Retraction notice

The following articles have been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the Journal of the Renin-Angiotensin Aldosterone System (JRAAS) (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

raas

Journal of the Renin-Angiotensin-Aldosterone System

© The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314557849 jra.sagepub.com **SAGE**

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System September 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011



Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

j<u>raas</u>

RETRACTED: Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(1) 165–171 © The Author(s) 2014 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314557849 jra.sagepub.com

(S)SAGE

Guohui Liu^{1†}, Tian-Biao Zhou^{2†}, Zongpei Jiang² and Dongwen Zheng¹

Abstract

Background and objective: The association of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism with type-2 diabetic nephropathy (T2DN) susceptibility and the risk of type-2 diabetes mellitus (T2DM) developing into T2DN in Caucasian populations is still controversial. A meta-analysis was performed to evaluate the association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in Caucasian populations.

Method: A predefined literature search and selection of eligible relevant studies were performed to collect data from electronic databases.

Results: Sixteen articles were identified for the analysis of the association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in Caucasian populations. ACE I/D gene polymorphism was not associated with T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations. Sensitivity analysis according to sample size of case (<100 vs. \geq 100) was also performed, and the results were similar to the non-sensitivity analysis.

Conclusions: ACE I/D gene polymorphism was not associated with T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations. However, more studies should be performed in the future.

Keywords

Type-2 diabetic nephropathy (T2DN), type-2 diabetes mellitus (T2DM), angiotensin-converting enzyme (ACE), insertion/deletion (I/D) gene polymorphism, meta-analysis

Date received: 14 September 2014; accepted: 28 September 2014

Introduction

Angiotensin-converting enzyme (ACE), converting angiotensin I into angiotensin II, inactivates bradykinin via the kallikrein–kininogen system, and angiotensin II is the main effector molecule of the renin–angiotensin system, is pleiotropic, and is a mediator of the development and progression of diseases.¹ The ACE insertion/deletion (I/D) gene polymorphism is a 287-bp sequence of DNA in intron 16 of the ACE gene.² The ACE gene consists of either an insertion (I) allele or a deletion (D) allele that form three possible genotypes: II, ID or DD.³ In adults, plasma ACE does not change with age and is influenced by environmental or lifestyle factors only to a minor extent.² Compared with II homozygotes, circulating ACE levels in plasma were found to be nearly 30% and 60% higher in ID heterozygotes and DD homozygotes, respectively.³ Moreover, DD homozygotes also have higher tissue levels of ACE. The ACE I/D gene polymorphism, correlating with circulating ACE concentration, may be implicated in

Corresponding author:

Zongpei Jiang, Department of Nephrology, the Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510655, China. Email: zongpeijiang@yeah.net

Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (http://www.uk.sagepub.com/aboutus/openaccess.htm).

Department of Nephrology, Dong Guan Municipal People's Hospital, Dongguan, China

²Department of Nephrology, the Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510655, China

[†]Guohui Liu and Tian-Biao Zhou contributed equally to this work.

the etiology of type-2 diabetic nephropathy (T2DN) and has been investigated in numerous epidemiologic studies to date.

Diabetes mellitus includes type-1 diabetes mellitus and type-2 diabetes mellitus (T2DM), and the incidence of diabetes mellitus has increased dramatically over the last several decades.⁴ Diabetic nephropathy (DN), a serious complication of diabetes mellitus, includes type-1 diabetic nephropathy (T1DN) due to type-1 diabetes mellitus and T2DN due to T2DM.^{4,5} Some 30–40% of diabetic patients develop DN, associated with a poor life expectancy and end-stage renal disease, causing serious socioeconomic problems.⁶

The present epidemiologic study aims to evaluate the association of the ACE I/D gene polymorphism in the etiology of T2DN and the risk of patients with T2DM developing T2DN. However, the available evidence reported to date is weak, due to sparseness of data or disagreements among studies. There is little meta-analysis exploring the association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations. We performed this meta-analysis from all reports published in English to investigate the relationship between ACE I/D gene polymorphism and T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations, with the intention to provide a much more reliable finding on the significance of the association.

Materials and methods

Search strategy

Relevant studies were identified from the PubMed and Cochrane Library electronic databases on 1 March 2014. The term "(diabetic nephropathy) AND (angiotensinconverting enzyme) AND (polymorphism OR variant)" was entered into PubMed and the Cochrane Library. The search in PubMed was limited to humans and English language. We also extended the search spectrum to the "related articles" and the bibliographies of all recruited studies. If multiple publications from the same study group occurred, we only used the most complete paper for our analysis.

Inclusion and exclusion criteria

Inclusion criteria were: (1) a case–control study; (2) the outcome had to be T2DN; (3) there had to be at least two comparison groups (T2DN group vs. control group); and (4) the study should be conducted in a Caucasian population.

Exclusion criteria were: (1) review articles, editorials and case reports; (2) articles that did not provide detailed genotype data; (3) articles investigating the association of other genes with T2DN; (4) articles investigating the role of ACE in diseases; and (5) multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study independently by two investigators: first author's surname, year of publication, ethnicity of study population, and the number of cases and controls for ACE I/D genotype. Frequencies of the D allele were calculated for case group and control group, from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data were entered into Cochrane Review Manager (RevMan, version 5, Oxford, UK) and analyzed. The pooled statistic was counted using the fixed-effects model, but a random-effects model was conducted when the *p*-value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. A value of p < 0.05 was required for the overall OR to be deemed statistically significant. I^2 was used to test the heterogeneity between the included studies. Sensitivity analysis was performed according to sample size of case (<100 vs. \geq 100). The Begg adjusted rank correlation test¹⁸ and the Egger regression asymmetry test¹⁹ were used for exploring publication bias (p < 0.1 was considered significant) when the sample number was more than 10.

Results

Study characteristics

The search yielded 261 references, 260 from PubMed and one from Cochrane Library. According to the inclusion and exclusion criteria, 16 articles⁷⁻²² were identified for the analysis of ACE I/D gene polymorphism and T2DN susceptibility and the risk of T2DM developing into T2DN in Caucasian populations in our review. Five studies⁷⁻¹¹ were conducted on the relationship between ACE I/D gene polymorphism and T2DN susceptibility (Table 1), and 15 rep orts^{7-10,12-22} were conducted on the relationship between ACE I/D gene polymorphism and the susceptibility of T2DM developing into T2DN (Table 2).

