Diabetes, Fasting Glucose, and the Risk of Glaucoma

A Meta-analysis

Di Zhao, MHS,[1,*] *Juhee Cho, PhD,*[1,2,3,*] *Myung Hun Kim, MD,*[4,5] *David S. Friedman, MD, PhD,*[6] *Eliseo Guallar, MD, DrPH*[1]

Topic: We performed a systematic review to summarize the association of diabetes and blood glucose levels with glaucoma, intraocular pressure (IOP), and ocular hypertension in the general population.

Clinical Relevance: Diabetes has been proposed as a risk factor for glaucoma, but epidemiologic studies have been inconsistent, and the association is still controversial. Furthermore, no systematic reviews evaluated other metabolic abnormalities, such as the metabolic syndrome, with the risk of glaucoma.

Methods: We identified the studies by searching the PubMed and EMBASE databases. We used inverse-variance weighted random-effects models to summarize relative risks across studies.

Results: We identified 47 studies including 2 981 342 individuals from 16 countries. The quality of evidence generally was higher in the cohort compared with case-control or cross-sectional studies. The pooled relative risk for glaucoma comparing patients with diabetes with those without diabetes was 1.48 (95% confidence interval [CI], 1.29−1.71), with significant heterogeneity across studies ($I^2 = 82.3\%$; $P < 0.001$). The risk of glaucoma increased by 5% (95% CI, 1%−9%) for each year since diabetes diagnosis. The pooled average difference in IOP comparing patients with diabetes with those without diabetes was 0.18 mmHg (95% CI, 0.09−0.27; $I^2 = 73.2\%$), whereas the pooled average increase in IOP associated with an increase in 10 mg/dl in fasting glucose was 0.09 mmHg (95% CI, 0.05−0.12; $I^2 = 34.8\%$).

Conclusions: Diabetes, diabetes duration, and fasting glucose levels were associated with a significantly increased risk of glaucoma, and diabetes and fasting glucose levels were associated with slightly higher IOP. *Ophthalmology 2014;■:1−7 © 2014 by the American Academy of Ophthalmology.*

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Glaucoma, the most common cause of irreversible blindness worldwide, represents a major public health problem.[1] The number of glaucoma patients in the United States is expected to increase from 2.7 million in 2010 to 6.3 million in 2050.[2] Elevated intraocular pressure (IOP) or ocular hypertension (OHT) is the only well-established modifiable risk factor for primary open-angle glaucoma (POAG), the most common form of glaucoma. Thus, there is considerable interest in identifying potentially modifiable risk factors for glaucoma to develop interventions that may reduce the incidence or improve the prognosis of the disease.

Diabetes mellitus has been suggested to causes microvascular damage and vascular dysregulation of the retina and the optic disc, increasing the susceptibility of the optic nerve head to damage in glaucoma.[3−5] Diabetes also may result in elevated IOP and increased risk of POAG by disrupting the trabecular meshwork function.[6] Diabetes has been proposed as a risk factor for elevated IOP and POAG, but epidemiologic studies of the association between diabetes mellitus and glaucoma have been inconsistent,[7−10] and the association is still controversial.

A meta-analysis published in 2004 evaluated the available literature on the association between diabetes mellitus and glaucoma.[11] This meta-analysis was based on 12 cross-sectional or case-control studies published before 2002. Several studies, including 6 longitudinal studies published in the past 10 years, have never been appraised systematically. Furthermore, there are no systematic reviews evaluating other metabolic abnormalities, such as the metabolic syndrome, with the risk of glaucoma. Our objective thus was to conduct a comprehensive and updated systematic review and meta-analysis to summarize the association between diabetes, diabetes duration, metabolic syndrome, and glucose levels with the risk of glaucoma and with IOP levels in the general population.

Methods

Search Strategy and Study Selection

Our systematic review and meta-analysis was reported according to the Meta-analysis of Observational Studies in Epidemiology guidelines.[12] The protocol for the systematic review was registered in the International Database of Prospectively Registered

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Systematic Reviews (no. CRD42013005989). We searched MEDLINE and EMBASE to identify relevant studies. The search items were based on established terminology using MESH and EMBASE extensive search terms when possible. Keywords included *diabetes mellitus*, *diabetes*, *metabolic syndrome*, *hyperglycemia*, *insulin resistance*, *hyperinsulinism*, *blood glucose*, *hemoglobin A1c*, *blood sugar*, *pancreas islet disease*, *intraocular pressure*, *intraocular tension*, *eye pressure*, *eye internal pressure*, *intraorbital pressure*, *ocular pressure*, *ocular tension*, *intraocular hypertension*, *intraocular tension*, and *glaucoma*. The terms *diabetes* and *glaucoma* are general key terms that cover their subtypes in MEDLINE and EMBASE database searches and details are included in Appendix A (available at www.aaojournal.org). We also manually reviewed the reference lists from retrieved articles and identified additional relevant studies. The databases were searched for reports published through May 2013 with no language restrictions.

