	511	14.6 ± 2.9	0.95	372	14.9 ± 2.8	0.36
≥ 200	493	14.9 ± 2.8		219	14.6 ± 2.8		274	15.2 ± 2.8	

STDR: sight threatening diabetic retinopathy (severe Nonproliferative diabetic retinopathy, proliferative diabetic retinopathy and clinically significant macular edema), CSME: clinically significant macular edema, HbA1c: glycosylated hemoglobin, BP: blood pressure, CCT: central corneal thickness, BMI: body mass index, FBS: fasting blood sugar.

Table 1. Continued

Mean±SD

Risk factors	Over all (n=1377)			Men (n=731)			Women (n=646)		
	n	IOP (mmHg)	p	n	IOP (mmHg)	p	n	IOP (mmHg)	p
Serum high density lipoproteins (mg/dL)									
≥ 60	1327	14.8 ± 2.9	0.56	715	14.6 ± 2.9	0.93	612	15.0 ± 2.8	0.72
< 60	49	15.0 ± 2.9		15	14.7 ± 3.1		34	15.2 ± 2.8	
Serum triglycerides (mg/dL)									
< 150	848	14.7 ± 2.9	0.37	448	14.5 ± 2.9	0.56	400	14.9 ± 2.7	0.46
≥150	528	14.9 ± 2.9		282	14.7 ± 2.9		246	15.1 ± 2.9	
HbA1c (%)									
Normal (< 5.6)	97	14.7 ± 2.9	0.31	49	14.9 ± 3.1	0.72	48	14.5 ± 2.8	0.06
Good to Fair (5.6 - 8.0)	654	14.7 ± 2.8		346	14.5 ± 2.9		308	14.8 ± 2.7	
Poor (≥ 8.1)	626	14.9 ± 2.9		336	14.6 ± 2.9		290	15.3 ± 2.9	
Albuminuria									
No micro / macroalbuminuria	1123	14.8 ± 2.8	0.43	594	14.6 ± 2.9	0.96	529	14.9 ± 2.7	0.09
Microalbuminuria	217	15.0 ± 3.1		115	14.5 ± 3.2		102	15.6 ± 2.9	
Macroalbuminuria	37	14.5 ± 2.7		22	14.5 ± 2.9		15	14.5 ± 2.6	
FBS (mg/dL)									
< 126	402	14.8 ± 2.9	0.85	226	14.6 ± 3.1	0.94	176	15.0 ± 2.6	0.97
≥ 126	975	14.8 ± 2.9		505	14.6 ± 2.9		470	15.0 ± 2.9	
CCT (microns)									
< 511	466	14.5 ± 2.8	0.002	233	14.3 ± 2.9	0.07	233	14.6 ± 2.7	0.004
≥ 511	911	14.9 ± 2.9		498	14.7 ± 2.9		413	15.3 ± 2.8	
Pulse (Beats/min)									
< 80	960	14.6 ± 2.9	<0.0001	529	14.4 ± 2.9	0.003	431	14.9 ± 2.8	0.06
≥ 80	417	15.2 ± 2.8		202	15.1 ± 2.8		215	15.3 ± 2.8	
Diabetes complications									
Diabetic retinopathy									
Absent	1130	14.8 ± 2.8	0.44	578	14.6 ± 2.9	0.39	554	15.0 ± 2.7	0.77
Present	247	14.7 ± 3.1		155	14.2 ± 3.1		92	15.1 ± 3.1	
STDR									
Absent	1333	14.8 ± 2.9	0.54	702	14.6 ± 2.9	0.23	631	15.0 ± 2.7	0.38
Present	44	14.5 ± 3.1		29	13.9 ± 2.9		15	15.7 ± 3.2	
CSME									
Absent	1361	14.8 ± 2.9	0.29	722	14.6 ± 2.9	0.62	639	15.0 ± 2.8	0.02
Present	16	15.7 ± 3.1		9	14.1 ± 3.0		7	17.4 ± 2.2	
Diabetic neuropathy									
Absent	1113	14.9 ± 2.8	0.008	581	14.7 ± 2.9	0.06	532	15.1 ± 2.8	0.09
Present	251	14.4 ± 2.9		146	14.2 ± 2.9		105	14.6 ± 2.9	

