STATE OF THE ART REVIEWS

Association of angiotensin-converting enzyme insertion/deletion polymorphism with type 1 diabetic nephropathy: a meta-analysis

Hai-Yan Xu a,b, Ming-Ming Liu a, Xu Wang a and Xue-Yuan He a

a The First Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing, China; b Department of Endocrinology, Xuzhou Traditional Chinese Medicine Hospital, Xuzhou, China

ABSTRACT

Objective: This study aimed to systematically evaluate the effect of an angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism on type 1 diabetic nephropathy (DN).

Methods: Cochrane Library, Embase, PubMed, Science Direct, Web of science, Wanfang data, VIP database, China Knowledge Resource Integrated Database, and SinoMed were searched. A total of 17 case–control studies analyzing ACE I/D polymorphism and type 1 DN risk were included in the present meta-analysis.

Results: Overall, a significant increased risk was found in allele comparison (OR = 1.16, 95% CI = 1.05–1.28, p = 0.04), dominant comparison (OR = 1.56, 95% CI = 1.14–2.15, p = 0.006) and homozygote comparison (OR = 1.52, 95% CI = 1.06–2.19, p = 0.02). In subgroup analyses according to ethnicity, the risk of type 1 DN in Asian population was increased in allele comparison (OR = 1.98, 95% CI = 1.15–3.42, p = 0.01), recessive comparison (OR = 2.48, 95% CI = 1.51–4.10, p = 0.0004), dominant comparison (OR = 3.15, 95% CI = 1.90–5.23, p < 0.00001), and homozygote comparison (OR = 2.87, 95% CI = 1.02–8.06, p = 0.05). However, there was no association between the ACE I/D genetic variants and type 1 DN in Caucasian populations.

Conclusions: Our meta-analysis results indicate that the ACE I/D polymorphism may contribute to type 1 DN development, especially in the Asian groups with type 1 diabetes. The current findings need to be confirmed by future well-designed and larger sample size primary studies in populations with different ethnicities.

Introduction

Diabetic nephropathy (DN) is a common and severe complication, especially in type 1 diabetes mellitus (T1DM) patients. As a leading cause of end-stage renal disease, DN is accompanied by serious socioeconomic problems.1 Various polymorphisms of genes, especially angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphisms, have been reported associated with DN. The ACE I/D gene polymorphism is characterized by the presence or absence of a 278 bp Alu repetitive sequence in intron 16.2 The genotypes of this polymorphism are II, ID, and DD.3 So far, studies have not come to an affirmative conclusion about the association between the ACE I/D polymorphism and type 1 DN, especially in Asian populations. To estimate the overall risk of ACE I/D polymorphism associated with type 1 DN and to quantify the potential between-study heterogeneity, we conducted a comprehensive meta-analysis on 17 published case–control studies from 1994 to 2015 that related variants of the ACE I/D polymorphism to the risk of developing type 1 DN.

Materials and methods

Publication search

We searched the relevant studies from the electronic databases of Cochrane Library, Embase, PubMed, Science Direct, Web of science, Wanfang data, VIP database, China Knowledge Resource Integrated Database, and SinoMed without a language limitation (the last search update was 30 March 2015). The following terms were included in the search: “diabetes mellitus” OR “diabetic patients” OR “type 1 diabetes mellitus” OR “type 1 diabetes” AND “diabetic nephropathy” OR “Diabetic kidney complications” OR “Diabetic kidney damage” AND “angiotensin converting enzyme gene polymorphism” OR “angiotensin-converting enzyme Genotype” OR “ACE gene polymorphism” OR “ACE Genotype”. Chinese databases were searched with the
equivalent Chinese terms. Additional articles were identified through references cited in recruited studies. If repeated publications were found, we recruited only the one with the most complete information. For studies without sufficient data, we sent e-mails to the corresponding authors for request.

**Inclusion and exclusion criteria**

The inclusion criteria were the following: (1) case–control study; (2) article should research the ACE I/D polymorphism with T1DN; (3) a comparison between a T1DN group and a control group; and (4) the investigation should provide detailed data on the genotype distribution or include data that could be calculated.

The exclusion criteria were the following: (1) reviews, editorials, meeting abstracts, and commentaries; (2) the study did not meet the inclusion criteria; and (3) the study contained overlapping data.

