Hypertension as a Risk Factor for Primary Open-angle Glaucoma: A Meta-analysis

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ABSTRACT

Hypertension (HTN) is not recognised as an independent risk factor for primary open-angle glaucoma (POAG). A search of PubMed, Embase, Medline, Wanfang, and Cochrane Library databases from the time each database was established up to July 2022 was performed. All studies were pooled and assessed for heterogeneity and the quality of the literature. Five cross-sectional studies were included in the meta-analysis with 1144 individuals with POAG and 29, 373 without POAG. The combined analysis found that the incidence of HTN was higher among the individuals with POAG than among those without (OR 1.55; p <0.001). There was also a significant difference in the incidence of diabetes among individuals with POAG compared with those without (OR: 1.31; p=0.002). A meta-analysis of cross-sectional studies revealed that the incidence of HTN and diabetes was significantly greater among individuals with POAG. HTN and diabetes were found to be independent risk factors for POAG.

Key Words: *Primary open-angle glaucoma (POAG), Hypertension (HTN), Diabetes, Meta-analysis*.

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INTRODUCTION

Glaucoma is an optic neuropathy characterised by damage to retinal ganglion cells in the inner nuclear layer of the eye, accompanied by structural changes in the optic nerve and loss of the visual field.[1] The most common type of glaucoma is primary open-angle glaucoma (POAG), which is the leading cause of irreversible blindness.[2]

The pathogenesis of POAG remains to be fully defined. Elevated intraocular pressure (IOP) is considered the most important risk factor for the development of POAG. To limit blindness, it is important to control and stabilize IOP.[3] A significant relationship between hypertension (HTN) and IOP was reported.[4-6] Among younger patients, HTN, by increasing the ocular perfusion pressure, increased the incidence of glaucoma.[7] Systematic review and meta-analysis to assess for a relationship between HTN and the incidence of open-angle glaucoma (OAG) were recently reported.[8] The objective of this meta-analysis was to explore the relationship between HTN, diabetes, and POAG.

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METHODOLOGY

A literature search through databases including PubMed, Medline, and Embase without language restrictions from inception to June 22, 2022 was completed. In all instances, a full-text search was done and employed the following terms and keywords in the Medical Subject Headings (MeSH) thesaurus: hypertension, or HTN, high blood pressure, or HBP, and open-angle glaucoma, or OAG.

Only cross-sectional studies were screened that assessed the association of HTN with POAG and asked whether HTN was a risk factor for POAG. Non–cross-sectional studies, studies not including POAG or HTN, and those that did not satisfy inclusion criteria were exclusive.

Data collection were done by a single investigator (HW) and cross-checked by the other investigators. The following data were extracted from each study: Lead author, time of publication, study area, study type, sample size, cohort demographics (gender and age), incidence data on exposure, and endpoint events. Four studies also included diabetes as a risk factor.

Data were processed using Review Manager V.5.3. Quality assessment was performed using the Newcastle-Ottawa scale (NOS). Three main aspects of the cross-sectional studies were assessed; selection, comparability, and exposure. Heterogeneity among studies was also analysed using the chi-square test for differences and the heterogeneity I^2 statistic.[9]

Table I: Demographic and clinical baseline characteristics of study patients.

Author/year	Age (years)	Gender (male/female)	Smoking	Migraine	Family history of glaucoma	Hypertension	Diabetes mellitus
Suzuki, 2006	63.8 ± 12.0/57.8 ± 11.6	1277/1597	1196	284	157	816	194
Wang, 2009	60.4 ± 10.0	1402/1820	NA	NA	NA	1500	NA
Ishikawa, 2011	54.7 ± 9.8	384/362	NA	NA	NA	130	56
Kim KE, 2016	55.1 ± 0.2	7873/5958	5597	2286	238	4135	1469
Tham, 2018	58.2 ± 10.1/63.4 ± (10.8)	4639/5238	NA	NA	NA	6266	2331

NA: Not available.

Table II: Characteristics of included studies and results of the quality assessment.

