Meta-analysis of the risk of cataract in type 2 diabetes

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Abstract

Background: This meta-analysis aimed to investigate the association between type 2 diabetes (T2D) and the risk of cataract.

Methods: Databases of Pubmed, Embase, and SpringerLink were retrieved for observational studies published before November 2013. The odds ratio (OR) and 95% confidence interval (CI) were used for estimating the association. All statistical analyses were performed by Stata 10.0 software.

Results: A total of 8 studies involving 20837 subjects were included in the meta-analysis. The risk of any cataract (AC) in T2D patients was higher than that in non-diabetic subjects (OR = 1.97, 95% CI: 1.45-2.67, P < 0.001). The risks of cortical cataract posterior (CC) (OR = 1.68, 95% CI: 1.47-1.91, P < 0.001) and posterior subcapsular (PSC) (OR = 1.55, 95% CI: 1.27-1.90, P < 0.001) were significantly elevated in T2D patients, while no significant association was found in nuclear sclerosis (NS) (OR = 1.36, 95% CI: 0.97-1.90, P = 0.070).

Conclusion: T2D patients had a higher risk of cataracts, excepting NS. Special attention should be paid on the ophthalmic extermination, especially for cataract in T2D patients.

Keywords: Non-diabetic, Nuclear sclerosis, Ophthalmology

Background

Cataract, a loss of the normal transparency of the crystalline lens due to an opacity (lens opacity or crystalline opacity), is one of the leading causes of blindness worldwide [1,2]. Hence, identification of the risk factors is of great importance for prevention and treatment of the blindness. Pollreisz [3] propose in a review article that diabetes is one of the widely perceived risk factors for cataract. Diabetes patients are more prone to develop cataracts [2]. The cataract incidence was estimated 3.31 per 1000 person-years of type 2 diabetic patients during 3.6 years' follow-up [4]. However, studies [5-8] found that not all types of cataracts [9], nuclear sclerosis (NS), cortical cataract (CC) or posterior subcapsular (PSC), are more prone to occurring in type 2 diabetes (T2D) patients. Evidence for their association has not been systematically assessed.

Therefore, we performed this meta-analysis to explore the association between T2D and the risk of cataract. We anticipate the findings of this study will provide reliable evidence for clinical cataract research and prevention.

Methods

Search strategy

The databases included PubMed, Embase and SpringerLink and the studies had to be published before November 2013. Only the articles written in English were screened. The key words were consisted of three parts: 1) cataract OR lens opacity OR crystalline opacity; 2) diabetes OR T2DM OR type 2 diabetes; 3) risk OR incidence.

The eligible criteria

Inclusion criteria were: (1) the study was designed as observational study (cross-sectional, case–control or cohort study); (2) the study explored the relationship between T2D and the risk of cataracts; (3) there was control group; (4) the outcomes include incidence of cataracts (AC, CC, NS and PSC); (5) the study provided...
enough information for calculating the Odds Ratio (OR) and 95% confidence interval (CI); (6) if there were multiple articles with same population or data, only the article with the longest follow-up and complete data was selected.

Exclusion criteria were: (1) the study with type 1 diabetes mellitus patients was excluded; (2) all duplicates were excluded; and (3) review articles, letters and comments were also excluded.

Study selection and quality assessment
Two investigators independently retrieved the eligible studies according to the search strategy and eligible criteria. The references were managed by Endnote software (Thomson ISI ResearchSoft, Carlsbad, CA, USA). Besides, the manual search was performed to retrieve some more eligible studies in the reviews and references of included studies. The quality of the selected studies were assessed by STROBE statement [10] including 22 items.

Data extraction
Study characteristics, including first author, publication year, study design, country, diagnosis of cataract and diabetes, age/gender of patient, were extracted independently by two researchers. The odds ratios (ORs) and 95% confidence intervals (CIs) of the exposures were extracted. The statistical methods of covariates adjustment were also noted. Any disagreement was resolved by discussion.

Heterogeneity test
The heterogeneity between studies was evaluated by $Q$ test [11] and $I^2$ statistics [12], where, $P > 0.05$ and/or $I^2 < 50\%$ was considered homogeneity, and a fixed-effect model was used for calculate pooled effect; otherwise, there was significant heterogeneity and random-effect model was used.

