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Research Article

Association between Glucose Levels and Intraocular Pressure in Diabetic Patients

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Abstract

Purpose: To assess whether high hemoglobin A1c levels influence intraocular pressure in patients with non-proliferative diabetic retinopathy.

Methods: A prospective case series study was performed on 75 patients with non-proliferative diabetic retinopathy and 25 healthy control subjects. Ophthalmic examinations included best corrected visual acuity, slit lamp biomicroscopy, and intraocular pressure measurement. A corresponding hemoglobin A1c were measured using capillary glucose testing. Exclusion criteria included a glaucoma or treatment with IOP lowering medications and oral or topical steroids. Multivariable logistic regression models were used after controlling for the same sets of confounders. A value of $P < 0.05$ was considered significant.

Results: There was non-statistically significant difference as regards age, systolic and diastolic systemic hypertension, BCVA, central corneal thickness, while, there was a statistically significant differences as regard body mass index, smoking states, HDL cholesterol, LDL cholesterol, triglyceride, HBA1c, and intraocular pressure (<0.001) between diabetic and non-diabetic groups. There was statistically significant difference between 25 diabetic patients had an IOP < 14.5 mmHg and mean HbA1c of 8.3 ± 1.2, in comparison with 50 diabetic patients had an IOP ≥ 14.5 mmHg and a mean HbA1c of 9.0 ± 3.4.

Conclusions: Diabetic patients with elevated HbA1c levels revealed statistically significantly higher IOPs compared to those with lower HbA1c levels. Thus, early HbA1c monitoring may be useful in assessing potential risk for developing increased IOP in patients with diabetes.

Keyword: IOP; Glucose Levels; Diabetic Mellitus.

Introduction

Epidemiological data suggests that patients with diabetes are at increased risk of developing primary open angle glaucoma (POAG) [1-4]. Various studies have reported a high prevalence of type 2 diabetes and POAG among different ethnic populations including Australians [5], Japanese [6]. Another study also found that intraocular pressure (IOP) of eyes in patients with uncontrolled diabetes was significantly higher than the IOP of eyes in patients with controlled diabetes [7].

Although the underlying mechanism remains unclear, in vitro studies suggest that high glucose conditions can induce excess extracellular matrix (ECM) synthesis by trabecular meshwork cells. This may lead to ECM accumulation in the trabecular meshwork, contributing to blockage of aqueous outflow [8].

Studies have suggested that changes in corneal biomechanics (increased corneal hysteresis) in diabetic eyes would lead to overestimated IOP measurements [9,10]. However, it is not known whether variations in glucose levels could lead to IOP changes in diabetic and non-diabetic individuals.

Diabetes is commonly accompanied by microvascular damage, which might contribute to numerous ocular complications, including elevated IOP and subsequent glaucoma [11], a leading cause of irreversible blindness worldwide. According to a recent meta-analysis of 47 studies from 16 countries [12], a history of diabetes was associated with an average increase of 0.18 mmHg in IOP and a 48% increased relative risk for primary open-angle glaucoma compared to the risk in non-diabetic patients.

The underlying mechanisms linking diabetes, central corneal thickness (CCT) and elevated IOP have not been fully elucidated. Accumulating evidence suggests that a high glucose level status may disrupt cell and repair functions in the cornea [13], thus potentially affecting the CCT [14]. Because IOP values rise by 0.11–1.00 mmHg per 10-µm increase in CCT [15], it is plausible that a positive association between diabetes and high IOP may be partly attributable to a greater CCT in patients with diabetes.

Furthermore, it is not clear whether diabetes is a CCT-independent cause of elevated IOPs or whether the observed positive association between diabetes and IOP is mediated by CCT increases. Also, the influence of type 2 diabetes, serum glucose, and hemoglobin A1c (HbA1c) levels on IOP was considered in patients with non-proliferative diabetic retinopathy (NPDR).

In the current study, we determined whether an association exists between elevated blood glucose levels, HbA1c and IOP in patients with NPDR.

Methods

This prospective observational cross section study adhered to the tenets of the Declaration of Helsinki in the period from December 2021 to July 2022. This study included 75 patients with non-proliferative diabetic retinopathy (NPD) and 25 healthy control subjects. Informed consent, demographic data and risk-benefit of examination procedures were explained. Both non-diabetic and diabetic patients age more than 40 years were included.