We aimed to identify all studies reporting an association between diabetes, metabolic syndrome, or glucose levels with glaucoma, IOP levels, or OHT in adults 18 years of age or older. The exclusion criteria were: (1) no original research (reviews, commentaries, editorials, or letters); (2) case reports or case series; (3) studies not conducted in humans or adults; (4) studies conducted in population samples comprising only patients with diabetes, metabolic syndrome, glaucoma, or OHT at baseline; (5) studies not reporting glaucoma, IOP, or OHT as outcomes; (6) studies not using diabetes, metabolic syndrome, blood glucose, or hemoglobin A1c as exposures; (7) studies mainly investigating drug effects or metabolism; or (8) studies conducted in population samples comprising only patients with specific conditions (e.g., hemodialysis, eye surgery) that limit their generalizability to general population samples. Because age is a strong risk factor for glaucoma and for diabetes development, we further excluded studies that did not adjust for age in the design or the analysis.

The study end points were POAG, IOP, and OHT. For studies that did not report POAG separately from other types of glaucoma, we used results for open-angle glaucoma or glaucoma as end points. If more than 1 published article reported on the same association within a study population, we selected the most recent publication or the publication with the longest follow-up. Studies reporting only correlation coefficients or point estimates of other measures of association without standard errors or any other estimates of statistical variability were included in the systematic review, but were excluded from the quantitative meta-analysis.

Data Extraction and Quality Assessment

Two authors (D.Z. and M.K.) independently reviewed all search results to identify eligible studies and abstracted data from selected articles. Discrepancies between reviewers were resolved by consensus or adjudication by the third reviewer (E.G.). The following data were extracted from each study: publication year, country where the study was performed, study period, study size, gender and age of study participants, measure and range of exposure, methods for identification of type 2 diabetes, variables adjusted for in the analysis, and reported measures of association with corresponding standard errors or 95% CIs. We assessed study quality using the methods described by Sanderson et al[13] and Viswanathan et al.[14] We examined the methods for selecting study participants, the criteria for defining exposures and outcomes, the risk of bias associated with different designs, the methods used to control for confounding, and potential conflicts of interest (Appendix B, available at www.aaojournal.org).

Statistical Analysis

We conducted a separate meta-analysis for each combination of exposure (diabetes, diabetes duration, metabolic syndrome, and glucose levels) and outcome (glaucoma, IOP, and OHT) using random-effects meta-analyses to combine study-specific measures of association. For binary outcomes (glaucoma and OHT), the measures of association abstracted (odds ratios, incidence risk ratios, and hazard ratios) were combined together and referred to as relative risk (RR). We estimated the pooled average difference in IOP in millimeters of mercury comparing patients with and without diabetes and comparing patients with and without metabolic syndrome, as well as the pooled average difference in IOP associated with an increase in 10 mg/dl of serum glucose. Finally, we estimated the increase in glaucoma risk associated with a 1-year increase in diabetes duration compared with no diabetes by using a random-effects dose-response meta-analysis.[15,16]

When a study reported several models for a given end point, we used the measure of association with the greatest degree of control for potential confounders. For studies reporting results separately by subgroup (e.g., reporting results separately by men and women, diabetes with treatment and without treatment in one study), we pooled results across subgroups for each study first. For studies reporting standardized regression coefficients (e.g., the change of outcome with 1-standard deviation increase in exposure), we used the standard deviations reported for that population to recalculate unstandardized regression coefficients (the change of outcome with 1 unit increase in exposure).

Between-study heterogeneity was quantified using the I^2 statistic. We also conducted sensitivity analyses omitting 1 study at a time to assess whether results were markedly affected by any single study. Publication bias was evaluated by funnel plots and by Egger's tests.[17] To examine potential sources of heterogeneity by study type (case-control, cross-sectional, longitudinal), location (Europe, America, Asia, other), year of publication (<2000, ≥ 2000), and exposure and outcome definitions, we used meta-regression models with restricted maximum likelihood estimation of between-study variance. Meta-analyses were conducted with Stata software version 12 (STATA Corp, College Station, TX).

Results

We identified 47 studies, including 2 981 342 individuals from 16 countries (Fig 1 and Table 1, available at www.aaojournal.org). Sixteen studies were performed in North America, 15 in Asia, 11 in Europe, 2 in Australia, 1 in Africa, 1 in the Middle East, and 1 in the West Indies (Table 2, available at www.aaojournal.org). Thirty-two studies were cross-sectional, 9 were case-control, and 6 were longitudinal. Twenty-nine studies reported on the association between diabetes and glaucoma, 5 on diabetes duration and glaucoma, 2 on hemoglobin A1c and glaucoma, 1 on metabolic syndrome, glucose levels and glaucoma, 11 on diabetes and IOP levels, 6 on glucose and IOP levels, 6 on diabetes and OHT, and 1 on glucose and OHT. The definitions of the exposures and outcomes and the factors used for adjustment in each study are summarized in Tables 3 and 4 (available at www.aaojournal.org).