

Research Article

Impact of Glycated Hemoglobin on Intraocular Pressure in Diabetic Patients

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Abstract: Diabetes mellitus (DM) is a metabolic disease associated with chronic hyperglycemia. It is a distressing epidemic and is considered one of the leading causes of death worldwide. Globally, the prevalence of DM is estimated to be 9.3% (463 million people), increasing to 10.2% (578 million) and 10.9% (700 million) by 2030 and 2045, respectively. The relationship between glycated hemoglobin (HbA1c) levels and intraocular pressure (IOP) in patients with diabetes mellitus (DM) is a subject of significant clinical interest due to its implications for glaucoma risk and diabetic eye disease progression. **Material and methods** This is a prospective and observational study was conducted in the Department of Ophthalmology, Dr. VRK Women's Medical College, Teaching Hospital & Research Centre. Subjects with provisional diabetes were confirmed to be having diabetes by re-estimating fasting blood glucose by enzymatic assay- based glucose oxidation method. 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. **Results** A total of 120 patients involving 240 eyes of Type 2 diabetes mellitus patients who satisfied the inclusion criteria were included in our study. Out of 120, 76 patients were male (63.3%), and 44 patients were female (36.7%). The patients ranged between the ages of 40-89 years. The mean age was 59.62 years with a standard deviation of 9.76. The mean intraocular pressure in males was 15.6 ± 2.9 mmHg, and in females, the mean intraocular pressure was 15.5 ± 3.2 mmHg. **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.

Keywords: Diabetes, Intraocular Pressure, Glaucoma, Glycated Hemoglobin

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease associated with chronic hyperglycemia. It is a distressing epidemic and is considered one of the leading causes of death worldwide. Globally, the prevalence of DM is estimated to be 9.3% (463 million people) in 2018, increasing to 10.2% (578 million) and 10.9% (700 million) by 2030 and 2045, respectively, with more than 29% incidence in Saudi Arabia alone from 1990 -2015. DM is diagnosed according to plasma glucose criteria in the form of fasting plasma glucose (FPG) levels, 2-h plasma postprandial glucose (2- h PPG) levels,[1] or the glycosylated hemoglobin (HbA1c) criteria reflecting the average plasma glucose concentration over the previous 8–12 weeks. The International Expert Committee recommends HbA1c as a reliable tool for diagnosing type 1 and type 2 DM with a cut-off point of $\geq 6.5\%$. [2]

HbA1c testing has multiple advantages over plasma glucose measurement, such as pre-analytical stability and less day-to-day variation due to stress or illness. Therefore, HbA1c is the gold standard for diabetes control. Besides reflecting the glycemic adjustment, HbA1c is used as a predictor to assess secondary microvascular complications, including retinopathy, neuropathy, and nephropathy in cases of insufficient glycemic control.[3] Diabetes contributes to the risk of

developing several types of glaucoma, most commonly, primary open-angle glaucoma (POAG) and neovascular glaucoma (NVG).[4]

POAG is a multifactorial disease that is caused by retinal ischemia, remodeling of the optic nerve head, and altered trabecular meshwork function. Diabetic patients are susceptible to retinal ischemia, which is believed to be the main cause of neovascular glaucoma by stimulating the

CME Journal of Geriatric Medicine 42 release of vascular endothelial growth factor-A (VEGF-A), leading to vasodilatation and increasing blood flow, which initiates new blood vessel formation leading to NVG. [5] Glaucoma is defined as a group of ocular disorders that are characterized by progressive optic neuropathy and associated visual field loss. Although treatable, it is the most common irreversible blinding disease worldwide. Therefore, early detection is required for a good prognosis. Normal intraocular pressure (IOP) is 10-21 mm Hg, which is preserved by a balance between the aqueous humor production and drainage. Any imbalance leads to elevated IOP, causing both vascular and mechanical stresses. Therefore, it is an important risk factor for glaucoma deterioration and progression, and currently, is the only modifiable factor.[6]