Pooled analysis
The meta-analysis was stratified for different types of cataract definition: AC, CC, NS and PSC. The pooled effect of each exposure on T2D was estimated by the values of ORs and 95% CIs. If the ORs were provided in the publications, they were used for pooled estimate. Otherwise, the ORs were calculated according to the provided data in the articles. All statistical analyses were conducted by Stata 11.0 software.

Sensitivity analysis and publication bias estimate
The sensitivity analysis was conducted to test the robustness of the results by: 1) only the cross-sectional studies were included; 2) only the studies with Eye examination to confirm the cataract were included. The publication bias was estimated by Begg’s test [13] and Egger’s test [14], using a significance level of $P < 0.05$ to indicate significant asymmetry.

Results
Study selection
The process of literature search and study selection was displayed in Figure 1. By retrieval of PubMed, Embase and SpringerLink databases according to the search strategy, 771, 238 and 677 documents were obtained, respectively. After excluding the duplicates, 1037 articles remained. By screening the title, we excluded 1014 documents that did not meet the inclusion criteria. Then by reading the abstracts 10 studies were excluded (3 without control group; 1 outcome was not incidence of cataract; 6 did not investigated the relationship between T2D and cataract). Then in the remaining 13 studies, we reviewed the full text and 5 studies were excluded including 1 with non T2D subjects, 3 with incomplete data and 1 with duplicated crowd. Finally, 8 studies [5-7,15-19] were included in this meta-analysis.

The characteristics of the included studies
The characteristics of the included studies were listed in Table 1. All studies are with high quality (17–21 STROBE scores, Additional file 1: Table S1). Among the 8 include studies there were 6 cross-sectional studies [5-7,15,17,18], 1 cohort study [19] and 1 case–control study [16], including 20837 subjects. Since Jacques’ study [5] did not provide the specific number of cases, so we could not obtain the accurate total number of cases in this meta-analysis. The area distributions of the 8 studies were: 2 in Europe (France and Sweden), 3 in American, 1 in African and one in Australian. Seven articles reported three kinds of outcomes of NS, CC
| Author year | Location | Ascertainment of cataract | Type of study | Ascertainment of diabetes | Definition of cataract | Age(y) sex | No. of case | Diabetes | No. of case | Non-diabetes | ORs (95% CI) | Adjustment for covariates | STROBE scores |
|-------------|----------|---------------------------|--------------|---------------------------|------------------------|-----------|-----------|----------|-----------|-------------|----------------|--------------------------|---------------|
| Machan 2012 [8] | French | Hospital records | Cross-sectional | Hospital records | LOCS II | <1-93 M&F | AC | 348 | 452 | 1885 | 5884 | 1.60 (1.13, 2.27) | Age, gender, smoking, systolic blood pressure, Statin use | 20 |
| | | | | | | | NS | 282 | 1546 | | | 1.62 (1.14, 2.29) | | |
| | | | | | | | CC | 104 | 525 | | | 1.37 (1.02, 1.83) | | |
| | | | | | | | PSC | 44 | 194 | | | 1.33 (0.90, 1.96) | | |
| Tan et al. 2008 [19] | Australia | Eye examination | Cohort | Medical record or IFG test | Wisconsin Cataract Grading System | ≥49 M&F | NS | 37 | 69 | 402 | 1149 | 6.76 (1.04,14.00)* | Age, gender, smoking, myopia, and pulse pressure, sun-related skin damage, ever use of steroids, myopia, and body mass index | 21 |
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| Rotimi et al. 2003 [18] | West African | Eye examination | Cross-sectional | IFG test | — | ≥20 M&F | AC | 373 | 831 | 35 | 191 | 3.63 (2.45, 5.37)* | | |
| | | | | | | | | | | | | | | |
| Olafsdottir et al. 2012 [7] | Sweden | Eye examination | Cross-sectional | IFG test | LOCS II score ≥ 2 | 24-93y M&F | AC | 208 | 275 | 175 | 256 | 1.44 (0.98,2.10)* | | |
| | | | | | | | | | | | | | | |
| Jacques et al. 2003 [5] | USA | Eye examination | Cross-sectional | IFG test | LOCS III | ≥2.5, NS; ≥1.0, CC; ≥0.5, PSC | 54-73 F | NS | NR | 31 | NR | 400 | 1.5 (0.6, 3.5) | Age, smoking , summertime sunlight exposure, and alcohol intake | 21 |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| Klein et al. 1995 [6] | USA | Eye examination | Cross-sectional | Medical record or IFG test | Wisconsin Cataract Grading System | 43-84 M&F | NS | 66 | 384 | 570 | 4285 | 0.93 (0.67,1.29) | | |
| | | | | | | | | | | | | | | |
| Leske et al. 1999 [16] | USA | Eye examination | Case-control | Medical record or IFG test | LOCS II grade ≥ 2 | 40-84 M&F | AC | 1800 | 448 | 2431 | 289# | 1.85 (1.51, 2.27) | | |
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Table 1 Characteristics of 8 studies on type 2 diabetes and cataract
Table 1 Characteristics of 8 studies on type 2 diabetes and cataract (Continued)

