Prospective Association between Diabetic Retinopathy and Cardiovascular Disease—A Systematic Review and Meta-analysis of Cohort Studies

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Background: Diabetic retinopathy (DR) is linked to increased risk of cardiovascular (CV) disease. However, the effect size of the association was not consistent. In this study, we performed a systematic review and meta-analysis of available cohort studies to determine the association between DR and CV disease, and to investigate the factors that influence the association. *Methods:* Terms related to DR and CV disease were searched from MEDLINE and EMBASE database. High-quality articles (Newcastle–Ottawa scales above 6) conducted in cohort studies reporting the association between DR and CV disease were identified. Study-specific estimates were pooled using random effects with inverse variance meta-analysis. Subgroup analysis was performed according to diabetes types. Heterogeneity of included studies was assessed using the I^2 test. The cause of the heterogeneity was examined using metaregression analyses. *Results:* A total of 13 studies representing 17,611 patients without CV disease at baseline were included. At follow-up, there were 1457 CV disease-related incidences. Overall, DR was associated with increased risk of CV disease (relative risk [RR]: 2.42, 95% confidence interval [CI]: 1.77-3.31) in diabetes. Specifically, the RR was 3.59 (95% CI: 1.79-7.20) for type 1 diabetes and 1.81 (95% CI: 1.47-2.23) for type 2 diabetes. Significant heterogeneity was found in studies with type 1 diabetes. Metaregression analysis showed that baseline systolic blood pressure was a key factor leading to the heterogeneity. *Conclusion:* In conclusion, DR is significantly associated with CV disease incidence and CV disease-related mortality in diabetes. Patients with DR may need more intensive management to control future CV disease attacks. **Key Words:** Cardiovascular disease—diabetes—diabetic retinopathy—meta-analysis—systematic review.

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Introduction

Cardiovascular (CV) disease is the leading cause of morbidity and mortality worldwide.[1] Individuals with diabetes are 2-5 times more likely to develop CV disease compared with nondiabetes people, partially due to the clustering of risk factors.[2] As one of the most common microvascular complications of diabetes, diabetic retinopathy (DR) affects around one third of diabetes patients[3] and is the leading cause of blindness among the working population all over the world.[4] The presence of DR is associated with increased risk of CV disease incidence and CV disease-related mortality in both type 1 diabetes mellitus (T1DM)[5] and type 2 diabetes mellitus (T2DM).[6,7] Furthermore, there was a positive association between DR severity and risk of CV disease demonstrated in the Action to Control Cardiovascular Risk in Diabetes trial.[8] However, the findings were not consistent across reports. One study in Japan with 1636 T2DM patients found no significant association between DR and coronary heart disease (CHD) mortality after a mean follow-up period of 9.4 years (relative risk [RR]: 1.36, 95% confidence interval [CI]: .81-2.26).[9] In contrast, another study conducted in Japan showed that the RR of developing CV disease in T2DM patients was 4.41 (95% CI: 1.81-10.75) compared to those without DR.[10] Therefore, in the present study, we performed a systematic review and meta-analysis to investigate the association between DR and CV disease in cohort studies using subgroup analysis according to diabetes types. The factors that caused the heterogeneity of the association were also explored.

Methods

Search Strategy and Study Selection

The electronic database of MEDLINE and EMBASE were searched from their inception to October 2015. We restricted our review to studies that reported the following diseases as an outcome: fatal or nonfatal CV disease, cerebrovascular disease, CHD, and stroke. We used the following search terms without restrictions: "retinopathy" and ("coronary" or "myocardial" or "stroke" or "cardiovascular disease" or "cerebrovascular diseases") and "diabetes." We further manually searched the reference list of identified reviews and research articles to include any eligible study.

To be included in the present study, an original research study had to meet following criteria: (1) the study design was a cohort study; (2) the study populations should be patients with either T1DM or T2DM, or the association between DR and CV disease was assessed separately in different diabetes types; (3) the included study should report data on the first attack of fatal and/or nonfatal CV disease, rather than the recurrent CV disease or with previous surgery; (4) the study should be written in English; and (5) the study should not be a letter, review, and commentary article. The quality of the cohort studies was assessed using the Newcastle–Ottawa scales.[11] Articles with a score of 6 or higher were considered of high quality.

Data Extraction

The data were collected using a form incorporating study details (author name, publication year, etc.) and characteristics of the study population (age, percentage of male patients, etc.), as well as the definition and evaluation criteria for DR and CV disease. To summarize unadjusted RR, outcome numbers in the DR group and in the non-DR group or reported unadjusted RRs were extracted; to summarize adjusted RR, the reported RRs with the maximum adjustment were extracted from the included studies. In particular, if a study included different subtypes of CV disease, the outcome with more incident cases was included in the analysis.

Statistical Analyses

Potential publication bias was visually inspected through Begg's funnel plot. We further performed Begg's and Egger's tests, and a P value less than .05 indicated significant publication bias.[12,13] If there was evidence of significant bias, we additionally applied the "trim and fill" method to adjust the publication bias.[14]

RR was used to measure the association between DR and CV disease risk across studies. Subgroup analyses were conducted based on diabetes types. We calculated pooled unadjusted and adjusted RRs with 95% CI using random effect with inverse variance. Heterogeneity between studies was tested using I^2 test. A P value less than .05 was used as the threshold of significance.[15] Differences in effect estimates between studies in T1DM and T2DM were assessed by comparing the pooled RRs using χ^2 test.

To explore the potential causes of the heterogeneity, metaregression analysis was performed. To assess the influence of single study, a "leave-one-out" sensitivity analysis was conducted by omitting 1 study at a time.

The meta-analysis and statistical analyses were performed using Review Manager software (RevMan 5.2; Cochrane Collaboration, Oxford, United Kingdom) and Stata/SE (Release 12.1; StataCorp LP, College Station, TX).

Results

Literature Search and Studies Included

The search identified 3984 articles (Fig 1). After screening of titles and abstracts, 61 articles were further assessed through full-text review. Finally, 13 cohort studies (5 in T1DM and 8 in T2DM) were included in the analysis. Of these, 2 studies in T1DM and 5 studies in T2DM reported the adjusted association between DR and CV disease events with adjustments of other risk factors and confounders.