A recent meta-analysis evaluated 47 studies from 16 different countries and found that patients with diabetes had been associated with an average of 0.18 mmHg increase in the IOP. Furthermore, other studies found that patients with increased levels of HbA1c had substantially higher IOP levels compared to the patients with lower levels of HbA1c.[7]

A study conducted in Riyadh, Saudi Arabia, found that diabetic patients had higher IOP compared to non-diabetic subjects. HbA1c was used as a criterion for diagnosing diabetes; however, the relationship between HbA1c value and IOP has not been studied. To the best of our knowledge, there have been no reports evaluating the relationship between HbA1c and IOP among the Saudi population.[8-10] Therefore, we aimed to investigate the effect of chronic hyperglycemia as determined by HbA1c on IOP in patients with diabetes and identify diabetic patients at risk of developing glaucoma

MATERIALS AND METHODS

This is a prospective and observational study was conducted in the Department of Ophthalmology, Dr. VRK Women's Medical College, Teaching Hospital & Research Centre.

The study population was selected by multistage, systematic random sampling based on the socio-economic status, which made the sample a true representation of subjects with type 2 DM in India.

Known diabetics and provisional diabetics were selected in accordance with the ADA criterion. 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). The biochemical analyses done using the semi-automated analyzer included total serum cholesterol (CHOD-POD method), high-density lipoproteins (after protein precipitation CHOD-POD method), serum triglycerides (CHOD-POD method), hemoglobin (calorimetric hemoglobinometer), packed cell volume (capillary method) and the glycosylated hemoglobin fraction.

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. Micro albuminuria was estimated using the first morning urine sample, by a semi quantitative procedure in which the subjects were considered to have micro albuminuria, if the albumin creatinine ratio (ACR) was between 30 and 299 mg/g. Diabetic neuropathy was assessed by measuring the vibration perception threshold (VPT) using a sensitometer by a single 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.

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 microscopy, 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 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, and Jena, Germany), using 0.05% proparacaine eyedrops as topical anaesthesia and 2% fluorescein to stain the tear film. 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 every week. After dilating the pupils with 5% phenylephrine and 1% tropic amide 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). 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).

Glycaemic 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). The fasting plasma glucose was considered to be high if the value was >126 mg/dL. The height and weight of all subjects were noted, after which the body mass index (BMI) was calculated using the formula: weight (kg)/height (m²). 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). The

mean Indian height and weight (Indian Council of Medical Research, 1990), axial length, CCT, pulse beat was taken for general characteristics, whereas, total cholesterol, high and low density cholesterol, triglycerides levels were taken from a previous study.

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

A total of 120 patients involving 240 eyes of Type 2 diabetes mellitus patients who satisfied the inclusion criteria were included in our study. Out of 120, 76 patients were male (63.3%), and 44 patients were female (36.7%). The patients ranged between the ages of 40-89 years. The mean age was 59.62 years with a standard deviation of 9.76. The mean intraocular pressure in males was 15.6 ± 2.9 mmHg, and in females, the mean intraocular pressure was 15.5 ± 3.2 mmHg. (Table 1)

Table 1: Gender distribution

Gender	Frequency	Percentage (%)	Mean IOP (mmHg)	SD IOP (mmHg)
Female	44	36.7	15.51	3.19
Male	76	63.3	15.62	2.90
Total	120	100.0	-	-

Number of patients in each age group were as follows 40- 49 years: 12 females and 8 males, with a mean intraocular pressure (IOP) of 14.70 ± 2.99 mmHg and 15.60 ± 3.75 mmHg, respectively. 50-59 years: 17 females and 24 males, with a mean IOP of 15.64 ± 3.27 mmHg and 15.50 ± 2.71 mmHg, respectively. 60-69 years: 14 females and 26 males, with a mean IOP of 14.75 ± 2.69 mmHg and 16.00 ± 2.86 mmHg, respectively. 70-79 years: 8 females and 12 males, with a mean IOP of 16.67 ± 3.45 mmHg and 16.20 ± 3.30 mmHg, respectively. 80-89 years: 3 females and 4 males, with a mean IOP of 15.00 ± 2.76 mmHg for both genders.