STDR: sight threatening diabetic retinopathy (severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy and clinically significant macular edema), CSME: clinically significant macular edema, HbA1c: glycosylated hemoglobin, BP: blood pressure, CCT: central corneal thickness, BMI: body mass index, FBS: fasting blood sugar.

every week. After dilating the pupils with 5% phenylephrine and 1% tropicamide eyedrops (if phenylephrine is contraindicated, 1% cyclopentolate eyedrops used), lens opacities were graded using the Lens Opacities Classification System (LOCS chart III, Leo T. Chylack, Harvard Medical School, Boston, MA), retro illuminated with a light box. Fundus photographs were taken using the 45° four-field stereoscopic digital photography Carl Zeiss fundus camera (Visucamlite, Jena, Germany). Diabetic retinopathy was diagnosed based on the modified Klein classification (Modified Early Treatment Diabetic Retinopathy Study scales) [25]. The diabetic retinopathy grading was done by two independent observers in a masked fashion and the grading agreement of both were high (k=0.83).

Glycemic control was categorized as normal (glycosylated hemoglobin [HbA1c] < 5.6), good (HbA1c 5.6 -7.0), fair (HbA1c 7.1- 8.0) and poor (HbA1c ≥ 8.1) [20]. The fasting plasma glucose was considered to be high if the value was >126 mg/dL [26]. The height and weight of all subjects were noted, after which the body mass index (BMI) was calculated using the formula: weight (kg)/height (m^2) [27]. Based on the BMI, individuals were classified as lean (male, <20; female, <19), normal (male, 20-25; female, 19-24), overweight (male, 25-30; female, 24-29) or obese (male, >30; female, >29) [28]. The mean Indian height and weight (Indian Council of Medical Research, 1990), axial length [27], CCT [29], pulse beat [30] was taken for general characteristics, whereas, total cholesterol, high and low density cholesterol, triglycerides levels were taken from a previous study [31].

Along with the age and gender-specific mean IOP (± standard deviation [SD]), the mean IOP (± SD), based on the stratification of each categorical predictor, was also calculated. Analysis of variance (ANOVA) was used to compare the demographic, anthropometric, biochemical factors with the IOP. Beta values were calculated for the continuous variables. Both unadjusted and adjusted regression analysis was performed for the variables. All analysis was done using SPSS version 15.0 (SPSS Inc., Chicago, IL). A p value of ≤ 0.05 was considered significant.

RESULTS

Figure 1 shows the normal distribution of intraocular pressure among subjects with type 2 diabetes. The mean IOP was 14.8±2.9 mmHg (men 14.6±2.9 and women 15.0±2.8 mmHg, p=0.005). There was no significant difference between the mean IOP in the right and left eye (p=0.185). Table 1 shows the IOP distribution in various sub-groups. Subjects with hypertension and a raised systolic blood pressure (SBP) had a higher IOP than those without (14.9±2.9 vs 14.6±2.9 mmHg, p=0.03 and 14.9±2.9 vs 14.4±2.9 mmHg, p=0.001 respectively). Those with diabetic neuropathy had a lower IOP than those without (14.4±2.9 vs 14.9±2.8 mmHg, p=0.008). Among women subjects, those with clinically significant macular edema (CSME) had a higher IOP than those without CSME (17.4±2.2 vs 15.0 ±2.8 mmHg, p=0.02). Smokers had a higher IOP than non-smokers (14.9±2.9 vs 14.3±2.9, p=0.001) whereas, alcoholics had a lower IOP than non-alcoholics (14.4±2.9 vs 14.9±2.9, p=0.002). Short stature, high central cormeal thickness (CCT) and raised pulse beat were significantly associated with a higher IOP, whereas, longer axial length was significantly associated with a higher IOP only in men subjects. Table 2 describes the correlation of the continuous variables with the intraocular pressure. height, SBP, pulse, CCT and serum total cholesterol were the variables found to be significantly associated with intraocular pressure. Pulse (men: r=0.076, p=0.021 and women r=0.058, p=0.011) and CCT (men: r=0.12, p=0.001 and women r=0.182, p<0.001) were the variables associated with an elevated IOP in men and women.