Author/year	Type	Year	Country	Sample size (n)	Primary endpoint events	Secondary endpoint events	NOS
Suzuki, 2006	Cross-sectional studies	2001	Japan	2,874	Hypertension	Diabetes	7
Wang, 2009	Cross-sectional studies	2006	China	3,222	Hypertension	Diabetes	9
Ishikawa, 2011	Cross-sectional studies	2007	Japan	710	Hypertension	Diabetes	9
Kim KE, 2016	Cross-sectional studies	2011	Korea	13,831	Hypertension	Diabetes	8
Tham, 2018	Cross-sectional studies	2017	Singapore	9,877	Hypertension	Diabetes	7

POAG, primary open-angle glaucoma; NOS, Newcastle-Ottawa scale.

In cases where heterogeneity was too high, effect sizes were recalculated after removing all studies that might have contributed to publication bias. Low, medium, and high heterogeneity were defined as 25%, 50%, and 75% of I^2 values, respectively.[10] The Mantel-Haenszel test provided a summary estimate of the 95% confidence interval (CI) and odds ratio (OR). Results were considered significant when p <0.05.

RESULTS

Sixteen hundred and sixty-eight publications were returned on search of the PubMed, Embase, Medline, Wanfang, and Cochrane Library databases. For primary screening removed 545 duplicates. A further 1060 studies were excluded based on inclusion criteria. The remaining 56 publications were closely scrutinised. Of these, 51 (including meta-analyses, reviews, letters to the editor, and clinical outcomes with no prognosis) were deleted. The remaining 5 studies were employed in this study (Figure 1).[11-15]

Five cross-sectional studies were included, comprising 30,517 individuals (1144 diagnosed with POAG and 29,373 without a diagnosis of POAG). The mean age of the entire cohort was 58.1 years. The demographic information of the cohort is summarised in Table I. A summary of the characteristics of inclusion studies and the results of the quality assessment are provided in Table II. The five included studies were found to have low risk of bias and a NOS score between 7 and 9.

All studies assessed the prevalence of HTN in the POAG and the non-POAG groups. A fixed-effects model that combined HTN incidence results with low heterogeneity (I^2 = 0%) was employed. There was a statistically significant difference in the prevalence of HTN between the POAG group and the non-POAG group (OR: 1.55; 95% CI: 1.37–1.75; p <0.00001, Figure 2).

The figure shows the number of events, number of individuals in the POAG, and non-POAG groups, odds ratio (OR), 95% confidence interval (CI) for each trial, overall OR estimate with 95% CI and p-value for association test, p-value for heterogeneity test, and measures (I^2) of trial inconsistency.

The incidence of diabetes between POAG and non-POAG groups was assessed in 4 studies. Using a random-effects model to pool data, there was a significant difference in the prevalence of diabetes between POAG and non-POAG groups (OR: 1.31; 95% CI: 1.10–1.55; p = 0.002). The heterogeneity among the studies was minimal (I^2 = 0%, Figure 3).

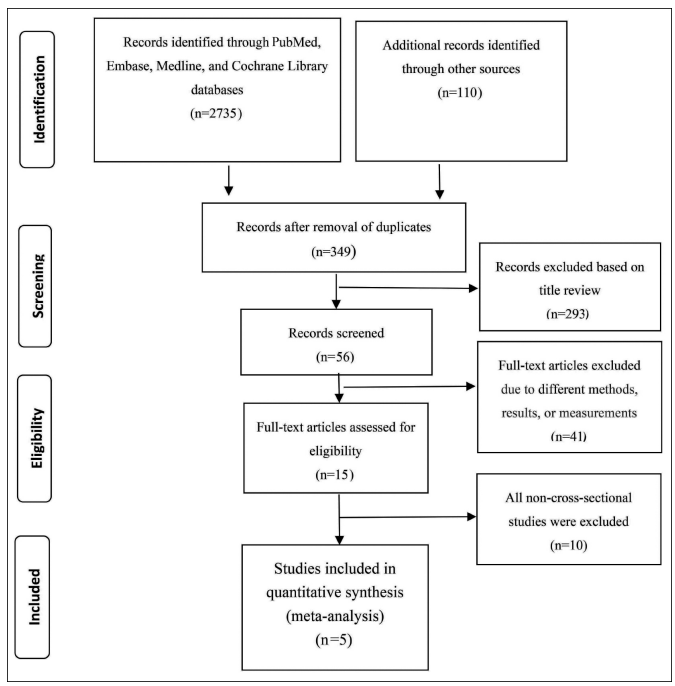

Figure 1: Flow diagram showing the process for study selection.

