Original article

Diabetes Mellitus and the risk of Primary open angle glaucoma

Lavaju P[1], Shah S[1], Sharma S[2], Maskey R[2]
[1]Department of Ophthalmology, BP Koirala Institute of Health Sciences
[2]Department of Internal Medicine, BP Koirala Institute of Health Sciences

Abstract

Background: Diabetes mellitus (DM) is one of the risk factors for Primary open angle glaucoma (POAG). Inclusion of DM as a risk factor for POAG is controversial. The objectives of the study were to investigate whether Type II (T2) DM is a risk factor for POAG and to determine central corneal thickness (CCT) in the subjects with T2DM and to examine the relationship between T2DM and intraocular pressure (IOP).**Materials and methods:** A comparative cross sectional study was conducted including 189 subjects of age > 40 years. In Group I, 113 patients diagnosed with T2DM and Group II, age and sex matched 76 subjects with POAG without DM was included. Detailed ocular examination, IOP, CCT and funduscopy evaluation was done. **Results:** Most of the patients were more than 60 years of age with mean age 58 ± 11 years. Male: female ratio was 1:1. POAG was seen in 27.4% of patients with T2DM. Mean IOP in T2DM was 14.67± 2.63mmHg and in non diabetic, 17.25±4.47 mmHg (p <0.00). In group I, mean CCT was 538.83± 22.7µm and in group II, 531.26 ± 20.9µm (p-0.126). There was no association between CCT and glaucoma (p=0.072, 95% CI: -0.76 –17.46). The study could not elicit an association of T2DM with glaucoma. Duration of T2DM did not affect an association between T2DM and glaucoma (p-0.757). Random blood sugar (p<0.001) and oral hypoglycemic drugs (p=0.030) showed an association with glaucoma. **Conclusion:** The study failed to show an association between T2DM and primary open angle glaucoma and CCT though an association seen with IOP. A larger prospective comparative study may be help in understanding this association.

Keywords: Glaucoma, diabetes mellitus, intraocular pressure, central corneal thickness

Introduction

Glaucoma is one of the causes of irreversible blindness worldwide. Diabetes mellitus (DM) has been suggested as a possible risk factor for glaucoma, particularly primary open angle glaucoma (POAG). It is known to cause microvascular damage and may affect vascular autoregulation of the retina and optic nerve. It is found to be associated with elevated intraocular pressure (IOP) (Dielemans et al,1996, Tielsch et al, 1995; Klein et al,1992; Wu et al,1997) . Several cross-sectional studies (Dielemans et al, 1996; Mitchell et al, 1997; Chopra et al, 2008) have found a positive association between diabetes and POAG, whereas others failed to confirm an association (Tielsch et al, 1995; Wilson, 1987; Gravin et al, 2009).

Although numerous studies have tried to investigate this association, the relationship between Type II DM (T2DM) and open angle

Received on: 05/09/16 Accepted on: 18/12/16
Address for correspondence
Dr Poonam Lavaju
Additional Professor
Department of Ophthalmology
B P Koirala Institute of Health Sciences, Dharan, Nepal
Tel: 00977-9852047026
E-mail: drpoonamlavaju@yahoo.com

glaucoma, remains a subject of debate. The studies to see an association between diabetes and glaucoma has not been conducted in this part of the world. So, the overall aim of this study was to observe the association between T2DM and POAG.

Materials and methods

A hospital based comparative cross sectional study was conducted to find out T2DM as a risk factor for POAG, to determine central corneal thickness (CCT) and to examine the relationship between T2DM and IOP. The study was conducted following an ethical approval by the Institutional Review Committee. Written informed consent was obtained from all the participants before enrollment.

A total of 189 patients >40 years of age were included in the study. One hundred and thirteen patients diagnosed with T2DM were included in Group I. They were evaluated meticulously for any evidence of findings suggestive of POAG as stated below by Foster et al (2002). Age and sex matched 76 subjects with POAG without diabetes was included in Group II. Detailed anterior segment examination, measurement of IOP, CCT and detailed funduscopic evaluation was carried out. Anterior chamber depth was graded according to Van Herrick method.

Goldmann applanation tonometer (Haag-Streit AG) was used to obtain three readings of IOP from each eye before dilation and mean taken for the analysis. Mean of five central corneal thickness (CCT) measurements were obtained from each eye with an ultrasound pachymeter. Any glaucomatous optic nerve changes noted was recorded. Diabetic retinopathy was graded according to ETDRS classification.

In participants with suspected glaucoma and those with Van Herrick anterior chamber depth grade less than II, gonioscopy was performed to rule out angle closure glaucoma. For participants meeting the glaucoma suspect criteria, automated perimetry was performed with near refractive correction (Humphrey Visual Field Analyzer). Test reliability was determined by the instrument's algorithm considering fixation losses - 20%, false positive - 33%, or false-negative results of 33%. Visual field testing was repeated once if deemed unreliable (Tan et al, 2009).