The overall mean intraocular pressure in different age groups was as follows: 40-49 years: 15.00 ± 3.23 mmHg, 50-59 years: 15.56 ± 2.93 mmHg 60-69 years: 15.53 ± 2.85 mmHg 70-79 years: 16.38 ± 3.31 mmHg 80-89 years: 15.00 ± 2.76 mmHg

Table 2: Age distribution

Age Group	Frequency	Percentage (%)	Mean IOP (mmHg)	SD IOP (mmHg)
40-49	18	15.0	15.00	3.2
50-59	41	34.2	15.56	2.9
60-69	38	31.7	15.53	2.8
70-79	19	15.8	16.38	3.3
80-89	4	3.3	15.00	2.8
Total	120	100.0	-	-

Table 3: Mean IOP in Different Gender by Age Group

Age Group	No. of Females	Mean IOP (Females)	SD IOP (Females)	No. of Males	Mean IOP (Males)	SD IOP (Males)
40–49	12	14.70	2.99	6	15.60	3.75
50–59	17	15.64	3.27	24	15.50	2.71
60–69	14	14.75	2.69	24	16.00	2.86
70–79	7	16.67	3.45	12	16.20	3.30
80–89	–	–	–	4	15.00	2.76

Table 4: Mean IOP Difference in Categories of HbA1c

HbA1c Category	N	Mean IOP (mmHg)	Std. Dev (mmHg)	F Value	p Value
6 to 8	86	15.06	2.808	15.246	0.001
9 to 10	91	14.82	2.637		
> 10	63	17.42	3.051		
Total	240	15.58	3.005		

Mean IOP was found to be increasing with HbA1c levels

The number of eyes in each group according to the ETDRS classification was as follows No diabetic retinopathy Patients: 46 (comprising 19 females and 27 males) Eyes: 92 (38.3% of 240 eyes) Mean IOP: 13.76 ± 2.141 mmHg Mild NPDR Patients 20 (5 females and 15 males) Eyes 40 (16.7% of 240 eyes) Mean IOP: 15.29 ± 2.646 mmHg Moderate NPDR Patients 26 (11 females and 15 males) Eyes: 52 (21.7% of 240 eyes) Mean IOP: 16.00 ± 2.762 mmHg Severe NPDR Patients 12 (4 females and 8 males) Eyes: 24 (10% of 240 eyes) Mean IOP: 16.80 ± 1.881 mmHg PDR Patients 16 (6 females and 10 males) Eyes 32 (13.3% of 240 eyes) Mean IOP: 19.62 ± 2.118 mmHg

Mean IOP was found to be increasing with the severity of diabetic retinopathy grading

Out of the 120 patients, 19 were found to have an intraocular pressure greater than 20 mmHg in one or both eyes. It was observed that patients in the moderate NPDR group (Group 3) had a higher mean IOP compared to those in the no retinopathy (Group 1) and mild NPDR (Group 2) groups. Additionally, no linear correlation was found between HbA1c levels and intraocular pressure.