Patients

Diabetic patients were reported by diagnosis of fasting glucose above 120 mg/ml or postprandial glucose >150 mg/ml and under treatment. Healthy non-diabetic individuals were included and self-reported normal glucose levels in previous 6 months were included in the study.

Any history of glaucoma, steroid medication topical/oral, corneal opacity, refractive error of >5D or cylindrical >2D, and central corneal thickness (based on ultrasound pachymetry) above 600 microns or below 450 microns were excluded. Any retinal pathology not associated with diabetes mellitus such as retinal arteriolar alterations, exudates, cotton wool spots, hemorrhage, extensive micro-vascular abnormalities and papilledema in hypertensive retinopathy were excluded. Vitrectomy, and buckling surgery, trauma or intraocular surgery for cataract were also excluded from the study.

All participants were asked about their socio-demographics, lifestyle factors (e.g., smoking status), medical history (e.g., history of diabetes or hypertension), ocular history (i.e., cataract surgery and refractive surgery), and medications. The health examination included anthropometry, blood pressure, laboratory measurements, and ocular examinations.

Anthropometric parameters, including weight, and height, were measured. The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood pressure was

taken twice in the sitting position, and the mean value of these two successive readings was recorded. Blood samples were collected for measurements of serum glucose (fasting or non-fasting), HbA1c, HDL cholesterol, LDL cholesterol and triglyceride concentrations.

All participants underwent a full ophthalmological examinations including best-corrected visual acuity (BCVA) assessment using Landolts broken ring chart then converted to Log MAR, slit-lamp biomicroscopy for anterior segment evaluation, intraocular pressure measurement using Goldmann applanation tonometer, gonioscopy with three-mirror lens, dilated funduscopic examination with Volks 90 D and fundus fluorescin angiography, and CCT was measured using a ultrasound pachymeter (DGH, Exton, PA, USA).

Diabetic retinopathy classified according to grades of severity as per International clinical diabetic retinopathy severity scale [16]. No apparent signs show no diabetic retinopathy. Mild to moderate non-proliferative diabetic retinopathy (NPDR) characterized with micro-aneurysms, retinal hemorrhages, exudates, cotton wool spots, venous beading and intraretinal microvascular aneurysms.

Capillary glucose testing

All participants underwent capillary glucose testing in two distinct situations: first, baseline measurements (fasting for exactly 8 hours, i.e., after overnight fasting) and, second, postprandial measurements (exactly 2 hours after the meal, i.e., after lunch time). The measurement of capillary glucose was performed by collecting blood from the patient's finger, pierced through the skin by a lancet and checked with an automated device (OneTouch LifeScan, Johnson and Johnson, CA, USA).

Glycated hemoglobin (HbA1c) is a blood test, which doesn't require not eating for a period of time (fasting), shows average blood sugar level for the past 2 to 3 months. It measures the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells. The higher blood glucose levels, the more hemoglobin with sugar attached. An HbA1c level of 6.5% or higher on two separate tests means that have diabetes. An HbA1c between 5.7% and 6.4% means that have pre-diabetes. Below 5.7% is considered normal.

Random blood sugar test, a blood sample will be taken at a random time. No matter when you last ate, a blood sugar level of 200 milligrams per deciliter (mg/dL) 11.1 millimoles per liter (mmol/L) or higher suggests diabetes. Fasting blood sugar test, a blood sample will be taken after haven't eaten anything the night before (fast). A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered pre-diabetes. If it's 120 mg/dL (7 mmol/L) or higher on two separate tests, or postprandial glucose >150mg/ml suggests diabetes.

Intraocular pressure assessment

Immediately after the capillary glucose testing, IOP was measured (i.e., fasting for exactly 8 hours and exactly 2 hours after lunch time) of each patient by Goldmann applanation tonometer (Haag-Streit, Köniz, Switzerland). The calibration of each instrument was checked at the beginning of each session, according to the manufacturers' instructions [16]. All measurements were taken with the patient in a sitting position. The same examiner performed all IOP measurements in a masked fashion.

The cut-off value of 14.5 mmHg for IOP level was chosen based on human and animal studies. A study investigating the efficacy of IOP lowering drugs used IOP level between 14 and 15 mmHg as the mean baseline value [14]. Subjects in this chart analysis were separated into two groups based on IOP level: those ≥14.5 mmHg and those <14.5 mmHg.