Glaucoma was defined according to the International Society of Geographical and Epidemiological Ophthalmology criteria on the basis of 3 categories by Foster et al (2002). Category 1: optic disc abnormality (vertical CDR [VCDR]/ VCDR asymmetry ≥97.5th percentile or neuroretinal rim (NRR) width between 11 and 1 o'clock or 5 and 7 o'clock<0.1 VCDR) and glaucomatous visual field defect. Category 2: severely damaged optic disc (VCDR or VCDR asymmetry ≥ 99.5th percentile) in the absence of an adequate visual field test. Assignment of category 1 or 2 glaucoma required that there be no other explanation for the VCDR finding (dysplastic disc or marked anisometropia) or visual field defect (retinal vascular disease, macular degeneration, or cerebrovascular diseases). Category 3: without visual field or optic disc data who were blind (corrected visual acuity, <3/60) and who had had previous glaucoma surgery or had IOP > 99.5th percentile. Cases of POAG were those meeting the definition of glaucoma without any evidence of narrow angles, primary angle-closure glaucoma, or a secondary causes (like abnormal anterior segment deposits or iris neovascularization). Ocular hypertension was defined if IOP was greater than 21 mm Hg, but not meeting the criteria for glaucoma.

Glaucoma suspect was defined as IOP greater than 21mmHg, gonioscopic findings of closed or occludable angles, presence of peripheral anterior synechiae, cup-disc ratio(CDR) greater than 0.6, disc asymmetry with CDR greater than 0.2 between the discs, abnormal deposits consistent with pseudoexfoliation syndrome,

pigment deposition on the cornea consistent with pigment dispersion syndrome and known glaucoma (Foster et al, 2002).

Definition of diabetes was based according to American Diabetes Association criteria. Diabetes mellitus was defined as random blood glucose levels of 200 mg/dl or greater or physician's diagnosis of diabetes mellitus and use of diabetes medications, HbA 1c of greater than 6.5 % and fasting blood sugar level of ≥ 126 mg/dl (7.0 mmol /l).

Statistical analysis was performed using the SPSS, version 11.5. Mean, standard deviation, odds ratio, relative risk and 95% CI were calculated. Proportions were compared using the Chi square test. A 'p' value of less than 0.05 was considered significant.

Results

A total of 189 patients meeting the inclusion criteria were enrolled in the study. There were 113 patients with T2DM in Group I and 76 patients without T2DM with POAG in Group II. There were 95 male and 94 female. Most of the patients were in the age group 60-69 years (61, 32.2%). In Group I, mean age was 60±10 years and in Group II, 57±12 years (p=0.585).

Table 1: Characteristics of study population by Type II DM status

Mean (±SD)	T2DM (n=113)	No diabetes (n=76)	P value
Age (years)	60.04±10.12	57.07± 12.04	0.585
Systolic BP, mmHg	133.81±15.37	130.29±16.31	0.020
Diastolic BP, mmHg	85.4±9.06	85.41±7.93	0.241
BMI	26.13±5.21	27.31±3.97	0.083
IOP, mmHg	14.67±3.10	17.25±4.47	<0.001
CCT, µm	538.83±22.73	531.26±20.96	0.126

The total subjects were again further categorized into three groups. Group A - patients with only T2DM (n=82, 43.3%), Group B with T2DM and glaucoma (31, 16.4%) and Group C included the patients without T2DM and with POAG (76, 40.2%). Mean age of the patient was 59.88±10.49 years, 60.45±9.25 and 57.07±12.048 in group A, B and C respectively (p=0.812). There were 37 males in Group A, 18 in Group B and 40 in Group C. Similarly, there were 45, 13 and 36 females in Group A, B and C respectively. Statistically there was no significant difference in distribution of gender in the between three groups (p-0. 408).

Table 2: Association of Type II Diabetes mellitus and POAG

POAG	Type II Diabetes mellitus		P value (Fisher's exact test)
	Yes	No	
Yes	31	76	*0.000
No	82	0	
Total	113	76	

**Not applicable*

The mean duration of T2DM was 7.97 years (SD= 7.54), median 6 years .In total population, the mean duration of glaucoma was 4.13 years (SD= 3.5) with median 3 years. The prevalence of glaucoma in patients with T2DM was 27.4 % (n=31). The study was not able to confirm an association betweenT2DM and glaucoma (Table 2). The mean duration of T2DM in subjects having glaucoma was 8.53± 8.1 years and without glaucoma were 7.75±7.33 years. The strength of the association between diabetes and glaucoma risk did not vary by diabetes duration (p=0.757, RR-2.38- 3.94).