Table 3 shows the gender-specific unadjusted analysis for continuous variables associated with IOP in subjects with type 2 diabetes. Factors associated with an elevated IOP included elevated systolic blood pressure (β=0.008, p=0.024), elevated resting pulse rate (β=0.019, p=0.006) and thicker central corneal thickness (β=0.011, p<0.001). Height was associated with a decrease in the IOP (β=-0.024, p=0.008). In men, the factors associated with an elevated IOP included higher resting pulse rate (β=0.021, p=0.04), thicker CCT (β=0.01, p=0.001) and systolic blood pressure (β=0.011, p=0.04); in women, elevated glycosylated hemoglobin (β=0.1, p=0.04) and CCT (β=0.015, p<0.001) were significant factors.

After adjusting the continuous variables associated with IOP in subjects with type 2 diabetes, the factors

Table 2. Correlation with intraocular pressure

Variable	r	p
Over All		
Age (y)	-0.015	0.29
Duration of diabetes (y)	-0.035	0.09
Weight (Kg)	-0.012	0.33
Height (cm)	-0.012	0.004
Systolic BP (mmHg)	0.061	0.01
Diastolic BP (mmHg)	0.041	0.06
Pulse (Beats/min)	0.074	0.003
CCT (μ)	0.139	< 0.001
Axial Length (mm)	0.026	0.16
Serum Total cholesterol (mg/dL)	0.047	0.04
Serum high density lipoproteins (mg/dL)	0.003	0.45
Serum Triglycerides (mg/dL)	0.021	0.16
HbA1C (%)	0.035	0.10
FBS (mg/dL)	0.045	0.04
Men		
Age (y)	0.014	0.35
Duration of diabetes (y)	-0.061	0.05
Weight (Kg)	-0.011	0.38
Height (cm)	-0.029	0.215
Systolic BP (mmHg)	0.076	0.02
Diastolic BP (mmHg)	0.057	0.06
Pulse (Beats/min)	0.076	0.02
CCT (μ)	0.12	0.00
Axial length (mm)	0.057	0.06
Serum total cholesterol (mg/dL)	0.013	0.36
Serum high density lipoproteins (mg/dL)	-0.008	0.41
Serum triglycerides (mg/dL)	0.027	0.23
HbA1C (%)	-0.003	0.47
FBS (mg/dL)	0.047	0.10
Women		
Age (y)	-0.041	0.14
Duration of diabetes (y)	0.025	0.26
Weight (kg)	0.016	0.34
Height (cm)	-0.027	0.24
Systolic BP (mmHg)	0.029	0.23
Diastolic BP (mmHg)	0.015	0.35
Pulse (Beats/min)	0.058	0.01
CCT (μ)	0.182	<0.001
Axial length (mm)	0.018	0.33
Serum total cholesterol (mg/dL)	0.063	0.05
Serum high density lipoproteins (mg/dL)	-0.008	0.41
Serum triglycerides (mg/dL)	0.037	0.17
HbA1C (%)	0.08	0.02
FBS (mg/dL)	0.039	0.16

BP: blood pressure, CCT: central corneal thickness, HbA1c: glycosylated hemoglobin, FBS: fasting blood sugar.