Association of the ACE I/D gene polymorphisms with T2DN risk

In this meta-analysis, ACE I/D gene polymorphisms was not associated with T2DN risk in Caucasian populations (D allele: OR = 1.10, 95% CI: 0.95–1.28, p = 0.19; DD genotype: OR = 1.11, 95% CI: 0.84–1.47, p = 0.46; II

First author, year	T2DN	٧					Control					,
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total(allele)
Gutiérrez, 1997	_	_	_	60	76	120	_	_	-	90	104	180
Schmidt, 1997	121	129	61	311	371	622	83	119	54	256	285	512
Araz, 2001	34	64	18	116	132	232	52	65	21	138	169	276
Arzu Ergen, 2004	9	11	5	25	29	50	10	22	5	37	42	74
Buraczynska, 2004	-	-	-	-	158	282	-		-	-	548	1040

Table I. Characteristics of the studies evaluating the effects of ACE I/D gene polymorphism on T2DN risk.

Table 2. Characteristics of the studies evaluating the effects of ACE I/D gene polymorphism on T2DM developing into T2DN.

First author, year	T2DN	I					T2D	М				
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	11	Total	D allele	Total (allele)
Fujisawa, 1995	7	23	24	54	37	108	6	12	17	35	24	70
Dudley, 1995	47	85	31	163	179	326	70	148	49	267	288	534
Ringel, 1997	44	84	33	161	172	322	35	69	36	140	139	280
Schmidt, 1997	121	129	61	311	371	622	131	154	62	347	416	694
Gutiérrez, 1997	_	_	-	-	76	120	-	<u> </u>	-	-	62	200
Jeffers, 1997	23	_	-	50	-	-	139	_	-	459	-	-
Grzeszczak, 1998	129	230	103	462	488	924	-73	118	63	254	264	508
Huang, 1 998	9	11	4	24	29	48	22	30	7	59	74	118
Araz, 2001	34	64	18	116	132	232	43	57	23	123	143	246
Fradin, 2002	38	61	18	117	137	234	44	54	20	118	142	236
Hadjadj, 2003	1119	1468	552	3139	3706	6278	208	282	115	605	698	1210
Arzu Ergen, 2004	9	11	5	25	29	50	24	21	5	50	69	100
Canani, 2005	126	181	66	373	433	746	181	308	120	609	670	1218
Eroglu 2008	16	17	13	46	49	92	19	24	13	56	62	112
Palomo–Piñón, 2009	43	105	87	235	191	470	24	91	85	200	139	400

genotype: OR = 0.97, 95% CI: 0.69–1.37, *p* = 0.87; Figure 1 and Table 3).

Sensitivity analysis for the relationship between ACE I/D gene polymorphism and T2DN risk in Caucasian populations was also performed according to sample size of case (<100 vs. \geq 100). We found that the results were similar to the non-sensitivity analysis. ACE I/D gene polymorphisms were not associated with T2DN risk in Caucasian populations (Table 3).

Association of ACE I/D gene polymorphisms with the risk of T2DM patients developing into T2DN

In this meta-analysis, ACE I/D gene polymorphisms were also not associated with the risk of patients with T2DM developing T2DN in Caucasian populations (D allele: OR = 1.10, 95% CI: 0.97–1.26, p = 0.15; DD genotype: OR = 1.08, 95% CI: 0.97–1.20, p = 0.16; II genotype: OR = 0.92, 95% CI: 0.81–1.04, p = 0.16; Figure 2 for D allele, Figure 3 for DD genotype and Figure 4 for II genotype; Table 3).

Sensitivity analysis for the relationship between ACE I/D gene polymorphism and the risk of T2DM developing into T2DN in Caucasian populations was also performed according to sample size of case (<100 vs. \geq 100). We found that the results were similar to the non-sensitivity analysis. ACE I/D gene polymorphisms were not associated with the risk of patients with T2DM developing T2DN in Caucasian populations (Table 3).

Evaluation of publication bias

No significant publication bias was found in the comparison of T2DN vs. T2DM (Begg p = 1.000, Egger p = 0.895; Figure 5 for Begg test).

Discussion

The dysfunction of ACE generation brought about by gene polymorphism is considered the major deterioration factor to associated with T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations. There are few data about genetic molecular markers



Figure 1. Association of ACE I/D gene polymorphism on T2DN susceptibility (T2DN vs. Control).

to predict the onset of T2DN and the risk of patients with T2DM developing into T2DN in Caucasian populations. This meta-analysis was performed to explore whether the ACE I/D gene polymorphism could predict the susceptibility of T2DN susceptibility and the risk of patients with T2DM developing into T2DN in Caucasian populations.

Al-Rubeaan et al.²³ conducted a meta-analysis to explore the relationship between ACE I/D gene polymorphism and the risk of T2DM, and reported that the ACE I/D polymorphism was found to be significantly associated with T2DM risk among the Arab population, whereas among Caucasians, this association was not found. However, was there an association between ACE I/D gene polymorphism and T2DN susceptibility or the risk of patients with T2DM developing into T2DN in Caucasian population? The metaanalysis was performed to assess this relationship.

In our meta-analysis, the relationship between ACE I/D gene polymorphism and the susceptibility of T2DN in Caucasian populations was assessed. We found that ACE I/D gene polymorphism was not associated with T2DN susceptibility in Caucasian populations. Furthermore, the results from the sensitivity analysis were similar to those from the non-sensitivity analysis. However, the number of included studies was small (only five studies included for meta-analysis), and the evidence was less robust. More studies should be performed in the future.

In this meta-analysis, the relationship between ACE I/D gene polymorphism and the risk of patients with T2DM developing T2DN in Caucasian populations was also assessed. We found that ACE I/D gene polymorphism was not associated with T2DN susceptibility. Furthermore, the results from the sensitivity analysis were similar to those from the non-sensitivity analysis, and there was no significant publication bias. The number of included studies was large, and the evidence may be robust to some extent.