**Data extraction and synthesis**

Two reviewers independently extracted data and reached a consensus by discussion with a third party. The data extracted from these articles included the first author’s name, year of publication, ethnicity of the study population, clinical characteristics (age, diabetic duration), the genotyping method, source of controls, sample size of cases and controls. The allelic frequencies and genotypic distributions were extracted or calculated for both cases and controls. In addition, whether the genotype distribution of the controls was consistent with Hardy–Weinberg equilibrium (HWE) was tested for each study.

**Statistical analyses**

The strength of the association between the ACE I/D gene polymorphism and DN risk in type 1 diabetic patients was assessed by odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs). The genetic models that were evaluated for pooled ORs of the polymorphisms were allele comparison (D versus I), dominant comparison (DD versus DI), recessive comparison (DD versus II), homozygote comparison (DD versus II), and heterozygote comparison (ID versus II). The OR was calculated using a fixed-effects model or a random-effects model according to the heterogeneity. The heterogeneity among the studies was checked by the chi-square-based Q statistic and was considered statistically significant at \( p < 0.10 \). When \( p > 0.10 \), the pooled OR was calculated using the fixed-effects model; otherwise, the random-effects model was used.

The significance of the pooled OR was determined by a Z-test and \( p < 0.05 \) was considered statistically significant. To evaluate the ethnicity-specific effects, subgroup analyses was performed by ethnic group. Publication bias was analyzed by Begg’s funnel plots and Egger’s test. All statistical tests were performed using Revman 5.1 software and STATA 12.0 software.

**Results**

**Characteristics of studies**

A flow diagram illustrating the study selection process is shown in Figure 1. Based on our search strategy, 410 potentially eligible articles were identified from the electronic databases. According to the inclusion and exclusion criteria, 393 articles were excluded, and 17 relevant studies (12 Caucasian, 5 Asian) concerning the ACE I/D gene polymorphism and T1DN risk were identified for the final meta-analysis.\(^4\)–\(^20\) The characteristics of the studies included in the meta-analysis are provided in Table 1. The genotype and allele distributions in each study and HWE status in controls were summarized in Table 1. Of all 17 study populations, the genotype distributions of the ACE I/D gene polymorphism in the controls conformed to HWE except for two studies\(^10\),\(^15\) (Table 1).

**Meta-analysis**

Results of pooled analysis on the association between the ACE I/D gene polymorphism and type 1 DN risk are shown in Table 2. Significant between-study heterogeneity existed in overall comparisons. Thus, we chose the random-effects model to evaluate the data. Overall, a significant increased risk was found between the ACE I/D gene polymorphism and type 1 DN in allele comparison (D versus I: OR = 1.16, 95% CI = 1.05–1.28, \( p = 0.04 \), Figure 2), dominant comparison (ID + DD versus II: OR = 1.56, 95% CI = 1.14–2.15, \( p = 0.006 \) and homozygote comparison (DD versus II: OR = 1.52, 95% CI = 1.06–2.19, \( p = 0.02 \)). No significant association was found in recessive comparison (DD versus ID + II: OR = 1.23, 95% CI = 0.97–1.55, \( p = 0.09 \)) or heterozygote comparison (ID versus II: OR = 1.37, 95% CI = 0.99–1.89, \( p = 0.06 \)).

Sub-group analysis was performed according to the geographic location (Caucasian and Asian) in this meta-analysis. For Asian populations, the ACE I/D gene polymorphism was found to contribute significantly to an increased type 1 DN risk in allele comparison (D versus I: OR = 1.98, 95% CI = 1.15–3.42, \( p = 0.01 \), Figure 2), recessive comparison (DD versus ID + II: OR = 2.48, 95% CI = 1.17–5.23, \( p = 0.02 \)), and heterozygote comparison (ID versus II: OR = 2.73, 95% CI = 1.31–5.69, \( p = 0.007 \)).

