Original Article

Association of metformin use among diabetics and the incidence of primary open-angle glaucoma – The Chennai Eye Disease Incidence Study

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Purpose: Studies have reported the usage of metformin being associated with the reduced risk of progression of glaucoma. The current study aims to determine the association of metformin usage among subjects with diabetes mellitus and the six-year incidence of primary open-angle glaucoma (POAG). **Methods:** In this prospective cohort study, subjects who did not have glaucoma at the baseline and had a follow-up after a six-year interval were included. Details such as medical and drug history, applanation tonometry, gonioscopy, pachymetry, optic disc evaluation, and automated perimetry were collected. Incident POAG was defined as subjects who do not have glaucoma at baseline and developed glaucoma as classified International Society of Geographical and Epidemiological Ophthalmology Classification at the follow-up. The association between the subjects who were on metformin for treatment of diabetes mellitus and development of incident POAG was assessed. **Results:** Among the 4302 eligible participants, 128 (3%) had incident POAG. There were 905 (21.0%) subjects who had diabetes mellitus of which 142 (15.7%) were using metformin. Of the subjects with POAG, 92 (71.9%) were nondiabetics and 36 were diabetics (28.1%). Among the diabetics, the incidence of POAG among those on metformin was 5.6% (8 participants) and those not on metformin was 3.6% (28 participants). There was no difference in the incidence of POAG in subjects with diabetes mellitus, with and without metformin use (P = 0.25). Logistic regression showed no association of metformin use with the incidence of POAG (OR: 1.33, 95 CI: 0.58–3.04, P = 0.49) after adjusting for age, gender, and place of residence. **Conclusion:** The current study did not find any association between the effects of metformin on the incidence of POAG.

Key words: Diabetes, glaucoma, metformin, POAG

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Glaucoma is a progressive optic neuropathy. There are many risk factors associated with primary open-angle glaucoma (POAG), with intraocular pressure (IOP) as the most important modifiable risk factor.[1,2] Diabetes mellitus as a possible risk factor has been studied. The relationship between diabetes and glaucoma is explained by the association of glycation of lipids and abnormalities of lipid metabolism in diabetes, which may increase oxidative stress and promote cellular apoptosis similar to the retinal ganglion cell loss in glaucoma.[3] Metformin, a synthetic biguanide, is frequently prescribed for treating type 2 diabetes. Metformin has been shown to delay or reduce risks for a variety of age-associated systemic diseases.[4] Lin *et al*.[5] recently reported that metformin, a caloric restriction mimetic drug, was associated with a reduced risk of POAG. They studied ten years of data from the Clinformatics Data-Mart Database for diabetic individuals and reported that metformin is associated with a reduced risk of developing POAG in people with diabetes when taken above a threshold prescription amount of 1110 g.[5] Studies have also shown metformin not being associated with the reduced risk of progression of glaucoma.[6] We explored the possible association between metformin use and the incidence of glaucoma among individuals of Indian ethnicity using population-based cohort data from the Chennai Glaucoma Study and the Chennai Eye Disease Incidence Study.

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Methods

This is a cohort study in which the subjects who participated in the Chennai Glaucoma study were reexamined after six years in the Chennai Eye Disease Incidence Study.[1] The methodology of the Chennai Glaucoma Study (CGS) was reported previously.[7] The CGS was a cross-sectional population-based study to measure the prevalence of glaucoma in a rural and urban South Indian population. The study cohort consisted of 9600 (rural: urban = 4800:4800) subjects aged 40 years or older and was carried out from 2001 to 2004. From the cohort, 7774 (rural: urban = 3924:3850) subjects participated in the study six years after the baseline examination (2007–2010). The study was performed in accordance with the tenets of the Declaration of Helsinki and after obtaining written informed consent. The institutional review board approved the study. Subjects who were diagnosed to have glaucoma at the baseline study were excluded. Subjects using metformin as a treatment for diabetes mellitus were studied for the risk of incident POAG.

A detailed history pertaining to medical and ophthalmic conditions was elicited, including any history of diabetes mellitus or hypertension or use of medication for either of the

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disease. Three ophthalmologists (glaucoma specialists) and three optometrists, who were trained for the study, performed the ophthalmic examination. The examination techniques used were the same as that of the baseline prevalence study. Comprehensive eye examination including stereoscopic evaluation of the optic nerve head was done using a + 78-D lens at the slit lamp. The vertical and horizontal cup-to-disc ratios (CDRs) were measured, and the presence of any notching, splinter hemorrhages, and peripapillary atrophy was documented. A nonsimultaneous stereo optic disc photograph was taken in the eyes with clear media. Central corneal thickness (CCT) was measured using the DGH 550 ultrasonic pachymeter (DGH Technology Inc., Exton, PA, USA).