In our investigation, we found that ACE I/D gene polymorphism was not associated with T2DN susceptibility and the risk of patients with T2DM developing T2DN. However, these findings should be regarded with caution because many other factors, such as heterogeneity of

Genetic contrasts	Number of studies	Q test p-value	Model selected	OR (95%Cl)	Þ
T2DN vs. Control		·			
D vs. I	5	0.55	Fixed	► 10(0.95, 1.28)	0.19
DD vs. (ID+II)	3	0.10	Fixed	1.11(0.84, 1.47)	0.46
II vs. (ID+DD)	3	0.73	Fixed	0.97(0.69, 1.37)	0.87
T2DN vs. Control (S	ensitivity analysis: ≥100)				
D vs. I	3	0.26	Fixed	1.09(0.93, 1.28)	0.29
DD vs. (ID+II)	2	0.04	Random	0.98(0.52, 1.87)	0.96
II vs. (ID+DD)	2	0.78	Fixed	0.94(0.66,1.34)	0.73
T2DN vs. Control (S	ensitivity analysis: <100)				
D vs. I	2	0.68	Fixed	1.20(0.80, 1.78)	0.38
DD vs. (ID+II)	I	_	Fixed	1.52(0.51, 4.53)	0.45
II vs. (ID+DD)	I	_	Fixed	1.60(0.41, 6.23)	0.50
T2DN vs. T2DM				4 · ·	
D vs. I	14	0.001	Random	1.10(0.97, 1.26)	0.15
DD vs. (ID+II)	14	0.54	Fixed	1.08(0.97, 1.20)	0.16
II vs. (ID+DD)	13	0.94	Fixed	0.92(0.81, 1.04)	0.16
T2DN vs. T2DM (Se	nsitivity analysis: \geq 100)				
D vs. I	9	0.87	Fixed	1.07(0.99, 1.15)	0.08
DD vs. (ID+II)	9	0.63	Fixed	1.07(0.96, 1.20)	0.23
II vs. (ID+DD)	9	0.96	Fixed	0.90(0.79, 1.02)	0.10
T2DN vs. T2DM (Se	nsitivity analysis: < 100)				
D vs. I	5	<0.0001	Random	1.17(0.58, 2.36)	0.66
DD vs. (ID+II)	5	0.25	Fixed	1.18(0.81, 1.71)	0.39
II vs. (ID+DD)	4	0.66	Fixed	1.22(0.73, 2.05)	0.45

Table 3.	Meta-analysis of the association	of ACE I/D gene pol	ymorphism with risk	of T2DN and the T2DM	1 developing into T2DN.
----------	----------------------------------	---------------------	---------------------	----------------------	-------------------------

	T2D	4	T2DA	4		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight N	I-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Dudley 1995	179	326	288	534	8.6%	1.04 [0.79, 1.37]	1995	+
Fujisawa 1995	37	108	24	70	3.3%	1.00 [0.53, 1.88]	1995	
Schmidt 1997	371	622	416	694	10.0%	0.99 [0.79, 1.23]	1997	+
Ringel 1997	172	[°] 322	139	280	7.7%	1.16 [0.84, 1.60]	1997	+
Gutiérrez 1997	76	120	62	200	5.0%	3.84 [2.39, 6.20]	1997	
Huang 1998	29	48	74	118	2.9%	0.91 [0.46, 1.81]	1998	
Grzeszczak 1998	488	924	264	508	10.1%	1.03 [0.83, 1.28]	1998	+
Araz 2001	132	232	143	246	6.8%	0.95 [0.66, 1.37]	2001	+
Fradin 2002	137	234	142	236	6.7%	0.93 [0.65, 1.35]	2002	+
Hadjadj 2003	3706	6278	698	1210	12.4%	1.06 (0.93, 1.20)	2003	•
Arzu Ergen 2004	29	50	69	100	2.8%	0.62 [0.31, 1.25]	2004	+
Canani 2005	433	746	670	1218	11.0%	1.13 [0.94, 1.36]	2005	-
Eroglu 2008	49	92	62	112	4.0%	0.92 [0.53, 1.60]	2008	-
Palomo-Piñón 2009	191	470	139	400	8.7%	1.29 [0.98, 1.69]	2009	-
Total (95% CI)		10572		5926	100.0%	1.10 [0.97, 1.26]		•
Total events	6029		3190					
Heterogeneity: Tau ² = 0	.03; Chi ^z :	= 34.21,	df = 13 (P = 0.0	01); I ² = 62 ^o	%		
Test for overall effect Z	= 1.46 (P	= 0.15)						Favours T2DN Favours T2DM

Figure 2. Association of ACE D allele on the risk of T2DM developing into T2DN (T2DN vs. T2DM).

enrolled cases, limited statistical power, variable study designs and different interventions, could affect the results. Undoubtedly, the limitations mentioned above might affect our final conclusions.

Liu et al.

In conclusion, the results in our study support that ACE I/D gene polymorphism was not associated with T2DN

susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations. However, more association investigations on larger, stratified populations are required to further clarify the role of ACE I/D gene polymorphism in T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations.

March and Carls and and	12U	N	T2D	/		Odds Ratio		Odds Ratio
study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Fujisawa 1995	7	54	6	35	1.0%	0.72 [0.22, 2.35]	1995	-+ /
Dudley 1995	47	163	70	267	5.8%	1.14 [0.74, 1.76]	1995	+
Jeffers 1997	23	50	139	459	2.3%	1.96 [1.09, 3.54]	1997	
Schmidt 1997	121	311	131	347	11.6%	1.05 [0.77, 1.44]	1997	+
Ringel 1997	44	161	35	140	4.2%	1.13 [0.67, 1.89]	1997	
Grzeszczak 1998	129	462	73	254	10.4%	0.96 [0.68, 1.35]	1998	
Huang 1998	9	24	22	59	1.2%	1.01 [0.38, 2.69]	1998	
Araz 2001	34	116	43	123	4.5%	0.77 [0.45, 1.33]	2001	-+
Fradin 2002	38	117	44	118	4.5%	0.81 [0.47, 1.38]	2002	-+
Hadjadj 2003	1119	3139	208	605	34.3%	1.06 [0.88, 1.27]	2003	
Arzu Ergen 2004	9	25	24	50	1.6%	0.61 [0.23, 1.64]	2004	
Canani 2005	126	373	181	609	13.9%	1.21 [0.92, 1.59]	2005	+
Erogiu 2008	16	46	19	56	1.7%	1.04 [0.46, 2.36]	2008	— Y
Palomo-Piñón 2009	43	235	24	200	3.2%	1.64 [0.96, 2.82]	2009	
Fotal (95% CI)		5276		3322	100.0%	1.08 [0.97, 1.20]		
Total events	1765		1019					
Heterogeneity: Chi ² = 1	11.82, df=	= 13 (P	= 0.54); P	²= 0%				
Test for overall effect 2	Z = 1.40 (F	P = 0.16	3)					Eavoure T2DNL Eavoure T2DM

Figure 3. Association of ACE DD genotype on the risk of T2DM developing into T2DN (T2DN vs. T2DM).