Table 3. Univariate associations with Intraocular Pressure (IOP) in participants of SN DREAMS 1

Risk factors	Unadjusted				
	β	95% CI		SE	p
		Lower bound	Upper bound		
Over All					
Age (y)	-0.004	-0.02	0.011	0.008	0.58
Duration of diabetes (y)	-0.016	-0.041	0.008	0.013	0.19
Weight (Kg)	-0.003	-0.017	0.011	0.007	0.66
Height (cm)	-0.024	-0.041	-0.006	0.009	0.008
Systolic BP (mmHg)	0.008	0.001	0.016	0.004	0.02
Diastolic BP (mmHg)	0.01	-0.003	0.024	0.007	0.13
Pulse (Beats/min)	0.019	0.005	0.033	0.007	0.006
CCT (μ)	0.011	0.007	0.016	0.002	<0.0001
Axial length (mm)	0.061	-0.062	0.183	0.063	0.33
Serum total cholesterol (mg/dL)	0.003	0.000	0.007	0.002	0.08
Serum high density lipoproteins (mg/dL)	0.001	-0.014	0.016	0.008	0.91
Serum triglycerides (mmg/dL)	0.001	-0.001	0.002	0.001	0.32
HbA1C (%)	0.045	-0.024	0.115	0.035	0.20
FBS (mg/dL)	0.002	0.000	0.005	0.045	0.09
Men					
Age (y)	0.004	-0.016	0.024	0.01	0.70
Duration of diabetes (y)	-0.027	-0.058	0.005	0.016	0.10
Weight (Kg)	-0.003	-0.023	0.017	0.01	0.77
Height (cm)	-0.013	-0.044	0.019	0.016	0.43
Systolic BP (mmHg)	0.011	0.001	0.022	0.005	0.04
Diastolic BP (mmHg)	0.015	-0.004	0.034	0.01	0.12
Pulse (Beats/min)	0.021	0.001	0.041	0.01	0.04
CCT (μ)	0.01	0.004	0.016	0.003	0.001
Axial length (mm)	0.131	-0.038	0.299	0.086	0.12
Serum total cholesterol (mg/dL)	0.001	-0.005	0.007	0.003	0.73
Serum high density lipoproteins (mg/dL)	-0.003	-0.025	0.02	0.011	0.82
Serum triglycerides (mg/dL)	0.001	-0.001	0.003	0.001	0.46
HbA1C (%)	-0.004	-0.102	0.094	0.05	0.99
FBS (mg/dL)	0.002	-0.001	0.006	0.047	0.20
Women					
Age (y)	-0.012	-0.035	0.011	0.012	0.29
Duration of diabetes (in years)	0.013	-0.027	0.053	0.02	0.53
Weight (kg)	0.004	-0.015	0.023	0.01	0.68
Height (cm)	-0.013	-0.049	0.023	0.018	0.49
Systolic BP (mmHg)	0.004	-0.006	0.014	0.005	0.47
Diastolic BP (mmHg)	0.004	-0.015	0.022	0.009	0.70
Pulse (Beats/min)	0.014	-0.005	0.032	0.009	0.14
CCT (μ)	0.015	0.009	0.021	0.003	<0.0001
Axial length (mm)	0.041	-0.142	0.224	0.093	0.66
Serum total cholesterol (mg/dL)	0.004	-0.001	0.009	0.003	0.11
Serum high density lipoproteins (mg/dL)	-0.005	-0.026	0.016	0.011	0.63
Serum triglycerides (mg/dL)	0.001	-0.001	0.004	0.001	0.35
HbA1C (%)	0.1	0.003	0.197	0.049	0.04
FBS (mg/dL)	0.002	-0.002	0.005	0.002	0.78

CCT: central corneal thickness, HbA1c: glycosylated hemoglobin, FBS: fasting blood sugar, CI: confidence interval, SE: standard error, SN-DREAMS 1: Sankara Nethralaya-diabetic Retinopathy Epidemiology and Molecular Genetic Study.

associated with elevated IOP are included in Table 4 as thicker central corneal thickness ($\beta = 0.011$, $p < 0.001$) and elevated resting pulse rate ($\beta = 0.001$, $p = 0.03$); height was associated with a decrease in the IOP ($\beta = -0.028$, $p = 0.008$). A thicker central corneal thickness was the single variable associated with an elevated IOP in men and women (men: $\beta = 0.01$, $p = 0.002$ and women $\beta = 0.015$, $p < 0.001$).