A provisional diagnosis of suspected POAG was made when the subject with open angle had one or more of the following conditions: IOP ≥ 21 mm Hg in either eye; vertical CDR (VCDR) ≥ 0.7 in either eye or CDR asymmetry ≥0.2 (with no other reason for asymmetry); and focal thinning, notching, or a splinter hemorrhage. All these subjects were advised threshold visual field test using SITA standard 24-2 program (Model 750, Humphrey Instruments, San Leandro, CA, USA). A glaucomatous field defect was diagnosed using a single, reliable threshold visual field examination of the central 24° (SITA standard 24-2). The field was considered to be abnormal if the glaucoma hemifield test (GHT) results were outside normal limits and three or more abnormal contiguous non-edge points were depressed to $P < 5\%$. Reliability criteria were as recommended by the instrument's algorithm (fixation losses: <20%; false-positive and false-negative: <33%).

Diabetes mellitus and systemic hypertension were detected based on self-reported history and the current usage of anti-diabetic or systemic anti-hypertensive medication. Cases of glaucoma were defined using the International Society of Geographical and Epidemiologic Ophthalmology (ISGEO) classification[8] Glaucoma was classified according to three levels of evidence. In category 1, the diagnosis was based on structural and functional evidence. It required CDR or CDR asymmetry equal to or greater than the 97.5th percentile for the normal population or a neuroretinal rim width reduced to 0.1 CDR (between 10 and 1 o'clock or between 5 and 7 o'clock) with definite visual field defects consistent with glaucoma. Category 2 was based on advanced structural damage with unproven field loss. This included those subjects in whom visual fields could not be done or were unreliable, with CDR or CDR asymmetry equal to or greater than the 99.5th percentile for the normal population. Lastly, category 3 consisted of persons with an IOP greater than the 99.5th percentile for the normal population, whose optic discs could not be examined because of media opacities. For the current study population, the 97.5th and 99.5th percentiles were as follows: for CDR, it was 0.7 and 0.8; 0.2 for CDR asymmetry; for IOP, in urban population, it was 24 and 30 mm Hg, and the corresponding figures for the rural population were 21 and 25 mmHg.[1]

Statistical analysis was performed using SPSS Version 15 (SPSS Inc., Chicago, IL, USA). All collected data were entered into a central database with inbuilt range checks and were rechecked for data entry accuracy. Incident POAG was defined as the development of POAG during the follow-up in subjects without POAG at baseline. Participants were categorized into four groups based on baseline age: 40–49 years, 50–59 years, 60–69 years, and 70 years and above. We compared variables between POAG and controls using *t*-test for continuous variables and Chi-square test for categorical variables. Multivariable logistic regression was performed to look for associations between factors such as age, gender, location of residence, IOP, and usage of metformin for diabetes and for incident POAG after adjusting for age and gender. Statistical significance was assessed at $P < 0.05$, and odds for POAG are presented with 95% confidence intervals (CI).

Results

4302 participants were included, of whom 128 (3%) had incident POAG; 905 participants (21.0%) had diabetes mellitus, of whom 142 (15.7%) were using metformin. Table 1 provides the details on the demographics of the study population.

Diabetes and POAG

Of the subjects with POAG, 92 (71.9%) were nondiabetic and 36 (28.1%) were diabetic. There was no significant difference with the incidence of POAG among diabetics who were metformin users (8/142, 5.6%, 95%CI: 1.8–9.4) and nonusers (28/763, 3.6%, 95% CI: 2.3–4.9) ($P = 0.25$). There was no difference noted in IOP at the follow-up ($P = 0.22$) with and without metformin use among the diabetics.

Risk factors for incident POAG among diabetics

Logistic regression was performed to analyze the association of metformin usage and incidence of POAG after adjusting for age, gender, and place of residence among the diabetics [Table 2]. Increasing age and male gender were found to be at risk for incident POAG among diabetics. Usage of metformin was not found to be associated with incident POAG.

Intraocular pressure was different among diabetic and nondiabetic groups [Table 3]. There was no difference in the vertical cup to disc ratio [Table 3]. We did not find any association with IOP (mean difference: 0.52 mm Hg, 95% CI: −0.2–1.4, $P = 0.16$) or with vertical cup to disc ratio (mean difference: −0.006, 95% CI: −0.04–0.02, $P = 0.72$) between metformin users and non-metformin users among diabetics.