Statistical analysis

Statistical Package for the Social Sciences windows version 26 (IBM, Armonk, NY, USA) was used for statistical analysis of the collected data. The association between changes in glucose levels and IOP variation was investigated using univariable and multivariable regression analyses. The baseline glucose level was not included in the multivariable model to avoid collinearity between glucose level variations and baseline glucose level.

The HbA1c values of each group were averaged and expressed as mean ± SD. The results were analyzed by one-way ANOVA, and significance was determined using post hoc comparison test. Multivariable logistic regression models were used after controlling for the same sets of confounders. A value of $P < 0.05$ was considered significant.

Results

Demographic, systemic, and ocular characteristics of the diabetic versus non-diabetic patients revealed that there was non-statistically significant difference as regards age, systolic and diastolic systemic hypertension, BCVA, central corneal thickness (0.071, 0.021, 0.163,0.165) between diabetic and non-diabetic patients. There was a statistically significant differences as regard body mass index, smoking states, HDL cholesterol, LDL cholesterol, triglyceride, HBA1c, and intraocular pressure between diabetic and non-diabetic patients (<0.001) (Table 1).

Regarding adjustment of mean intraocular pressure by diabetes, HbA1c, and serum glucose using Multivariable-adjusted, there was a statistically significant differences between IOP and diabetes, HBA1c, and serum glucose levels (<0.001) (Table 2).

Demographic and clinical characteristic of the diabetic patients with cut-off value of 14.5 mmHg for IOP level are presented in (Table 3 and Figure 1). Twenty-five patients had an IOL of <14.5 mmHg, ranging from 10.2-15.3 mmHg, with an average HbA1c of 8.1 ± 1.1. Fifty patients had an IOP of ≥ 14.5 mmHg, ranging from 14.5–22.1 mmHg, with an average HbA1c of 9.0 ± 2.1 (P = 0.001.).

Regression analysis indicated that diabetic subjects with higher HbA1c levels exhibited an IOP less than 14.5 mmHg. In addition an association between IOP and HbA1c levels was noted in patients with HbA1c level at 9.5 and higher but not in patients with HbA1c level below 9.5.

Characteristics	Diabetes[b] (n = 75)	No-diabetes (n = 25)	P-value[a]
Demographic features			
Mean age in years (SD)[c]	61.9 (7.8)	58.3 (10.0)	0.071
Male participants, n (%)	38 (50.1)	10 (40.0)	0.051
Body mass index, kg/m^2 (SD)	26.6 (3.6)	21.0 (3.0)	<0.001
Weight, kg (SD)	64.6 (12.1)	57.0 (11.4)	<0.001
Height, cm (SD)	158.6 (9.3)	151.0 (9.1)	<0.001
Smoking status, n (%)			<0.001
Non- smokers	31.0	20.0	
Current smokers	44.0	5.0	
Systemic features			
Hypertension, n (%)	55.2	45.9	0.021
Systolic BL P, mmHg (SD)	129.3 (16.1)	123.1 (16.6)	0.026
Diastolic BL P, mmHg (SD)	76.3 (11.1)	73.6 (11.6)	0.063
HDL cholesterol, mg/dL (SD)	72.4 (13.2)	51.0 (12.8)	<0.001
LDL cholesterol, mg/dL (SD)	129.3 (31.6)	112.9 (29.1)	<0.001
Triglyceride, mg/dL (SD)	116.0 (75.9)	98.0 (66.5)	<0.001
HbA1c, % (SD)	6.9 (1.3)	5.1 (0.2)	<0.001
Fasting glucose, mg/dL (SD)	131.4 (34.3)	97.3 (6.1)	<0.001
Postprandial glucose , mg/dL (SD)	159.2 (43.6)	99.6 (14.1)	<0.001
Ocular features			
BCVA Log MAR (SD)	0.29 (0.23)	0.19 (0.20)	0.163
CCT, µm (SD)	553.3 (48.2)	551.0 (58.3)	0.165
Intraocular pressure, mmHg (SD)	17.3 (2.3)	14.1 (2.9)	<0.001

Table 1: Demographic, systemic, and ocular characteristics of the participants according to their diabetic status.

[a]Values are presented as the means (SDs) for continuous variables and percentages for categorical variables.

[b]Diabetes was defined as self-reported anti-diabetic medication use, physician-diagnosed diabetes, or HbA1c ≥ 6.5%.