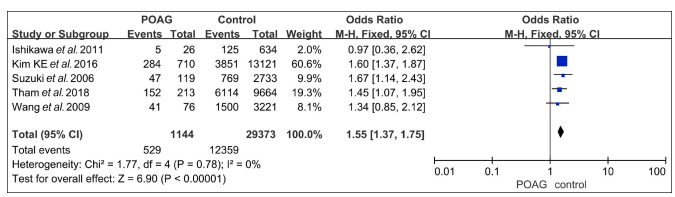

Figure 2: Fixed-effect meta-analysis for the incidence of hypertension.

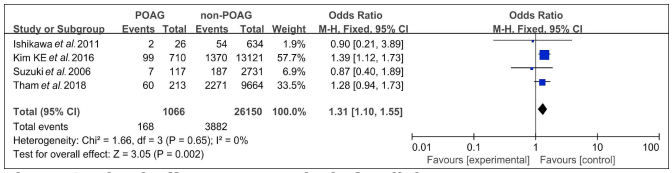

Figure 3: Fixed-effect meta-analysis for diabetes.

DISCUSSION

HTN increases the intravascular and intraocular pressure gradient by increasing ciliary capillary pressure leading to the increased production of aqueous humor. It also reduces the flow of fluid by increasing episcleral venous pressure to impede the return of fluid and its absorption.[1,3,6] Increased intraocular pressure acts on the sieve plate of the eye to damage the optic nerve and promotes glaucoma.[16] HTN was associated with spasm of the central retinal artery and decreased blood flow to the optic nerve head and cribriform plate leading to glaucoma.[15,17] Others noted that HTN increased arterial perfusion pressure and optic nerve ischemia with damage to the retinal ganglion cells.[18] In contrast, HTN increased ocular perfusion pressure and was associated with less pathophysiology.[19]

Herein, the authors completed a meta-analysis of 5 cross-sectional studies to assess whether HTN is an independent risk factor for POAG. The prevalence of HTN was significantly higher in the POAG group (20%) than in the non-POAG group (10%). Related to this, diastolic blood pressure correlated with mean ocular perfusion pressure.[6,8,20] These studies suggested that unstable diastolic blood pressure, both high and low, increased risk of OAG events. However, a significant difference between systolic blood pressure and the incidence of OAG was not reported.

Beyond this, prior data relating HTN to POAG provided opportunity for more in-depth analysis (REF). First, differentiation between primary and secondary OAG was not made likely introducing selection bias. Second, previous work in this area mixed case-control, cohort, and cross-sectional studies obviating any conclusions. To minimise the bias, the present meta-analysis included only cross-sectional studies of POAG with low data heterogeneity. Consequently, the finding that HTN significantly increased the risk of POAG imparted reliability to the result. Unexpectedly, it was found that information on diabetes among the cohort subjects was available for analysis. Here it was noted that diabetes imparted an increased risk for POAG ($p = 0.002$). Together these data reveal a role for chronic elevation in blood pressure and hyperglycemia for increased risk of POAG.

The present study has several limitations. First, the included studies are all cross-sectional. No retrospective and prospective studies were included in the analysis. While dampening selection bias, this approach might exclude important information. The authors intend to analyse retrospective and prospective studies to determine if similar associations are found. Second, the study cohort was all from Asian countries. This limits the application of the finding to non-Asian populations. Third, as with all post hoc analysis, the results are dependent on the overall quality of the studies reviewed, the rigor of their design and the data therein. Thus, meta-analysis is inherently hampered by factors often unknown and indeterminate.

CONCLUSION

The present meta-analysis revealed strong and separate risk factor relationships between hypertension and diabetes and POAG. It remains for future inquiry to assess if these two discriminators function together to further increase the risk of PAOG.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

JW, HW, SY: Contributed equally in conceiving the study, data curation and analysis, project administration, and writing of the manuscript.

All the authors have approved the final version of the manuscript to be published.

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