Figure 4. Association of ACE II genotype on the risk of T2DM developing into T2DN (T2DN vs. T2DM).



Figure 5. Begg's funnel plots with pseudo 95% confidence limits. Evaluation of publication bias for the association of ACE I/D gene polymorphism with the risk of T2DM developing into T2DN.

Conflict of interest

None declared.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

- Song GG and Lee YH. The insertion/deletion polymorphism in the angiotensin-converting enzyme and susceptibility to schizophrenia or Parkinson's disease: A meta-analysis. J Renin Angiotensin Aldosterone Syst 2014 [Epub ahead of print].
- Zhou TB, Qin YH, Su LN, et al. The association between angiotensin-converting enzyme insertion/deletion gene variant and risk of focal segmental glomerulosclerosis: A systematic review and meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 624–633.
- Zhou TB, Yin SS and Qin YH. Association between angiotensin-converting enzyme insertion/deletion gene polymorphism and end-stage renal disease susceptibility. *J Renin Angiotensin Aldosterone Syst* 2014; 15: 22–31.
- Yu ZY, Chen LS, Zhang LC, et al. Meta-analysis of the relationship between ACE I/D gene polymorphism and endstage renal disease in patients with diabetic nephropathy. *Nephrology (Carlton)* 2012; 17: 480–487.
- Hussain H, Ramachandran V, Ravi S, et al. TCF7L2 rs7903146 polymorphism and diabetic nephropathy association is not independent of type 2 diabetes – a study in a south Indian population and meta-analysis. *Endokrynol Pol* 2014; 65: 298–305.
- Kaur M, Bedi O, Sachdeva S, et al. Rodent animal models: From mild to advanced stages of diabetic nephropathy. *Inflammopharmacology* 2014; 22: 279–293.
- Gutierrez C, Vendrell J, Pastor R, et al. Angiotensin I-converting enzyme and angiotensinogen gene polymorphisms in noninsulin-dependent diabetes mellitus. Lack of relationship with diabetic nephropathy and retinopathy in a Caucasian Mediterranean population. *Metabolism* 1997; 46: 976–980.
- Schmidt S, Strojek K, Grzeszczak W, et al. Excess of DD homozygotes in haemodialysed patients with type II diabetes. The Diabetic Nephropathy Study Group. *Nephrol Dial Transplant* 1997; 12: 427–429.
- Araz M, Yilmaz N, Gungor K, et al. Angiotensin-converting enzyme gene polymorphism and microvascular complications in Turkish type 2 diabetic patients. *Diabetes Res Clin Pract* 2001; 54: 95–104.
- Arzu Ergen H, Hatemi H, Agachan B, et al. Angiotensin-I converting enzyme gene polymorphism in Turkish type 2 diabetic patients. *Exp Mol Med* 2004; 36: 345–350.
- Buraczynska M, Ksiazek P, Drop A, et al. Genetic polymorphisms of the renin-angiotensin system in end-stage renal disease. *Nephrol Dial Transplant* 2006; 21: 979–983.
- 12. Fujisawa T, Ikegami H, Shen GQ, et al. Angiotensin I-converting enzyme gene polymorphism is associated with

myocardial infarction, but not with retinopathy or nephropathy, in NIDDM. *Diabetes Care* 1995; 18: 983–985.

- Dudley CR, Keavney B, Stratton IM, et al. UK Prospective Diabetes Study. XV: Relationship of renin-angiotensin system gene polymorphisms with microalbuminuria in NIDDM. *Kidney Int* 1995; 48: 1907–1911.
- Ringel J, Beige J, Kunz R, et al. Genetic variants of the renin-angiotensin system, diabetic nephropathy and hypertension. *Diabetologia* 1997; 40: 193–199.
- Jeffers BW, Estacio RO, Raynolds MV, et al. Angiotensinconverting enzyme gene polymorphism in non-insulin dependent diabetes mellitus and its relationship with diabetic nephropathy. *Kidney Int* 1997; 52: 473–477.
- Huang XH, Rantalaiho V, Wirta O, et al. Angiotensinconverting enzyme insertion/deletion polymorphism and diabetic albuminuria in patients with NIDDM followed Up for 9 years. *Nephron* 1998; 80: 17–24.
- Fradin S, Goulet-Salmon B, Chantepie M, et al. Relationship between polymorphisms in the renin-angiotensin system and nephropathy in type 2 diabetic patients. *Diabetes Metab* 2002; 28: 27–32.
- Hadjadj S, Gallois Y, Alhenc-Gelas F, et al. Angiotensin-I-converting enzyme insertion/deletion polymorphism and high urinary albumin concentration in French Type 2 diabetes patients. *Diabet Med* 2003; 20: 677–682.
- Canani LH, Costa LA, Crispim D, et al. The presence of allele D of angiotensin-converting enzyme polymorphism is associated with diabetic nephropathy in patients with less than 10 years duration of Type 2 diabetes. *Diabet Med* 2005; 22: 1167–1172.
- Eroglu Z, Cetinkalp S, Erdogan M, et al. Association of the angiotensinogen M235T and angiotensin-converting enzyme insertion/deletion gene polymorphisms in Turkish type 2 diabetic patients with and without nephropathy. J Diabetes Complications 2008; 22: 186–190.
- Palomo-Pinon S, Gutierrez-Rodriguez ME, Diaz-Flores M, et al. DD genotype of angiotensin-converting enzyme in type 2 diabetes mellitus with renal disease in Mexican Mestizos. *Nephrology (Carlton)* 2009; 14: 235–239.
- 22. Grzeszczak W, Zychma MJ, Lacka B, et al. Angiotensin I-converting enzyme gene polymorphisms: Relationship to nephropathy in patients with non-insulin dependent diabetes mellitus. *J Am Soc Nephrol* 1998; 9: 1664–1669.
- 23. Al-Rubeaan K, Siddiqui K, Saeb AT, et al. ACE I/D and MTHFR C677T polymorphisms are significantly associated with type 2 diabetes in Arab ethnicity: A meta-analysis. *Gene* 2013; 520: 166–177.
- Cao N, Chen T, Guo ZP, et al. Elevated serum levels of visfatin in patients with henoch-schonlein purpura. *Ann Dermatol* 2014; 26: 303–307.
- Ren P, Han F, Chen L, et al. The combination of mycophenolate mofetil with corticosteroids induces remission of Henoch-Schonlein purpura nephritis. *Am J Nephrol* 2012; 36: 271–277.
- Davin JC and Coppo R. Henoch-Schonlein purpura nephritis in children. *Nat Rev Nephrol* 2014; 10: 563–573.