For Caucasian populations, the ACE I/D gene polymorphism was found to contribute significantly in allele comparison (D versus I: OR = 2.97, 95% CI = 1.20–7.25, \( p = 0.01 \)), dominant comparison (ID + DD versus II: OR = 2.48, 95% CI = 1.49–4.12, \( p < 0.001 \)), and homozygote comparison (DD versus II: OR = 3.42, 95% CI = 1.48–7.92, \( p = 0.003 \)). No significant association was found in recessive comparison (DD versus ID + II: OR = 1.37, 95% CI = 0.99–1.89, \( p = 0.06 \)).
CI = 1.51–4.10, p = 0.0004), dominant comparison (ID + DD versus II: OR = 3.15, 95% CI = 1.90–5.23, p < 0.00001) and homozygote comparison (DD versus DD: OR = 2.87, 95% CI = 1.02–8.06, p = 0.05) but not for heterozygote comparison (ID versus DD: OR = 1.88, 95% CI = 0.65–5.44, p = 0.24). No significant association was found in any of the above mentioned models for Caucasian population (allele comparison: OR = 1.12, 95% CI = 0.95–1.31, p = 0.18; recessive comparison: OR = 1.04, 95% CI = 0.89–1.22, p = 0.62; dominant comparison: OR = 1.27, 95% CI = 0.93–1.73, p = 0.13; homozygote comparison: OR = 1.27, 95% CI = 0.89–1.81, p = 0.18; heterozygote comparison: OR = 1.26, 95% CI 0.92–1.72, p = 0.15). The data are shown in Table 2.

Heterogeneity analysis

In the present meta-analysis, significant heterogeneity existed in the overall comparisons (for D versus I: $P_Q = 0.0002$, $I^2 = 65%$; for ID + DD versus II: $P_Q = 0.005$, $I^2 = 62%$; for DD versus II: $P_Q = 0.0007$, $I^2 = 60%$; for DD versus ID + II: $P_Q = 0.01$, $I^2 = 49%$; for ID versus II: $P_Q = 0.001$, $I^2 = 58%$). To clarify the sources of heterogeneity, we conducted subgroup analysis based on ethnicity (Asian or Caucasian) and sensitivity analysis based on HWE status. The heterogeneity was decreased, but it could not be effectively removed (shown in Table 2). Then, meta-regression was performed to explore the potential sources of heterogeneity under the allele genetic model. The confounding factors included publication year, ethnicity, sample size, source of controls, quality score, and HWE status. The genotyping method in each study was similar, so it was not included. The meta-regression results revealed that none of these six factors could explain significant between-study heterogeneity: publication year ($p = 0.796$), ethnicity ($p = 0.494$), sample size ($p = 0.720$), control source ($p = 0.410$), quality score ($p = 0.397$), and HWE status ($p = 0.517$). In addition, we replaced the fixed-effects model with a random-effects model to calculate the pooled ORs, and the results were not materially altered.

Sensitivity analysis

First, a sensitivity analysis was performed by omitting one study at a time and calculating the pooled ORs for the remaining studies (data are shown in Table 3). Second, we conducted the analyses excluding the two studies that did not conform to HWE.10,15 The pooled ORs are listed in Table 2. We found that the results
Table 1. Characteristics of 17 studies included into the meta-analysis.