Mean body mass index (BMI) in patients with T2DM was 26.13±5. 21 and without was 27.31± 3.97. BMI in patient with glaucoma was 27.1 ± 4.6 and without glaucoma was 25.9± 4.8. Statistically there was no significant association between BMI and glaucoma (p=0.540). Intake of oral hypoglycemic agents (OHA) was significantly associated with glaucoma (p=0.030). Fourteen patients (12.3%) were in insulin. Use of insulin did not have positive association with glaucoma (p=0.919).

Ninety-five subjects were hypertensive (49.7%). In patients with T2DM, 84 patients had hypertension (74.3%), which was

statistically significant (p<0.00). Increase in blood pressure had positive correlation with glaucoma (<p-0.001, 95% CI 0.23-0.52, RR 0.35). While taking systolic blood pressure (SBP) and diastolic blood pressure (DBP) and its relation with glaucoma, it was found that they were not statistically significantly correlated with glaucoma with p value 0.162 and 0.336 respectively.

Statistically there was no difference between right and left eyes of the subjects in terms of CCT and IOP, so right eye was considered for analysis. In both the groups (I and II), majority of patients, IOP range between 16-21 mmHg (84.34%). In group I, mean IOP was 14.67± 3.10 mm Hg and in group II, 17.25±4.47 mm Hg. There was statistically significant difference in mean IOP, between the two groups (p<0.001). It was seen that the mean IOP was lower in patients with T2DM.

Mean IOP was 14.19±2.63 mmHg, 15.94±3.88 and 17.85±4.47 in group A, B and C respectively (p<0.001). While comparing IOP in between patients with and without glaucoma, mean IOP in patient with glaucoma was 16.87±4.33 mm Hg and without glaucoma was 14.19± 2.63 mm Hg (p<0.001). In our study, patients with glaucoma 74/107 (69%) were on anti-glaucoma drugs that may be the reason for lower ranged IOP.

Table 3: Distribution of IOP in the three groups

IOP	GROUP			TOTAL
	A	B	C	
<21mm Hg	81	28	58	167
>21mmHg	1	3	18	22
TOTAL	82	31	76	189

Table 3 shows the distribution of IOP in between the three groups. IOP was < 21mm Hg in 82 diabetic subjects, 31 in group B and 76 in group C.

In Group I, mean CCT was 538.83±22.7 µm and in Group II, 531.26 ±20.9 µm. Diabetic patient had thicker cornea then non diabetic subjects, but was statistically not significant (p - 0.126). Most of the patients with DM and without DM, CCT ranged between 500-599 µm, in 63.71% and 77.63% respectively. Thirty one percent of subjects in diabetic had CCT >600 µm and 19% in non diabetic group. When comparing CCT in between patients with glaucoma and without glaucoma; patients with glaucoma had thinner CCT in comparison with non glaucomatous (p- 0.019). Mean CCT was 541.12±23.48 µ, 532.77±19.69 and 531.26±20.96 in group A, B and C respectively (p-0.014). Diabetic retinopathy was seen in 33 patients (29.2%). Diabetic retinopathy failed to confirm correlation with glaucoma (p=0.625, RR: 0.84, 95% CI 0.42-1.69).

Table 4: Association of various parameters in T2DM patients with and without glaucoma (n=113)

Parameters	P value
Age	0.854
Sex	0.219
Hypertension	0.983
IOP	0.004
Random blood sugar, mg/dl	<0.001
Fasting blood sugar (FBS)	0.453
2 hour Post prandil blood sugar (2hr PP)	0.593
Serum HbA1c %	0.389
BMI	0.565
Total cholesterol , mg/dl	0.702
LDL, mg/dl	0.769
HDL, mg/dl	0.537
Triglycerides, mg/dl	0.740
Oral hypoglycemic agents	0.030
CCT	0.174
Duration of Type II DM	0.757
Diabetic retinopathy	0.625

The strength of association between T2DM and glaucoma vary with the level of random blood sugar (p<0.001). Other parameters; diabetic retinopathy, HbA1c, total cholesterol, LDL, HDL, triglycerides, BMI, FBS and 2hours PP failed to show a positive association with glaucoma (Table 4).

Discussion

In this study, the prevalence of glaucoma in patients with Type II DM was 27.4%. Many studies have been conducted to see the association between T2DM and primary open angle glaucoma.

Chopra et al (2008) did a population based cross sectional study to examine the relationship between type 2 diabetes mellitus (T2DM) and the risk of having open-angle glaucoma (OAG) in an adult Latino population, Los Angeles Latino Eye Study (LALES). Of the total 5894 participants, 1157 (19.6%) had T2DM and 288 (4.9%) had OAG. The prevalence of OAG was 40% higher in participants with Type 2 DM than in those without Type 2 DM (age/gender/ intraocular pressure–adjusted odds ratio, 1.4; 95% confidence interval, 1.03–1.8; $P \leq 0.03$).