DISCUSSION

This is the first study to use MR analysis to estimate the causal associations of type 2 diabetes and fasting glucose and HbA1c levels with the risk of POAG. This MR study showed that a genetic predisposition to type 2 diabetes was associated with an increased risk of POAG in the European population without pleiotropy regardless of whether type 2 diabetes is unadjusted or adjusted for BMI.[11] However, no statistically significant association was observed between genetically predicted type 2 diabetes and the risk of POAG in the East Asian population. We did not find any association between genetically predicted fasting glucose and HbA1c levels and the risk of PAOG.[12]

Several observational studies have reported an association between type 2 diabetes and POAG. For example, the Los Angeles Latino Eye Study demonstrated that the risk of POAG was 40% higher in participants with type 2 diabetes than in those without type 2 diabetes. [13] Similarly, women with type 2 diabetes were independently associated with an 82% increased risk of incident primary POAG in the Nurses’ Health Study.[14] Moreover, a meta-analysis

The estimate of type 2 diabetes represents the average causal effect on the subgroup of individuals only under a plausible monotonicity assumption, which is that an increase in the number of risk alleles does not lower the likelihood of type 2 diabetes for any individual.

[16] Although the underlying pathways between type 2 diabetes and POAG remain unclear, several mechanisms have been proposed. One possible explanation is that type 2 diabetes may be related to elevated IOP, which is the only widely recognized modifiable risk factor for POAG. In this regard, a genome-wide meta-analysis indicated that most of the risk loci associated with POAG have also been associated with IOP or vertical cup-to-disc ratio. [17] The pooled mean values estimated that participants with diabetes have higher 0.18 mm Hg of IOP than those without diabetes. The increasing glucose levels may increase IOP by increasing fibronectin production in the bovine trabecular meshwork. [18] In addition, type 2 diabetes increases corneal stiffness and central corneal thickness, which increases IOP measurement values artificially. Another possible explanation for popularity is vascular mechanisms. Diabetes mellitus may lead to microvascular structural and functional damage.[19]

Hence, dysfunction in these vessels induces poor vascular autoregulation of the retina and optic nerve to protect against IOP and blood pressure fluctuations. In addition to these vascular changes, diabetes can impair physiological glial and neuronal function in the retina, which may increase the susceptibility of retinal ganglion cells to glaucomatous damage. Nonetheless, the potential mechanisms underlying this association need to be evaluated more thoroughly.[20]

However, in contrast to several observational studies, this MR study found that there was no significant causal association between type 2 diabetes and POAG among the East Asian population. On the one hand, the variety of SNPs associated with type 2 diabetes between East Asian and European ancestries caused different effect sizes. [21] On the other hand, the differences in clinical characteristics across ethnic groups were an important interpretation method for the subtle discrepancy in the association between type 2 diabetes and POAG. For example, there is a preponderance of normal-tension glaucoma over high-tension glaucoma in Asians compared with the White population. [22]

Furthermore, the statistical power may be an important explanation for such variance, since there was a relatively small sample size (6935 POAG cases) and limited valid IVs of type 2 diabetes in the East Asia population compared to European ancestry. An accurate estimate of the causal association between type 2 diabetes and the occurrence of POAG is difficult in observational studies. Except for POAG, type 2 diabetes results in many ocular diseases; thus patients with type 2 diabetes are more likely to receive more ophthalmological examinations.[23]

This may lead to an overestimation of the association between type 2 diabetes and POAG. In addition, it is possible that diabetes complications could lead to retinal diseases and visual field defects, resulting in

overdiagnosis of POAG. It is also possible that the effect sizes of such observational studies were influenced by various confounding factors. Therefore confounding, reverse causation, and various biases in these studies may generate unreliable indicators of the causal effects of type 2 diabetes on the risk of POAG. [24] Analogous to randomized controlled trials, the MR analysis assumes that the alleles of interest are randomly and equally distributed in the population of interest and can infer causality to some extent. Given the largely asymptomatic nature of early glaucoma and the long latent phase of the disease, the results of this study provide valuable information for the screening and early detection of POAG among patients with type 2 diabetes. It is important for the management of type 2 diabetes and prevention of POAG.[24]

CONCLUSION

In conclusion, type 2 diabetes is causally associated with the risk of POAG in European instead of East Asian populations. The point estimates of fasting glucose and Hb1Ac with POAG are large but not statistically significant, which prompts the question of statistical power.

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