[c]All values other than age were adjusted for age and sex.

HbA1c = Glycosylated hemoglobin A1c; HDL= High-Density Lipoprotein; LDL = Low-Density Lipoprotein; SD = Standard Deviation, BCVA = Best Corrected Visual Acuity; BLP = Blood Pressure, CCT = Central Corneal Thickness.

Characteristics	No. (%)	Mean intraocular pressure, mmHg (SE)			
		Multivariable-adjusted[a]	P-value	Multivariable-adjusted[b]	P-value
Diabetes[c]					
No	25	13.6 (0.1)	<0.001	13.6 (0.1)	<0.001
Yes	75	14.1 (0.1)		14.1 (0.1)	
Serum HbA1c, %					
<7.0%	5,21	13.7 (0.1)	<0.001	13.6 (0.1)	<0.001
≥7.0%	1,58	14.3 (0.1)		14.2 (0.1)	
Serum glucose, mg/dL					
Fasting <120 or non-fasting <150	5,28	13.7 (0.1)	<0.001	13.5 (0.1)	<0.001
Fasting ≥ 120 or non-fasting ≥ 150	851	14.3 (0.1)		14.3 (0.1)	

Table 2: Adjusted mean intraocular pressure by diabetes, HbA1c, and serum glucose.

[a]Adjusted for age, sex, smoking status, hypertension, and body mass index.

[b]Adjusted for age, sex, smoking status, hypertension, body mass index, and central corneal thickness.

[c]Diabetes was defined as self-reported anti-diabetic medication use, physician-diagnosed diabetes, or HbA1c ≥ 6.5%.

HbA1c, haemoglobin A1c; SE, standard error.

Subjects	Low IOP (<14.5)	High IOP (≥14.5)	P-value*
Number	25	50	0.036
Gender (F/M)	15/10	35/15	0.078
Mean age (yrs)	56.2	53.8	0.054
IOP measurement (mmhg)	12:18	13:17	0.069
Mean HbA1c	8.3 ± 1.2	9.0 ± 2.4	<0.001

Table 3: Demographic and clinical characteristic of the diabetic patients with cut-off value of 14.5 mmHg for IOP level.

Patients with an IOP of less than 14.5 mmHg and those with greater than equal to14.5 mmHg revealed mean HbA1c between the two groups are statistically significantly different (*P = 0.001).

Discussion

Diabetic retinopathy and glaucoma are major causes of irreversible blindness. Diabetes mellitus affects microvascular system affecting the auto-regulatory mechanism of retinal blood vessels and optic nerve and subsequently associated with increase of intraocular pressure. Therefore, diabetes is suggested to be a

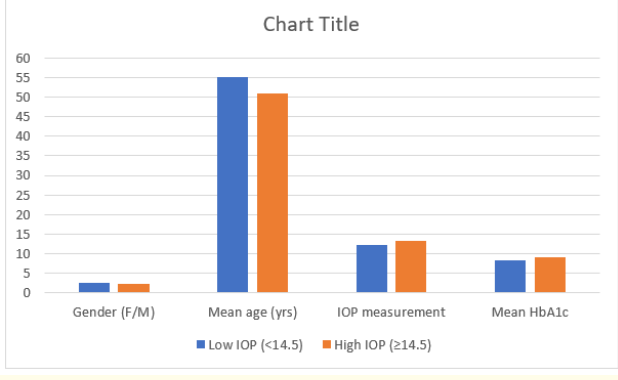

Figure 1: Demographic and clinical characteristic of the diabetic patients with cut-off value of 14.5 mmHg for IOP level.

potential risk factor for glaucoma, specifically open-angle glaucoma [17,18].

Studies like Baltimore Eye Survey [19] and Singapore Malay Eye Study [20] reported that diabetes influences increase of IOP but not related with open-angle glaucoma development. The Beijing Eye Study [21] showed ocular hypertension was associated with diabetes but not with glaucomatous optic neuropathy. Sakata., *et al*. [22] and Dongguan Eye Study [23] shows IOP values not associated with diabetes which is inconsistent with the present study.

Diabetes shows a positive association with IOP in the Singapore Epidemiology of Eye diseases Study [24] which reported that increased IOP in diabetes in long-term hyperglycemia measured by Goldmann applanation tonometer. Larsen and colleagues [25] reported that lower IOP values during severe hypoglycemia. In addition, Traisman., *et al*. [26] found that IOP in patients with blood glucose values under and above 200 mg/dL, observed higher IOP values in those with glucose levels above 200 mg/dL.