| Author      | Year | Ethnicity | Sample size | Age (year) | DM duration (year) | DD | ID | II | Sample size | Age (year) | DM duration (year) | DD | ID | II |
|-------------|------|-----------|-------------|------------|-------------------|----|----|----|-------------|------------|-------------------|----|----|----|
| Barnas      | 1997 | Caucasian | 50          | 47 ± 11    | 31 ± 8.5          | 14 | 27 | 9  | 40          | 47 ± 12    | 29 ± 8            | 4  | 21 | 15 |
| Azar        | 2001 | Caucasian | 52          | 22.8 ± 5.2 | 13.8 ± 5.8       | 23 | 27 | 2  | 10          | 26 ± 9     | 20.7 ± 7.4        | 1  | 7  | 2  |
| Tarnow      | 1995 | Caucasian | 198         | 40.9 ± 9.6 | 26.7 ± 7.9       | 63 | 95 | 40 | 190         | 42.7 ± 10.2 | 25.8 ± 8.5        | 67 | 77 | 46 |
| Mare        | 1994 | Caucasian | 62          | 39 ± 14    | 20 ± 11          | 23 | 35 | 4  | 62          | 43 ± 18    | 22 ± 12           | 19 | 28 | 15 |
| Freire      | 1998 | Caucasian | 77          | Age at onset 10 ± 6 | 18 ± 6 | 33 | 32 | 12 | 89          | Age at onset 11 ± 7 | 17 ± 6 | 34 | 45 | 10 |
| Chowdhury   | 1996 | Caucasian | 242         | 39.23 ± 7.62 | 27.58 ± 8.00 | 78 | 124 | 40 | 166         | 37.87 ± 6.27 | 26.65 ± 8.7 | 55 | 79 | 32 |
| Ringel      | 1997 | Caucasian | 134         | 38.9 ± 13.1 | 18.8 ± 10.5 | 35 | 68 | 31 | 226         | 35.7 ± 11.4 | 14.8 ± 10.3 | 57 | 130 | 39 |
| Shestakova  | 2006 | Caucasian | 63          | 25.69 ± 6.48 | 12.59 ± 2.79 | 13 | 35 | 15 | 66          | 40.82 ± 10.24 | 26.75 ± 8.88 | 12 | 30 | 24 |
| Oh          | 1996 | Asian     | 31           | 34.6 ± 7.7  | 14.8 ± 6.8     | 11 | 10 | 11 | 44          | 35.8 ± 8.2  | 13.0 ± 8.5    | 9  | 21 | 9  |
| Li XY       | 1999 | Asian     | 24           | 35.9 ± 6.5  | 13.9 ± 6.7     | 5  | 22 | 11 | 39          | 36.1 ± 6.2  | 13.6 ± 6.5   | 6  | 10 | 23 |
| Han         | 1997 | Asian     | 23           | 40.2 ± 17.3 | 12.2 ± 8.4     | 10 | 11 | 2  | 32          | 38.3 ± 11.3 | 10.8 ± 7.3   | 7  | 12 | 13 |
| Schmidt     | 1995 | Caucasian | 114         | 45 ± 15.5   | 22.7 ± 9.1     | 52 | 38 | 24 | 133         | 44 ± 15.4   | 20.7 ± 8.5   | 55 | 55 | 23 |
| Maré        | 1997 | Caucasian | 337         | 43 ± 13     | 27 ± 9          | 119 | 168 | 50 | 157         | 46 ± 13     | 31 ± 10       | 48 | 69 | 40 |
| Hibberd     | 1997 | Caucasian | 72           | Mean current age 43 | Mean duration 26.9 | 21 | 42 | 9  | 86          | Mean current age 50.9 | Mean duration 31.5 | 36 | 43 | 7  |
| Guan        | 1999 | Asian     | 34           | 35 ± 12.4   | 16.3 ± 7.1     | 18 | 12 | 4  | 40          | 30.9 ± 15.1 | 15.3 ± 8.2   | 6  | 16 | 18 |

HWE: Hardy–Weinberg equilibrium for controls; Y: yes; N: no.

Table 2. Meta-analyses of ACE I/D gene polymorphism and type 1 diabetic nephropathy risk.

| Category         | Sample size (case/control) | D versus I | DD versus ID + II | ID + DD versus II | ID versus II | DD versus II |
|------------------|-----------------------------|-------------|--------------------|-------------------|--------------|--------------|
|                  | OR [95% CI] | p | P(Q) | OR [95% CI] | p | P(Q) | OR [95% CI] | p | P(Q) | OR [95% CI] | p | P(Q) |
| Overall          | 3465/3708 | 1.16 [1.05, 1.28] | 0.04 | 0.0001 | 1.23 [0.97, 1.53] | 0.09 | 0.01 | 1.56 [1.14, 2.15] | 0.006 | 0.0005 | 1.37 [0.99, 1.89] | 0.06 | 0.001 |
| Caucasian        | 3152/2722 | 1.12 [0.95, 1.31] | 0.18 | 0.02 | 1.04 [0.89, 1.22] | 0.62 | 0.21 | 1.27 [0.93, 1.73] | 0.13 | 0.01 | 1.26 [0.92, 1.72] | 0.15 | 0.02 |
| Asian            | 313/356   | 1.98 [1.15, 3.42] | 0.01 | 0.02 | 2.48 [1.51, 4.10] | 0.0004 | 0.15 | 3.15 [1.90, 5.23] | <0.0001 | 0.16 | 1.88 [0.65, 5.44] | 0.24 | 0.007 |
| Sensitivity analysis | 3121/2548 | 1.29 [1.06, 1.58] | 0.01 | 0.02 | 1.28 [0.98, 1.67] | 0.07 | 0.005 | 1.58 [1.15, 2.18] | 0.005 | 0.005 | 1.26 [0.99, 1.56] | 0.06 | 0.02 |

*Significant heterogeneity existing, the random-effects model was chosen to summarize the result.

Sensitivity analysis: studies without HWE were excluded.
P(Q): Test for heterogeneity.
were not materially altered after these two sensitivity analyses.