Retraction notice

This article has been included in a multiple retraction: Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

This article has been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System (JRAAS)* (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

(cc)

jraas

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP51 © The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314568521 jra.sagepub.com SAGE

Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System September 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011

Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

RETRACTED: Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP52–NP56 © The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314568521 jra.sagepub.com

(S)SAGE

raas

Chun-Hua Yang¹ and Tian-Biao Zhou²

Abstract

Aim: Association of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism with sepsis susceptibility and sepsis progression is still controversial. This study was performed to evaluate the association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression using a meta-analysis method.

Methods: A predefined literature search and selection of eligible relevant studies were performed to collect data from electronic databases.

Results: The ACE DD genotype was associated with sepsis susceptibility (DD genotype: OR = 0.69, 95% CI: 0.51–0.92, p = 0.01). However, the ACE D allele and II genotype were not associated with sepsis susceptibility. Furthermore, the ACE I/D gene polymorphism was not associated with sepsis progression.

Conclusions: The ACE DD genotype was associated with sepsis susceptibility. However, more studies should be performed in the future.

Keywords

Sepsis susceptibility, sepsis progression, angiotensin-converting enzyme (ACE), insertion/deletion (I/D) gene polymorphism, meta-analysis

Date received: 08 December 2014; accepted: 16 December 2014

Introduction

Sepsis is a systemic inflammatory response that follows bacterial infection, and sepsis and sepsis-associated multiorgan failure represent the major cause of mortality in intensive care units worldwide.^{1,2} Sepsis progression (mortality) is most often attributed to the development of multiple organ failure. In sepsis, inflammation-mediated endothelial activation, defined as a proinflammatory and procoagulant state of the endothelial cells, has been associated with severity of disease.³

The angiotensin-converting enzyme (*ACE*) insertion/ deletion (I/D) gene polymorphism is a 287-bp sequence of DNA in the intron 16 of the *ACE* gene, and the *ACE* gene includes either an insertion (I) allele or a deletion (D) allele that form three possible genotypes: II, ID or DD.^{4,5} *ACE*, directly involved in the process of cell proliferation, differentiation, apoptosis and angiogenesis,⁶ can convert angiotensin I into angiotensin II, and angiotensin II is the main effector molecule of the renin-angiotensin system, is pleiotropic, and is a mediator of the development and progression of diseases.⁷ The *ACE* I/D gene polymorphism, correlating with circulating ACE concentration, might be implicated in the etiology of sepsis and has been investigated in some epidemiologic studies.

Present epidemiologic studies show that the ACE I/D gene polymorphism has been implicated in the etiology of sepsis and sepsis progression. However, the available evidence reported to date is weak owing to the sparseness of the data or disagreements among studies. We performed this meta-analysis to investigate the relation between the ACE I/D gene polymorphism and sepsis susceptibility and sepsis progression.

Corresponding author:

Tian-Biao Zhou, Department of Nephrology, the Sixth Affiliated Hospital, Sun Yat-Sen University, Yuancunerheng Road No. 26, Guangzhou, Guangdong 510655, China. Email: tianbiaozhou@163.com

Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (http://www.uk.sagepub.com/aboutus/openaccess.htm).

Department of Emergency, the First Affiliated Hospital, Sun Yat-Sen University, China

²Department of Nephrology, the Sixth Affiliated Hospital, Sun Yat-Sen University, China

First author, year	Case		Control		
	DD ID II Total	D allele Total (allele)	DD ID II	Total D allele	Total (allele)
Sepsis susceptibility					
Villar, 2008 ⁸	7 94 41 212	248 424	152 155 57	364 459	728
Cogulu, 2008 ⁹	.1 52 25 98	94 196	102 129 56	287 333	574
Bunker-Wiersma, 2008 ¹⁰	6 26 11 53	58 106	38 64 33	135 140	270
Davis, 201011	5 15 8 28	25 56	12 22 19	53 46	106
Spiegler, 2010 ¹²	0 142 44 246	262 492	281 482 200	963 1044	1926
Sepsis progression					
Villar, 2008 ⁸	2 46 17 95	110 190	45 48 24	7 38	234
Cogulu, 2008 ⁹	4 6 4 14	14 28	17 46 21	84 80	168
Tsantes, 2012 ¹³	6 90 31 187	222 374	60 90 31	181 210	362
Davis, 2010 ¹¹ Spiegler, 2010 ¹² Sepsis progression Villar, 2008 ⁸ Cogulu, 2008 ⁹ Tsantes, 2012 ¹³	5 15 8 28 0 142 44 246 12 46 17 95 4 6 4 14 66 90 31 187	25 56 262 492 110 190 14 28 222 374	12 22 19 281 482 200 45 48 24 17 46 21 60 90 31	53 46 963 1044 117 138 84 80 181 210	1926 234 168 362

Table I. Characteristics of the studies evaluating the effects of ACE I/D gene polymorphism on sepsis susceptibility and sepsis progression.

ACE: angiotensin-converting enzyme; I/D: insertion/deletion.

Materials and methods

Search strategy

The relevant studies were searched from the electronic databases of PubMed and Cochrane Library on October 1, 2014. The terms "Sepsis AND (angiotensin converting enzyme OR ACE)" were entered into PubMed and Cochrane Library for the search. We also extended the search spectrum to "related articles" and the bibliographies of all recruited studies.

Inclusion and exclusion criteria

Inclusion criteria. Inclusion criteria included: (1) a casecontrol study or a prospective study; (2) the outcome had to be sepsis; (3) there had to be at least two comparison groups (sepsis group vs control group or sepsis group vs sepsis progression group).

Exclusion criteria. Exclusion criteria included: (1) review articles, editorials and case reports; (2) articles that did not provide the detailed genotype data; (3) investigating the association of other genes with sepsis; (4) investigating the role of *ACE* in diseases; (5) multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study independently by two investigators: first author's surname, year of publication, and the number of cases and controls for the *ACE* I/D genotype. Frequencies of the D allele were calculated for the case group and control group from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data were entered into Cochrane Review Manager (RevMan, version 5, Oxford, UK) and analyzed. The pooled statistic was counted using the fixed-effects model, but a random-effects model was conducted when the *p* value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. P < 0.05 was required for the overall OR to be deemed statistically significant. I^2 was used to test the heterogeneity between the included studies.