| Study          | Country | Design       | Method          | Age Range | Gender | Number | OR (95% CI) | Associated Factors |
|----------------|---------|--------------|-----------------|-----------|--------|---------|-------------|--------------------|
| Foster et al.  | Singapore | Cross-sectional | Medical record | 40-81 M&F | 27     | 1066    | 2.0 (0.9, 4.5) | Age, gender, body mass index and occupation. |
|                |         |              | LOCS III ≥ 4 NS ≥ 2 for NS ≥ 2 for CC ≥ 2 for PSC |           |        |         |             |                    |
|                |         |              | NS              |           |        |         | 2.8 (0.8, 9.4) |                    |
|                |         |              | CC              |           |        |         | 3.1 (1.6, 6.1) |                    |
|                |         |              | PSC             |           |        |         | 2.2 (1.2, 4.1) |                    |

*: ORs was calculated based on literature data; AC: any cataract; NS: nuclear sclerosis; CC: cortical cataract; PSC: posterior subcapsular cataract; NR: not recorded; LOCS, lens opacities classification system #: number of diabetes.
and PSC. Five studies reported the overall incidence of any cataract (AC). Six literatures provided adjusted OR and 95% CI, two studies provided OR calculable data.

**Meta-analysis of the risk of cataract in T2D patients**

By heterogeneity analysis of the five studies [7,15-18] that reported the overall incidence of AC, there were significant heterogeneity among studies ($I^2 = 70.4\%$, $P = 0.009$), and a random-effect model was used for estimate of the pooled effect. It was showed that (Figure 2) the OR of AC risk between T2D patients and non-diabetic subjects was $1.97$ (95% CI: $1.45$-$2.67$, $P < 0.001$), indicating that the risk of AC was significantly elevated in T2D patients compared with non-diabetic subjects.

Figures 3, 4 and 5 showed the pooled results of three types of cataract [5-7,15-17,19], NS, CC and PSC, in T2D patients. There was significant heterogeneity among studies of NS and T2D patients ($I^2 = 65.8\%$, $P = 0.007$), and a random-effect model was used to produce an OR of $1.36$ (95% CI: $0.97$-$1.90$, $P = 0.070$), indicating a higher risk of NS in T2D patients over non-T2D patients. There was no significant heterogeneity among studies of CC ($I^2 = 3.3\%$, $P = 0.400$) and PSC ($I^2 = 34.9\%$, $P = 0.162$), and fixed-effect models were used. The pooled ORs were respectively $1.68$ for CC (95% CI: $1.47$-$1.91$, $P < 0.001$) and $1.55$ for PSC (95% CI: $1.27$-$1.90$, $P < 0.001$). These results indicated that patients with T2D had a higher risk of cataracts than those without.

**Sensitivity analysis and publication bias estimate**

The result of sensitivity analysis indicated that the results of the present meta-analysis were robust (Table 2). The
pooled results for the outcomes of cross-sectional studies or the studies with Eye examination for cataract diagnosis were consistent with those before sensitivity analysis.

Begg’s test and Egger’s test showed no significant publish bias among studies ($P > 0.05$, Table 3).

**Discussion**

Cataract is a major cause of blindness worldwide, and it largely results from occurrence of diabetes. The present meta-analysis with a substantial number of subjects (20837 subjects) indicated the risk of cataracts was elevated in T2D patients compared with the non-diabetic subjects.

It was reported that cataract is one of the most common complications of diabetes mellitus on the eye [20,21] and up to 20% of all cataract procedures are performed for diabetic patients [22]. Cataracts were more frequently in patients with diabetes [23,24]. In the present study, approximate 2 times risk of AC was found in T2D patients compared with the non-diabetic subjects. Visual improvement was seen following extracapsular cataract extraction surgery for advanced cataract in diabetics and postoperative monitoring for treatment of diabetic retinopathy may enhance visual outcome [25].