**Publication bias**

Begg’s funnel plot and Egger’s regression test were performed to assess the publication bias in allele comparison (D versus I). The shapes of the funnel plots, as shown in Figure 3, revealed obvious asymmetry. The results of the Egger’s regression test \( (p = 0.011) \) also suggested possible publication bias. Given that publication bias existed in the comparison, the Trim and Fill method was added to the contour-enhanced meta-analysis funnel plot to adjust the results (shown in Figure 4). Three of the four supplemented articles were in the statistically significant area \( (p < 0.05) \), suggesting that publication bias was not the main cause of the asymmetric funnel plot. As shown in the plot, the corresponding pooled ORs were not materially altered after the Trim and Fill method was applied.

**Discussion**

The ACE I/D gene polymorphism has been suggested to be a susceptibility gene for DN. However, association studies, including three meta-analyses, have reported conflicting results for type 1 DN, especially in Asian populations. To derive a more precise conclusion, we conducted a meta-analysis of 17 case–control studies to evaluate the association of ACE I/D genetic variants and type 1 DN risk. Our results were not completely in accordance with the previous meta-analysis results.

This meta-analysis summarized all of the available data on the association between the ACE I/D gene polymorphism and type 1 DN risk. In the overall population, a significant increased risk was found in allele
comparison, dominant comparison, and homozygote comparison. Though no significant association was found in recessive comparison or heterozygote comparison, a trend of increased susceptibility still existed. In subgroup analyses according to ethnicity, we determined the following: (1) In the Asian population, the risk of type 1 DN was increased in allele comparison, recessive comparison, dominant comparison, homozygote comparison. A trend of increased susceptibility existed in heterozygote comparison. (2) There was no association between the ACE I/D genetic variants and type 1 DN in Caucasian populations.

Some reasons may account for the different results between Asians and Caucasians. First, different genetic

Figure 3. Begg’s funnel plot for a publication bias test of the association between the ACE I/D gene polymorphism and the risk of type 1 diabetic nephropathy. Each point represents a separate study for the indicated association. Log OR, natural logarithm of OR. Horizontal line indicates the effect size.

Figure 4. Contour-enhanced meta-analysis funnel plots for publication bias analysis of the association between the ACE I/D gene polymorphism and the risk of type 1 diabetic nephropathy.
backgrounds in different races may influence genetic phenotypes. Second, environmental exposure, lifestyle, and socioeconomic status may modify individual susceptibility in different ethnic groups.

In this meta-analysis, the heterogeneity between studies were decreased but could not be effectively removed after subgroup analyses based on ethnicity. Meta-regression results showed that none of the six confounding factors (publication year, ethnicity, sample size, source of controls, quality score, and HWE status) could explain the heterogeneity. We inferred that the heterogeneity may come from significant differences between studies. Then, we conducted sensitivity analysis by omitting one study at a time and then by excluding the two studies that deviated from HWE. The pooled ORs for the remaining studies were not materially altered. Moreover, we replaced the fixed-effects model for the random-effects model to calculate the corresponding pooled ORs were not materially altered and stable.

The Begg’s funnel plot and Egger’s regression test revealed possible publication bias. However, contour-enhanced meta-analysis funnel plots combined with the Trim and Fill method showed that publication bias was not the main cause of the asymmetric funnel plot. We speculated that the asymmetry of the funnel plot may be associated with heterogeneity between the studies. After the Trim and Fill method was applied, the corresponding pooled ORs were not materially altered, which suggested that the results of this meta-analysis were reliable and stable.

However, several limitations of this meta-analysis still should be acknowledged when interpreting the results of our analysis. First, this meta-analysis only contained case–control studies in Caucasians and Asians. So our results are only applicable to these two ethnic groups. We cannot know the genotype distributions in other ethnic groups, such as Africans and Latinos. Second, if more detailed information about other covariables were available in the original studies, a more accurate OR would have been estimated after making adjustments. Third, the heterogeneity among the studies should be noted, which is a potential problem when interpreting the results of a meta-analysis.

In conclusion, the present meta-analysis of 17 studies suggests that the ACE I/D gene polymorphism may be associated with an increased risk of type 1 DN, especially among Asian populations. However, larger sample size studies conducted in different ethnic populations are required in the future to further evaluate the link between the ACE I/D gene polymorphism and type 1 DN risk.

Disclosure statement
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding
This research was supported by Research Fund for the Doctoral Program of Higher Education [20133237110004] and Natural Science Foundation of Jiangsu Province of China [BK20151572]

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