Results

Study characteristics

The search yielded 144 references, 141 from PubMed, and three from Cochrane Library. According to the inclusion and exclusion criteria, six articles^{8–13} were identified for the analysis between the *ACE* I/D gene polymorphism and sepsis susceptibility and sepsis progression in our meta-analysis. Five studies^{8–12} were conducted on the relationship between the *ACE* I/D gene polymorphism and sepsis susceptibility (Table 1), and three reports^{8,9,13} were conducted on the relationship between the *ACE* I/D gene polymorphism and sepsis morphism and sepsis progression (Table 1).

Association of the ACE I/D gene polymorphism with sepsis risk

In this meta-analysis, the *ACE* DD genotype was associated with sepsis risk, but the D allele and II genotype were not (DD genotype: OR = 0.75, 95% CI: 0.62–0.92, p = 0.006; D allele: OR = 0.81, 95% CI: 0.61–1.08, p = 0.15; II genotype: OR = 1.01, 95% CI: 0.81–1.27, p = 0.91; Figure 1 and Table 2).

	Case	•	Contr	ol		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	M-H. Rando	m. 95% Cl
Bunker-Wiersma 2008	58	106	140	270	17.0%	1.12 (0.71, 1.76)	-	-
Cogulu 2008	94	196	333	574	21.3%	0.67 [0.48, 0.92]		4
Davis 2010	25	56	46	106	11.6%	1.05 [0.55, 2.02]		-
Spiegler 2010	262	492	1044	1926	25.8%	0.96 [0.79, 1.17]		
Villar 2008	208	424	459	728	24.3%	0.56 [0.44, 0.72]	-	
Total (95% CI)		1274		3604	100.0%	0 81 [0 61 1 08]		
Total events	647	1214	2022	5004	100.070	0.01[0.01, 1.00]		
Hotorogeneity: Tou ² – 0.0	047 17: Chi≧ = 1	15 28 7	2022 If = A (P -	- 0 004	· IZ = 74%			
Test for overall effect: 7 =	1.45 (P =	0.15)	a – 4 (r –	- 0.004,	,1 - 74%		0.01 0.1 1	10 100
restion overall ellect. Z =	1.45 (1 -	0.13)					Favors case	Favors control
DD vs ID+II								
	Cas	е	Cont	rol		Odds Ratio	Odds F	latio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed	, 95% Cl
Bunker-Wiersma 2008	16	53	38	135	6.8%	1.10 [0.55, 2.21]	-	_
Cogulu 2008	21	98	102	287	18.5%	0.49 [0.29, 0.85]		
Davis 2010	5	28	12	53	3.1%	0.74 [0.23, 2.37]		_
Spiegler 2010	60	246	281	963	39.3%	0.78 [0.57, 1.08]) =	
Villar 2008	77	212	152	364	32.3%	0.80 [0.56, 1.13]		
Total (95% CI)		637		1802	100.0%	0.75 [0.62, 0.92]	•	
Total events	179		585					
Heterogeneity: Chi ^z = 3.6	54, df = 4 (P = 0.4	6); I ^z = 0	%				
Test for overall effect: Z =	= 2.72 (P =	- 0.006	.					111 1111
	-	- 0.000	,				Favors case	Favors control
	-	. 0.000	,				Favors case	Favors control
II vs ID+DD	-	- 0.000	,				Favors case	Favors control
II vs ID+DD	Cas	e	, Cont	rol	7	Odds Ratio	OUT O.T Favors case	Favors control
II vs ID+DD Study or Subgroup	Cas Events	e Total	Cont	rol Total	Weight	Odds Ratio M-H, Fixed, 95% Cl	O.01 O.1 Favors case Odds F	Favors control
II vs ID+DD Study or Subgroup Bunker-Wiersma 2008	Cas Events 11	e <u>Total</u> 53	, Cont <u>Events</u> 33	rol <u>Total</u> 135	Weight 10.1%	Odds Ratio M-H, Fixed, 95% Cl 0.81 [0.37, 1.75]	Odds F Odds F M-H, Fixed	Favors control
II vs ID+DD Study or Subgroup Bunker-Wiersma 2008 Cogulu 2008	Cas Events 11 25	e <u>Total</u> 53 98	, <u>Events</u> 33 56	rol <u>Total</u> 135 287	Weight 10.1% 14.5%	Odds Ratio M-H, Fixed, 95% Cl 0.81 [0.37, 1.75] 1.41 [0.82, 2.42]	Odds F Odds F M-H, Fixed	Favors control
II vs ID+DD Study or Subgroup Bunker-Wiersma 2008 Cogulu 2008 Davis 2010	Cas <u>Events</u> 11 25 8	e <u>Total</u> 53 98 28	, <u>Events</u> 33 56 1 <u>9</u>	rol <u>Total</u> 135 287 53	Weight 10.1% 14.5% 6.4%	Odds Ratio M-H, Fixed, 95% Cl 0.81 [0.37, 1.75] 1.41 [0.82, 2.42] 0.72 [0.26, 1.93]	Odds F Odds F M-H, Fixed	Favors control
II vs ID+DD Study or Subgroup Bunker-Wiersma 2008 Cogulu 2008 Davis 2010 Spiegler 2010	Cas Events 11 25 8 44	e <u>Total</u> 53 98 28 246	Cont <u>Events</u> 33 56 19 200	rol <u>Total</u> 135 287 53 963	Weight 10.1% 14.5% 6.4% 45.8%	Odds Ratio M-H, Fixed, 95% Cl 0.81 [0.37, 1.75] 1.41 [0.82, 2.42] 0.72 [0.26, 1.93] 0.83 [0.58, 1.19]	Odds F Odds F M-H, Fixed	Favors control
II vs ID+DD Study or Subgroup Bunker-Wiersma 2008 Cogulu 2008 Davis 2010 Spiegler 2010 Villar 2008	Cas Events 11 25 8 44 41	e <u>Total</u> 53 98 28 246 212	Cont <u>Events</u> 33 56 19 200 57	rol <u>Total</u> 135 287 53 963 364	Weight 10.1% 14.5% 6.4% 45.8% 23.2%	Odds Ratio M-H, Fixed, 95% C1 0.81 [0.37, 1.75] 1.41 [0.82, 2.42] 0.72 [0.26, 1.93] 0.83 [0.58, 1.19] 1.29 [0.83, 2.01]	Odds F Odds F M-H, Fixed	Favors control
II vs ID+DD <u>Study or Subgroup</u> Bunker-Wiersma 2008 Cogulu 2008 Davis 2010 Spiegler 2010 Villar 2008 Total (95% CI)	Cas Events 11 25 8 44 41	e <u>Total</u> 53 98 28 246 212 637	Cont <u>Events</u> 33 56 19 200 57	rol 135 287 53 963 364 1802	Weight 10.1% 14.5% 6.4% 45.8% 23.2% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.81 [0.37, 1.75] 1.41 [0.82, 2.42] 0.72 [0.26, 1.93] 0.83 [0.58, 1.19] 1.29 [0.83, 2.01] 1.01 [0.81, 1.27]	Odds F Odds F M-H, Fixed	Favors control
II vs ID+DD <u>Study or Subgroup</u> Bunker-Wiersma 2008 Cogulu 2008 Davis 2010 Spiegler 2010 Villar 2008 Total (95% CI) Total events	Cas Events 11 25 8 44 41 129	e <u>Total</u> 53 98 28 246 212 637	Cont <u>Events</u> 33 56 19 200 57 365	rol 135 287 53 963 364 1802	Weight 10.1% 14.5% 6.4% 45.8% 23.2% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.81 [0.37, 1.75] 1.41 [0.82, 2.42] 0.72 [0.26, 1.93] 0.83 [0.58, 1.19] 1.29 [0.83, 2.01] 1.01 [0.81, 1.27]	Odds F Odds F M-H, Fixed	Favors control
II vs ID+DD <u>Study or Subgroup</u> Bunker-Wiersma 2008 Cogulu 2008 Davis 2010 Spiegler 2010 Villar 2008 Total (95% CI) Total events Heterogeneity: Chi ² = 4.5	Cas Events 11 25 8 44 41 129 i6, df = 4 (e <u>Total</u> 53 98 28 246 212 637 P = 0.3	Cont <u>Events</u> 33 56 19 200 57 365 (4); ² = 1	rol 135 287 53 963 364 1802 2%	Weight 10.1% 14.5% 6.4% 45.8% 23.2% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.81 [0.37, 1.75] 1.41 [0.82, 2.42] 0.72 [0.26, 1.93] 0.83 [0.58, 1.19] 1.29 [0.83, 2.01] 1.01 [0.81, 1.27]	Odds F Odds F M-H, Fixed	Favors control
II vs ID+DD <u>Study or Subgroup</u> Bunker-Wiersma 2008 Cogulu 2008 Davis 2010 Spiegler 2010 Villar 2008 Total (95% CI) Total events Heterogeneity: Chi ² = 4.5 Test for overall effect: Z =	Cas Events 11 25 8 44 41 129 i6, df = 4 (: 0.11 (P =	e <u>Total</u> 53 98 246 212 637 P = 0.3 0(91)	Cont <u>Events</u> 33 56 19 200 57 365 (4); ² = 1	rol 135 287 53 963 364 1802 2%	Weight 10.1% 14.5% 6.4% 45.8% 23.2% 100.0%	Odds Ratio M-H, Fixed, 95% Cl 0.81 [0.37, 1.75] 1.41 [0.82, 2.42] 0.72 [0.26, 1.93] 0.83 [0.58, 1.19] 1.29 [0.83, 2.01] 1.01 [0.81, 1.27]	Odds F Odds F M-H, Fixed	Favors control