DISCUSSION

The supplementary Table shows the comparison of the mean IOP in published population-based reports among type 2 diabetes. The mean IOP among diabetics in our study was lower than other studies [2,8,9]. When compared to other races, the IOP in the Asian ethnicity is lower [7,10]. The Barbados Eye Study and the Los Angeles Latino Eye Study, like our study, has also found

Table 4. Multivariate associations with intraocular pressure (IOP) in participants of SN-DREAMS 1

Risk factors	Adjusted					
	Coefficient (β)	95% CI		Standard error	Partial r^2	p
		Lower bound	Upper bound			
Over All						
Height (cm)	-0.028	-0.048	-0.007	0.01	0.005	0.007
Pulse (Beats/min)	0.015	0.001	0.029	0.007	0.003	0.03
CCT (μ)	0.011	0.007	0.016	0.002	0.018	<0.001
Model r^2					0.037	<0.001
Men						
CCT (μ)	0.01	0.004	0.016	0.003	0.014	0.002
Model r^2					0.035	<0.02
Women						
CCT (μ)	0.015	0.008	0.021	0.003	0.031	<0.001
Model r^2					0.052	0.002

CCT: central corneal thickness, CI: confidence interval, SN-DREAMS 1: Sankara Nethralaya-diabetic Retinopathy Epidemiology and Molecular Genetic Study. The variables adjusted in multiple regression analysis are age, duration of diabetes, weight, height, systolic and diastolic blood pressure, pulse, central corneal thickness, axial length, total serum cholesterol, serum high density lipoproteins, serum triglycerides, glycosylated hemoglobin and fasting blood sugar.

a higher IOP among women with diabetes [2,11]. However, Kawase et al. [32] did not find any gender difference in IOP. We assume that the increased IOP among women with elevated glycosylated hemoglobin in our study is related to accumulation of fibronectin in trabecular meshwork [12]. Higher prevalence of obesity, hypertension and probably a higher life expectancy can best explain higher IOP among women [11]. Similar to our study, many other studies have reported a higher prevalence of elevated IOP among subjects with hypertension [2-4,11]. Although, the rationale for this is poorly understood, possible reasons could be increased aqueous humor production by ultrafiltration due to the elevated ciliary artery pressure, a generalized increase in the sympathetic tone or elevated serum corticosteroid levels as seen in hypertension subjects [4].

We found a higher IOP among women with CSME. The reason for this is unknown. But, this can probably be explained by a complex interplay between the change in retinal hemodynamics, ocular perfusion, scleral rigidity and hormonal influence among women [33].

We found an inverse relationship between the presence of diabetic neuropathy and IOP. al-Sereiti et al. [13] reported normal IOP among patients with diabetes having autonomic neuropathy. However, one study has shown that autonomic denervation may be a prerequisite of peripheral diabetic neuropathy [34]. It has been postulated that in autonomic neuropathy, the pupil/iris diameter is reduced, which increases the aqueous drainage, reducing the IOP [13].

Similar to previous studies, alcohol has been shown to lower the IOP, possibly through a reduction of net water movement into the eye [35], whereas, smoking was found to increase the IOP, hypothesized to be due to smoking induced degenerative changes in the arteries and increase in blood viscosity [36].

Wu et al. [3] found a positive association between pulse rate and IOP, similar to our study. Even on multivariate analysis after adjusting for variables like age, gender, duration of diabetes, BMI and glycemic control, the association between the resting pulse rate and the IOP remained the same.

Like earlier study [37], the present study also found a negative relationship between height and IOP. However, one study by Bulpitt et al. [4] found no relationship between the two. The height of an individual is related to genetic and acquired factors like status of growth hormone and childhood nutrition [38] which may probably affect the IOP. BMI and IOP being directly proportional, and height being inversely proportional to BMI [19], we can expect a similar inverse relationship between height and IOP.