Discussion

In the current study using data from a large population-based study, we studied the possible association of metformin usage and POAG among diabetics. Our study reported 147 (15.7%) subjects who were on metformin as a treatment for diabetes. There was no association between the usage of metformin and the incidence of POAG (OR: 1.3, 95% CI: 0.58–3.04). Increasing age and IOP was found to be a significant risk factor for incident POAG.

The literature suggests that the increased risk of glaucoma in patients with diabetes is due to increased corneal stiffness, corneal hysteresis, and enlargement of the optic cup.[9] In our study, IOP was found to be increased in diabetics than the nondiabetics whereas there was no difference in VCDR among diabetics and non-diabetics.

Metformin has been reported to impact IOP, an independent risk factor of glaucoma incidence. Chatterjee *et al*.[10] reported that extracellular matrix (ECM) and cellular tone in the trabecular meshwork (TM) is influenced by adenosine monophosphate-activated protein kinase (AMPK), which regulates cellular homeostasis. They hypothesize that because metformin is an AMPK activator, its influence on the TM can reduce IOP. Our results showed that nondiabetics had lower intraocular pressure than the diabetics on treatment (mean difference: 1.85 mm Hg). This could explain the relationship of diabetes as a risk factor for glaucoma. However, there was no difference in IOP among diabetics with and without metformin usage. Thus the beneficial effects of metformin in controlling the IOP could not be explained.

Lin *et al*.[5] studied a large hospital-based ten-year data from diabetic patients and showed that POAG risk was increased by 8% for each unit of increase in HbA1c level. They also

Table 1: Demographic characteristics of the study population

Variables	No POAG (*n*=4174)	POAG (*n*=128)	*P*
Age in years (Mean±SD)	58.2±9.7	62.8±9.2	<0.001
Gender			
Male	1861	64	0.225
Female	2313	64	
Place of residence			
Rural	2405	59	0.009
Urban	1769	69	
Diabetes mellitus			
No	3305	92	0.05
Yes	869	36	
Metformin usage			
No	3305	92	0.06
DM & metformin	134	8	
DM & other anti-diabetics	735	28	
IOP (Mean±SD)	15.06±4.15	17.03±6.06	<0.001

POAG: Primary Open Angle Glaucoma, SD: Standard Deviation, IOP: Intraocular Pressure, DM: Diabetes Mellitus

Table 2: Risk factors for incident primary open angle glaucoma among the diabetics

Risk Factors	No of subjects	Adjusted Odds Ratio (95%CI)	*P*
Age (years)			
40-49	304	1.00	
50-59	311	4.7 (1.3-16.4)	0.017
60-69	234	7.1 (2.0-24.7)	0.002
70+	56	3.0 (0.4-18.7)	0.233
Gender			
Male	435	1.00	
Female	470	0.49 (0.24-0.99)	0.049
Residence			
Rural	294	1.00	
Urban	611	0.97 (0.46-2.02)	0.94
Metformin Usage			
No	763	1.00	
Yes	142	1.3 (0.58-3.04)	0.49
IOP (mm Hg)	905	1.09 (1.04-1.15)	<0.001

IOP: Intraocular Pressure, CI: Confidence interval

Table 3: IOP and optic disc characteristics among diabetics and non-diabetics

Variable	IOP (mm Hg) Mean (SD)	VCDR Mean (SD)
Non Diabetics	13.91 (3.86)	0.40 (0.19)
DM with Metformin	15.76 (5.19)	0.41 (0.20)
DM with other drugs	15.19 (4.37)	0.42 (0.19)
P	<0.001	0.128

IOP: Intraocular Pressure, VCDR: Vertical Cup to Disc Ratio, DM: Diabetes Mellitus

found that above a threshold prescription amount of 1110 g, metformin use was associated with a reduced risk of developing OAG in people with diabetes. There are fewer diabetics and POAG patients among our cohort as would be expected for a population-based study. As participants were evaluated only at two points of time, we could not gather exact information on long-term HbA1c and threshold prescription amount of metformin. Because of these differences, we feel we cannot compare our results directly with that of a large hospital-based study. As our study is a population-based cohort study that is best suited to study causality, we believe it reflects the true picture and suggests metformin may not have any significant beneficial effect on reducing the incidence of POAG compared to the general population.

Though the study is from a large population-based dataset, we were limited to less number of subjects with metformin usage for diabetes mellitus. There are some deficiencies in our study: the diagnosis was based on self-reported history or use of any diabetic medication, and we would possibly have missed undetected diabetics in the population. The number of people with diabetes and on treatment with metformin was small in numbers and this could have affected our results.

Conclusion

Our study did not find any association between the effects of metformin on the incidence of POAG. We also have limitations as we did not measure the HbA1c levels and also the actual dosage of medications used.

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Conflicts of interest

There are no conflicts of interest.

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