Figure 1. Association of ACE I/D gene polymorphism with sepsis susceptibility.

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; M-H: Mantel-Haenszel; CI: confidence interval.

Association of ACE I/D gene polymorphism with sepsis progression

In this meta-analysis, the *ACE* I/D gene polymorphism was not associated with sepsis progression (D allele: OR = 1.03, 95% CI: 0.82–1.28, p = 0.83; DD genotype: OR = 1.01, 95% CI: 0.73–1.41, p = 0.94; II genotype: OR = 0.94, 95% CI: 0.63–1.41, p = 0.76; Figure 2 and Table 2).

Discussion

In our previous meta-analyses, we reported that the *ACE* I/D gene polymorphism was associated with the risk of

some diseases.^{4,14–16} Dysfunction of *ACE* generation brought by the *ACE* I/D gene polymorphism might be considered as an important deterioration factor to be associated with sepsis susceptibility and sepsis progression. There was a rare genetic molecular marker to predict the onset of sepsis and sepsis progression. This study using a meta-analysis method was performed to explore whether the *ACE* I/D gene polymorphism could predict the susceptibility of sepsis and sepsis progression.

In this meta-analysis, the association between the *ACE* I/D gene polymorphism and sepsis susceptibility/sepsis progression was assessed using a meta-analysis method. We found that the *ACE* DD genotype was associated with sepsis

Genetic	Number of	Q test	Model	OR	Þ
contrasts	studies	þ value	selected	(95% CI)	
Sepsis susceptibility					
D vs I	5	0.004	Fixed	0.81 (0.61, 1.08)	0.15
DD vs (ID+II)	5	0.46	Fixed	0.75 (0.62, 0.92)	0.006
II vs (ID+DD)	5	0.34	Fixed	1.01 (0.81, 1.27)	0.91
Sepsis progression					
D vs I	3	0.91	Fixed	1.03 (0.82, 1.28)	0.83
DD vs (ID+II)	3	0.55	Fixed	1.01 (0.73, 1.41)	0.94
II vs (ID+DD)	3	0.89	Fixed	0.94 (0.63, 1.41)	0.76

Table 2. Meta-analysis of the association of ACE I/D gene polymorphism on sepsis susceptibility and sepsis pro-	ressic
---	--------

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; OR: odds ratio; CI: confidence interval.



Figure 2. Association of ACE I/D gene polymorphism with sepsis progression.

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; M-H: Mantel-Haenszel; CI: confidence interval.

susceptibility (DD genotype: OR = 0.69, 95% CI: 0.51– 0.92, p = 0.01). However, the *ACE* D allele and II genotype were not associated with sepsis susceptibility. Interestingly, when the fixed model was chosen to calculate for the relationship between the D allele and sepsis risk, we found that the D allele was associated with sepsis risk, but the *p* value of heterogeneity test was 0.004. The number of included studies was small, and the results should be confirmed in the future. More studies should be performed in the future.