A Waterloo Eye Study by reviewing of 6397 clinic files found that diagnosis of T2D resulted in an earlier development of all three cataract subtypes [8]. Similarly in the present study, we found that the risks of CC and PSC were
Table 2 Sensitivity analysis of meta-analysis of type 2 diabetes and cataract risks

| Outcomes | Pooled OR (95%CI) | PA | PH | Sensitivity analysis |
|----------|------------------|----|----|----------------------|
|          |                  |    |    | Cross-sectional study | Eye examination |                  |
|          |                  |    |    | PA        | PH        | PA        | PH        |
| Any Cataract | 1.97(1.45, 2.67) | <0.001 | 0.009 | 2.02(1.27, 3.21) | 0.003 | 0.004 | 2.09(1.41, 3.09) | <0.001 | 0.008 |
| NS       | 1.36(0.97, 1.90) | 0.070 | 0.007 | 1.20(0.86, 1.69) | 0.288 | 0.040 | 1.31(0.89, 1.93) | 0.164 | 0.017 |
| CC       | 1.68(1.47, 1.91) | <0.001 | 0.400 | 1.65(1.39, 1.94) | <0.001 | 0.196 | 1.77(1.52, 2.05) | <0.001 | 0.564 |
| PSC      | 1.55(1.27, 1.90) | <0.001 | 0.162 | 1.54(1.25, 1.90) | <0.001 | 0.059 | 1.64(1.30, 2.07) | <0.001 | 0.136 |

PA: P-value of association; PH: P-value of Heterogeneity. AC: any cataract; NS: nuclear sclerosis; CC: cortical cataract; PSC: posterior subcapsular cataract.

Conclusion
In summary, the present meta-analysis of five included studies involving 20837 subjects suggests that T2D is a risk factor of cataract, especially CC and PSC. The findings here attract attentions to the importance of regular ophthalmic examination in T2D. However, the conclusions need more experimental verification.

Additional file

Additional file 1: Table S1. Methodological quality (STROBE Statement-checklist) of included studies in the meta-analysis.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
LL carried out the design and coordinated the study, participated in most of the experiments and prepared the manuscript. XW provide assistance in the experiments and prepared the manuscript. GZ provided assistance for all experiments. All authors have read and approved the content of the manuscript.

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Table 3 The results of publication bias estimate

|          | Begg’s test | Egger’s test |
|----------|-------------|--------------|
| AC       | 0.806       | 0.790        |
| NS       | 0.368       | 0.200        |
| CC       | 1.000       | 0.906        |
| PSC      | 0.368       | 0.198        |

Data were represented with P value.
AC: any cataract; NS: nuclear sclerosis; CC: cortical cataract; PSC: posterior subcapsular cataract.

elevated for patients with the T2D (P < 0.05). However, we did not find significant association between T2D and risk of NS. Olafsdottir [7] and Klein [6] reported rather different results about NS from other included studies, which are the main sources of the high heterogeneity, however, they draw similar conclusions in CC and PSC with other included studies. These results highlight the necessary of regular eye examination in T2D patients.

Klein et al. [26] indicated that glycemia may be the risk factor of cataracts in T2D patients. Three molecular mechanisms may be involved in the development of diabetic cataract: nonenzymatic glycation of eye lens proteins, oxidative stress, and activated polyol pathway in glucose disposition [27]. In addition, a genetic study showed that three single-nucleotide polymorphisms (SNPs) in chromosome 3p14.1-3p14.2 which related to functions of voltage-dependent anion-selective channel protein, long myosin light chain kinase, adenylyl cyclase-associated protein, and retinoic acid receptor were significantly different in the T2D with cataracts and T2D without cataracts groups [28].

There were limitations in this meta-analysis. Although ORs were corrected by taking account of influences of age, sex and smoking in some included studies, the pooled results might also be influenced by other factors, for instance different treatments of T2D, regions of studies, and body mass index (BMI). Significant heterogeneity still exists among studies, which might be caused by the above factors. In addition, the different methods of definition of cataract (LOCS III, LOCS II, and Wisconsin Cataract Grading System) in deferent studies might also be an important source of heterogeneity.
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