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Original article

Type 2 diabetes mellitus and risk of open-angle glaucoma development in Koreans: An 11-year nationwide propensity-score-matched study

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ABSTRACT

Purpose. – To evaluate the risk of primary open-angle glaucoma (POAG) development in type 2 diabetes mellitus (T2DM) patients.
Methods. – In this 11-year longitudinal study based on the Korean National Health Insurance research database, the data collected comprised 1,025,340 (2.2%) participants who were randomly selected from 46,605,433 Korean residents in 2002. The database was analyzed to identify participants with an initial diagnosis of T2DM in 2003–2004. The control group was composed of participants without T2DM who were propensity-score-matched, five controls per T2DM patient, according to age, gender, household income, residential area and underlying diseases, including hypertension, dyslipidaemia, coronary heart disease, cerebrovascular disease and thyroid disease. Cox proportional-hazards regression was used to calculate the overall hazard ratios (HRs) in participants with and without T2DM for development of POAG before and after adjusting for confounding factors.
Results. – There were 12,657 participants with T2DM and 63,285 propensity-score-matched controls without T2DM. POAG developed in 413 (3.3%) and 1188 (1.9%) participants in the T2DM and control groups, respectively. T2DM was associated with an increased risk of POAG development [HR: 1.80; 95% confidence interval (CI): 1.58–2.04] after adjusting for age, gender, household income and other potential confounders.
Conclusion. – T2DM was significantly associated with the development of POAG after adjusting for potential confounders in the Korean population.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide [1]. It is a progressive optic neuropathy characterized by typical optic-disc changes and alterations in the visual field; its main risk factor is ocular hypertension, although a number of patients with glaucoma do not present with any increase in intraocular pressure [2–5]. Nevertheless, these latter patients still require treatment [6]. In addition, glaucoma does not cause any symptoms in its early stages, thereby earning the appellation of 'silent thief of sight'. Thus, identifying the risk factors for glaucoma is important.

Type 2 diabetes mellitus (T2DM) is an increasingly prevalent health problem around the world that is associated with many serious complications. The prevalence of DM worldwide was estimated to be 8.5% in 2014 [7].

The relationship between DM and primary open-angle glaucoma (POAG) is controversial. The Blue Mountains Eye Study found that patients with DM have an increased risk of developing glaucoma [8,9]. However, other studies, including the Rotterdam Study and Baltimore Eye Survey, failed to show any significant relationship between DM and open-angle glaucoma [10–13].

While there are a few longitudinal studies evaluating the relationship between DM and POAG [10,11,14–17], to the best of our knowledge, there is none based on an Asian population. Yet, the clinical characteristics of both T2DM and POAG in Asians differ from those reported in other parts of the world. People in Asia develop insulin resistance at a lower level of obesity and at

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younger ages and show early dysfunction in insulin secretion [18]. As for POAG, there is a preponderance of normal-tension glaucoma over high-tension glaucoma in Asians compared with white and African populations [19]. These clinical differences may result in a different relationship between DM and POAG in Asian populations.

Therefore, the purpose of the present study was to evaluate the relationship between T2DM and the prospective risk of POAG development in Koreans, using the Korean National Health Insurance Service National Sample Cohort (KNHIS–NSC) 2002–2013, comprising 1,025,340 representative residents of South Korea.

Methods

A propensity-score-matched analysis was performed using a retrospective population-based cohort design. The KNHIS–NSC 2002–2013 was approved by the Institutional Review Board of the Korean National Health Insurance Service (KNHIS). The present study design was approved by the Institutional Review Board of the Seoul St. Mary's Hospital and followed the tenets of the Declaration of Helsinki.

Database

The KNHIS was introduced in 1977 and covered all Koreans by 1989 [20]. In South Korea, all Korean nationals are required to enrol in the KNHIS. In this system, all patients pay for 30% of their total medical expenses when using medical facilities, and medical providers receive the remaining 70% from the KNHIS, for which they must submit claims. These claims include data regarding diagnostic codes, procedures, prescription drugs, personal information about the patient, information about the hospital, direct medical costs of both inpatient and outpatient care and dental services. With these data, each patient is identified by a 13-digit social identification number allocated at birth; therefore, no healthcare records for any patient can be either duplicated or omitted. Furthermore, the diagnostic code used by the KNHIS is based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10).