Several hypotheses explained the association between high glucose levels and IOP. Some researchers believe that there are genetic factors associated in family history of diabetes [27]. Other researchers agree with the idea that a diabetic person could have an autonomic dysfunction which would lead to an IOP increase [28]. However, some authors believe that elevated blood glucose results in the induction of an osmotic gradient which leads to fluid shifts into the intraocular space [29].

It is likely that patients with HbA1c above 9.5 were unable to maintain appropriate clinical care. These results suggest an association between elevated glucose levels and increased IOP. In the current study, the exclusion criteria were carefully selected so as not to bias the results. Exclusion of patients using medications that lower IOP or topical or systemic steroids was important since these drugs add a potential confounding variable to the relationship between HbA1c and IOP. Overall, our findings are consistent with Framingham heart study that reported a positive correlation between blood glucose levels and IOP [1].

Mechanism to explain why high blood glucose levels in diabetic patients may promote increased IOP still remains unclear. Studies reported that trabecular meshwork may play a role through which much of the aqueous drainage occurs represents a specialized tissue composed of various extracellular matrix components including fibronectin, laminin, and collagen IV [30,31].

These ECM components assemble together in a highly organized manner to form a network that is cross-linked, and integrated. A study using an in vitro cell culture model, shown that trabecular meshwork cells grown in high-glucose condition upregulates mRNA and protein synthesis of fibronectin, and excess deposition of ECM components which may play a role in the blockage of aqueous outflow through the trabecular meshwork and subsequently elevated IOP and the development of POAG [32]. A significant increase in aqueous humor glucose levels of patients with diabetes was reported by Davies., *et al.* [33].

The present study showed that intraocular pressure was not related with gender in both diabetic and non-diabetic groups. This is also in tandem with the results of Kumejima Study [34] and Beijing Eye Study [35]. On a contrary IOP is revealed to be more in females than male in diabetes in Dongguan Eye Study [36].

The present study provides evidence that the positive relationships between hyper-glycaemic status and IOP were significant, even after controlling for CCT. Increases in CCT may lead to overestimated IOP values [37], and diabetic patients have relatively greater CCTs due to the osmotic gradients induced by accumulated sorbitol in the cornea [38]. A study suggested that a greater CCT may mediate the association between higher glucose levels and elevated IOP [39].

In the current study, we assess the potential role of CCT as a mediator of diabetes and IOP. In the multiple linear regression analyses with diabetes predicting CCT and with CCT predicting IOP, both relationships were statistically significant ($P < 0.05$). In addition, the diabetes-IOP relationship was also statistically significant after CCT adjustment [40]. These results are consistent with those of a previous study from Singapore findings that a higher IOP in patients with diabetes was not primarily mediated by a greater CCT in these patients [39]. Thus, controlling blood glucose levels in diabetic patients is important to reduce future glaucoma susceptibility.

Hanyuda., *et al.* [41] concluded that diabetes, elevated HbA1c, and increased serum glucose are significant contributing factors

for elevated IOP. Choi., *et al.* [42] reported that a nationwide population-based cohort study showed that the fasting blood glucose (FBG) was associated with an increased risk of OAG. These findings suggest that subjects with high FBG levels require special attention when screening for glaucoma.

Hyperbaric oxygen therapy (HBOT) increases IOP in diabetic patients especially in ones with impaired blood glucose regulation without changes in CCT. As diabetic retinopathy and diabetic foot ulcer are in common pathologies, thus should explore the potential interaction of HBOT on CCT and IOP in diabetic patients with glucose impairment [43].

Conclusion

Findings from this study indicate that early HbA1c monitoring may be useful in assessing potential risk for increased IOP in patients with diabetes. Association between hyperglycemia and elevated IOP with poor glycemic control may related to increased IOP levels in long-term diabetic patients.

Ethics Approval and Consent to Participate

This prospective observational cross section study was approved by the ethics committee and adhered to the tents of Declaration of Helsinki. All subjects provided written informed consent prior to study participation.

Consent for Publication

Not applicable.

Availability of Data And Materials

Data are available upon request.

Competing of Interests

The authors declare that they have no conflict of interests.

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Standards of Reporting

Consort guidelines.

Authors Contributions

All authors read and approved the final manuscript.

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