Earlier study has reported a similar relationship between CCT and IOP among subjects with diabetes [11]. However, as diabetes affects corneal biomechanics, this results in lower corneal hysteresis values than those in healthy control subjects [39]. This may cause clinically relevant high IOP measurements independent of CCT. Also, the GAT gives an accurate intraocular pressure reading for an eye with average CCT, but tends to underestimate or overestimate the true intraocular pressure for thinner and thicker cornea, respectively [11]. Our study confirmed this correlation between increasing IOP and increasing CCT as measured by GAT.

The strength of this study was that it used photography and standard grading techniques. Further, the study was representative of a large population, and the results could be extrapolated to the whole of urban India. One of the

limitations of this study was the absence of non-diabetic subjects, including them may have elicited a better relationship between IOP and subjects with DM. Also, in subjects with known DM, a second estimation of blood glucose was not performed; the diagnostic accuracy of the treating diabetologists was relied upon totally. The sample size for this study was calculated for the estimation of the prevalence of diabetic retinopathy in the general population; the power to elucidate associated risk factors in the subgroup analysis may be inadequate. This study does not have any data on progression, as no follow-up is envisaged. These data stress on the need for regular ocular examinations in subjects with type 2 DM in countries like India, especially for smokers and when associated with systemic hypertension. Even the IOP distribution in subjects with type 2 diabetes is gender specific. In conclusion, identifying the risk factors for high IOP in this population will prevent blindness in this vulnerable population.

CONFLICT OF INTEREST

The authors have no conflicts of interest with the material presented in this paper.

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Appendix. Comparison of mean IOP in published population-based reports among type 2 diabetes

Study name	Country	Publication year	Ethnicity	Gender	Age range (y)	Age (mean ± SD) (y)	Sample (n)	IOP measurement technique	IOP (mean ± SD) (mmHg)
Bankes JL [14]	England	1967	Mixed	Both	≥40	NA	212	GAT	16.69 ± 3.32
Bouzas AG, et al [15]	New England	1971	Mixed	Both	51 - 68	NA	56	GAT	15.19 ± 3.15
Williams B, et al [16]	England	1980	Mixed	Both	25 - 70	53.36 ± 13.3	14	Perkins handheld	18.9 ± 2.25
Wisconsin epidemiologic study [17]	USA	1984	Mixed	Both	0 to >75	NA	2990	GAT	16.3 ± 4.12
Arora VK, et al [7]	India	1989	Asian	Males	NA	NA	46	Schiotz	19.26
al-Sereiti MR, et al [13]	England	1991	Mixed	Both	NA	40 ± 15	38	Non-contact Pneumotonometer	15.5±3.9
Beaver dam eye study [3]	USA	1992	Mixed	Both	43 - 84	NA	438	GAT	16.05 ± 3.8
Baltimore eye survey [9]	USA	1995	Mixed	Both	≥ 40	NA	714	GAT	17.9 ± 0.24
Rotterdam study [18]	Netherland	1996	White	Both	≥ 55	55 - 94	256	GAT	14.86 ± 2.91
Barbados eye study [2]	West Indies	1997	Mixed	Both	40 - 84	58	17	GAT	18.6 ± 3.7
Barbados incidence study of eye diseases [8]	West Indies	2003	Mixed	Both	40 - 84	57.5 ± 11.5	559	GAT	21.5 ± 4.7
Oshitari T [12]	Japan	2007	Japanese	Both	NA	60.86 ± 10.76	190	GAT	16.0 ± 2.5
Los Angeles Latino eye study [11]	USA	2008	Mexicans	Both	≥ 40	NA	1416	GAT	15.2 ± 3.3
Beijing eye study [10]	China	2009	Chinese	Both	45 - 89	60.4 ± 10	381	Non-contact Pneumotonometer	16.14 ± 2.96
Present study	India	2010	Asian	Both	≥ 40	56.32 ± 10.02	1414	GAT	14.8 ± 2.9

GAT: goldmann applanation tonometry, IOP: intraocular pressure, SD: standard deviation.