Study sample

The present study used KNHIS data recorded from 2002 through to 2013, which was released in 2015. The dataset comprises 1,025,340 ($\sim$ 2.2%) randomly sampled participants from the entire population in the KNHIS in 2002. The data were produced by the KNHIS, using a systematic sampling method to generate a representative sample from the entire 46,605,433 Korean residential population in 2002, and include all medical claims filed from January 2002 to December 2013.

A T2DM group and a comparison (control) group matched by age, gender and comorbidities were generated. The DM group included all participants who received inpatient or outpatient care for the first time in 2003 or 2004 (index date) for an initial diagnosis of T2DM, which was defined based on ICD-10 codes E11–E14 and prescriptions for antidiabetic medications, as defined by the Korean Diabetes Association [21]. In addition, diabetic retinopathy was defined as H36.0 and macular oedema as H35.8. Participants who had been diagnosed with DM in 2002 were excluded to ensure that the T2DM group included only those with new-onset DM. Also excluded were patients who had been diagnosed with POAG before the index date. On the other hand, the study included subjects aged $>$ 40 years and control subjects without T2DM were selected from the remaining participants in the KNHIS and from 62,675 participants (five per DM patient) who were propensity-score-matched to the T2DM group based on age, gender, residential area, household income and comorbidities, including hypertension (ICD-10 codes I10–I13 and I15), dyslipidaemia (ICD-10 code E78), thyroid disease (ICD-10 codes E00–E07), coronary heart disease (ICD-10 codes I20–I25) and cerebrovascular disease (ICD-10 codes I60–I69). Comorbidity was defined based on information amassed from the year prior to the index date. Ophthalmological consultation was defined as at least one such consultation between 2003 and 2004.

Main outcome measure: POAG

All patients were tracked based on their index dates of ambulatory and inpatient care visits during the 11 years from 2003 to 2013 to detect the development of POAG. The POAG cohort was composed of participants with at least two visits between 2003 and 2013 for POAG (ICD-10 code H40.1), thereby excluding other, secondary forms of glaucoma such as neovascular glaucoma, steroid-induced glaucoma and glaucoma associated with lens disorders. In addition, only participants who had received antiglaucoma medications during the study period were included [22–25].

Statistical analysis

Standardized differences were used to evaluate covariates for predicting the propensity scores of matched pairs. Following the 1:5 propensity-score-matching ratio, data were compared between those with and without T2DM using a generalized linear model, while those with and without POAG were compared using χ^2chi-square tests for categorical variables and independent t tests for continuous variables. Cox proportional-hazards regression analysis was performed in the matched sample to compare the risk of POAG development between participants with and without DM. Also calculated were hazard ratios (HRs) by gender (men and women) and according to age group (40–64 years and $\geq$ 65 years). SAS statistical software (version 9.3, SAS Institute, Cary, NC, USA) was used for all statistical analyses, and a P value $<$ 0.05 was considered a statistically significant result.

Results

Table 1 shows the baseline characteristics of the present study population. A total of 12,535 participants met inclusion criteria for the T2DM group. After propensity-score-matching for age, gender

Table 1
Characteristics of type 2 diabetes mellitus (T2DM) patients and their propensity-score-matched controls.

Variable	Control group (n = 62,675)	T2DM group (n = 12,535)	P
Age $\geq$ 65 years	20,607 (32.9)	4,093 (32.7)	0.6220
Gender (male)	35,065 (56.0)	7,021 (56.0)	0.8955
Hypertension	34,339 (54.8)	6,854 (54.7)	0.8211
Dyslipidaemia	21,401 (34.1)	4287 (34.2)	0.9069
Thyroid disease	4,613 (7.4)	961 (7.7)	0.2320
Coronary heart disease	8,360 (13.3)	1,733 (13.8)	0.1445
Cerebrovascular disease	6,027 (9.6)	1269 (10.1)	0.0798
Residential area (rural)	33,990 (54.2)	6749 (53.8)	0.4226
Household income (lower 0–20%)	10,102 (16.1)	2057 (16.4)	0.4176
Primary open-angle glaucoma	1,188 (1.9)	413 (3.3)	$<$ 0.0001
Follow-up duration (years)	10.9 $\pm$ 0.8	9.9 $\pm$ 1.2	$<$ 0.0001
Ophthalmological consultation[a]	15,734 (25.1)	3775 (30.1)	$<$ 0.0001

Data are expressed as n (%) or mean $\pm$ standard deviation.
[a] At least one ophthalmological consultation during 2003–2004.

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