Several cross-sectional studies (Dielemans et al, 1996, Mitchell et al, 1997) have found a positive association between diabetes and POAG, whereas others failed to confirm an association (Tielsch et al, 1995; Klein et al, 1992).

In a meta-analysis done by Bonovas S et al (2004) in their study suggested that diabetic patients are at significantly increased risk of developing POAG with OR= 1.50, 95% CI: 1.16, 1.93. Unlike other studies, our study was not able to confirm an association between T2DM and POAG. This could be because we have included only patients diagnosed with T2DM and POAG.

Similar to our study, in a study done by Ellis et al (2000) in an unselected cohort of diabetic patients, failed to confirm an association between diabetes and POAG and ocular hypertension. Garvin et al (2009) found the prevalence of glaucoma was similar in patients with and without glaucoma (4.7% vs 4.5%).

For the further analysis the subjects were divided into three groups. There were 82 subjects with T2DM only, 31 with T2DM and glaucoma and 76 with POAG only. While comparing these three groups in terms of age, gender, BMI, SBP, DBP and CCT, no significant difference was seen. There was a significant difference seen between parameters like IOP ($P<0.001$), Cup: disc ratio ($p<0.001$) and level of RBS ($p<0.001$) in between these three groups. On reviewing the literature, we did not find similar type of study comparing these parameters in between the groups.

The mean duration of glaucoma in the subjects was 4.13 years (SD± 3.59), median of three years. We did not find statistically significant association between duration of T2DM and glaucoma (p-0.757). Similar to our study, in a prospective study conducted by Pasquale et al (2006), too did not find the association of POAG with longer duration of diabetes: RR = 2.24 (95% CI = 1.31–3.84) for duration < 5 years versus RR = 1.54 (95% CI = 0.90–2.62) for duration >5 years.

In a population based cross sectional study conducted by Chopra et al (2008) in an adult Latino population, the prevalence of OAG was 40% higher in participants with T2DM than in those without T2DM. A longer duration of T2DM was associated with a higher prevalence of OAG ($p<0.0001$). There was a higher risk of having OAG in participants with duration of Type II DM of ≥ 15 years duration (age/ gender/IOP- adjusted OR, 1.7; 95% CI, 1.04-2.8; $p=0.03$). They concluded that the presence of T2DM and a longer duration of T2DM were independently associated with a higher risk of having OAG in the LALES cohort.

In group I, mean IOP was 14.67± 3.10 mm Hg and in group II, was 17.25±4.47 mm Hg which was statistically significant ($p<0.00$). It was seen that the mean IOP was lower in patients with DM. This could be because in this study, group II included diagnosed cases of primary open angle glaucoma.

In a study conducted by Gavin et al (2009), patients with DM and metabolic abnormalities had higher IOP than without DM (16.7 vs 15.0mm Hg, p<0.001, with higher serum glucose levels (p< 0.001), glycosylated hemoglobin concentrations (p<0.001), total cholesterol levels (p=0.001), triglyceride levels (p=0.002), and body mass index (p=.001). The prevalence of glaucoma was similar between persons with and without diabetes (4.7% vs 4.5%). Age, sex, education, smoking, CCT and diabetes treatment, diabetes was not associated with glaucoma (odds ratio, 1.00; 95% confidence interval, 0.63-1.61). But they did not find its positive correlation with glaucomatous optic neuropathy. There was no statistically significant association between diabetes and POAG (OR, 1.02; 95% CI, 0.58-1.79).

Persons with diabetes have been shown to have greater CCT (Wong et al, 2008; Pfeiffer et al, 2007), which may artifactually increase IOP readings as measured by Goldmann applanation tonometer (Doughty et al, 2000). Wong et al (2008) reported a statistically significant increase in CCT in persons with diabetes compared with non-diabetic persons (547.2 vs 539.3µm, P<0.001).

Similarly in this study, diabetic patients had thicker CCT than in non diabetic, but was not statistically significant (p=0.126). Patients with glaucoma had thinner CCT in comparison with non glaucomatous patients (p-0.019). While comparing between three groups, there was no statistically significant difference in CCT (p-0.014). In our study random blood sugar level was only found to be statistically significant with glaucoma (p<0.001).

In conclusion, the prevalence of glaucoma (POAG) in patients with Type II diabetes mellitus was 27.4%. We could not elicit an association between Type II DM and glaucoma. A large sample prospective cohort study may further aid in understanding of these complex relationship between Type II DM and primary open angle glaucoma.

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Diabetes Care, Volume 33, Supplement 1, January 2010 Executive Summary: Standards of Medical Care in Diabetes—2010

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