Furthermore, the *ACE* I/D gene polymorphism was not associated with sepsis progression. There were only three included studies recruited into this meta-analysis, and the results should be confirmed in the future. More studies should be performed in the future too.

In this meta-analysis, we found that the *ACE* DD genotype was associated with sepsis susceptibility. However, these findings should be regarded cautiously because many other factors, such as heterogeneity of enrolled cases, limited statistical power, variable study designs and different interventions, were closely related to affect the results. Undoubtedly, the limitations mentioned above might affect our final conclusion.

In conclusion, the results of our study support that the *ACE* DD genotype was associated with sepsis susceptibility. However, the *ACE* D allele and II genotype were not associated with sepsis susceptibility. Furthermore, the *ACE* I/D gene polymorphism was not associated with sepsis progression. However, more association investigations on larger, stratified populations are required to further clarify the role of the *ACE* I/D gene polymorphism in the susceptibility of sepsis and sepsis progression.

Conflict of interest

None declared.

Funding

This work was supported by sub-item 985 of the Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation, no. 88000-3311300).

References

- Drosatos K, Lymperopoulos A, Kennel PJ, et al. Pathophysiology of sepsis-related cardiac dysfunction: driven by inflammation, energy mismanagement, or both? *Curr Heart Fail Rep.* Epub ahead of print 5 December 2014.
- Sand CA, Starr A, Wilder CD, et al. Quantification of microcirculatory blood flow: A sensitive and clinically relevant prognostic marker in murine models of sepsis. *J Appl Physiol (1985)*. Epub ahead of print 4 December 2014. DOI: 10.1152/japplphysiol.00793.2014.
- Escobar DA, Botero-Quintero AM, Kautza BC, et al. Adenosine monophosphate-activated protein kinase activation protects against sepsis-induced organ injury and inflammation. *J Surg Res*, Epub ahead of print 8 October 2014. DOI: 10.1016/j.jss.2014.10.009.

- 4. Zhou TB, Qin YH, Su LN, et al. The association between angiotensin-converting enzyme insertion/deletion gene variant and risk of focal segmental glomerulosclerosis: A systematic review and meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 624–633.
- Zhou TB, Yin SS and Qin YH. Association between angiotensin-converting enzyme insertion/deletion gene polymorphism and end-stage renal disease susceptibility. *J Renin Angiotensin Aldosterone Syst* 2014; 15: 22–31.
- Zha Y, Gan P, Liu Q, et al. Relationship between polymorphism of angiotensin-converting enzyme gene insertion/ deletion and risk of hepatocellular carcinoma in a Chinese Dai population. *J Renin Angiotensin Aldosterone Syst.* Epub ahead of print 10 September 2014.
- Song GG and Lee YH. The insertion/deletion polymorphism in the angiotensin-converting enzyme and susceptibility to schizophrenia or Parkinson's disease: A meta-analysis. J Renin Angiotensin Aldosterone Syst. Epub ahead of print 20 August 2014.
- Villar J, Flores C, Pérez-Méndez L, et al. Angiotensinconverting enzyme insertion/deletion polymorphism is not associated with susceptibility and outcome in sepsis and acute respiratory distress syndrome. *Intensive Care Med* 2008; 34: 488–495.
- Cogulu O, Onay H, Uzunkaya D, et al. Role of angiotensin-converting enzyme gene polymorphisms in children with sepsis and septic shock. *Pediatr Int* 2008; 50: 477–480.
- Bunker-Wiersma HE, Koopmans RP, Kuipers TW, et al. Single nucleotide polymorphisms in genes of circulatory homeostasis in surviving pediatric intensive care patients with meningococcal infection. *Pediatr Crit Care Med* 2008; 9: 517–523.
- Davis SM, Clark EA, Nelson LT, et al. The association of innate immune response gene polymorphisms and puerperal group A streptococcal sepsis. *Am J Obstet Gynecol* 2010; 202: 308.e1–e8.
- Spiegler J, Gilhaus A, Konig IR, et al. Polymorphisms in the renin-angiotensin system and outcome of very-lowbirthweight infants. *Neonatology* 2010; 97: 10–14.
- Tsantes A, Tsangaris I, Kopterides P, et al. Angiotensin converting enzyme (ACE) insertion/deletion (I/D) polymorphism and circulating ACE levels are not associated with outcome in critically ill septic patients. Clin Chem Lab Med 2012; 50: 293–299.
- Zhou TB, Yin SS and Liang R. A meta-analysis of the association between angiotensin-converting enzyme insertion/deletion gene polymorphism and end-stage renal disease risk in IgA nephropathy patients. *J Renin Angiotensin Aldosterone Syst* 2013; 14: 235–241.
- Zhou TB, Yin SS and Qin YH. Association between angiotensin-converting enzyme insertion/deletion gene polymorphism and end-stage renal disease susceptibility. *J Renin Angiotensin Aldosterone Syst* 2014; 15: 22–31.
- Zhou TB, Liu YG, Lin N, et al. Relationship between angiotensin-converting enzyme insertion/deletion gene polymorphism and systemic lupus erythematosus/lupus nephritis: A systematic review and metaanalysis. *J Rheumatol* 2012; 39: 686–693.

Retraction notice

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP35 © The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314566019 jra.sagepub.com SAGE

This article has been included in a multiple retraction:

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

This article has been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System (JRAAS)* (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System September 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011

Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

RETRACTED: Association between the *ACE* I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

jraas_

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP36–NP44 © The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314566019 jra.sagepub.com

(S)SAGE

Weiqiang Zhong¹, Zongpei Jiang² and Tian-Biao Zhou²

Abstract

Background and objective: The association between the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism and type-2 diabetic nephropathy (T2DN) susceptibility and the risk of type-2 diabetes mellitus (T2DM) developing into T2DN in the Asian population is still controversial. This study was performed to evaluate the association of the ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in the Asian population.

Methods: A predefined literature search and selection of eligible relevant studies were performed to collect data from electronic databases.

Results: Twenty-nine articles were identified for an analysis of an association of the ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in the Asian population. The ACE I/D gene polymorphism was associated with T2DN susceptibility. Furthermore, the ACE D allele and II genotype were associated with the risk of patients with T2DM developing T2DN in the Asian population.

Conclusions: The ACE I/D gene polymorphism was associated with T2DN susceptibility, and the ACE D allele and II genotype were associated with the risk of patients with T2DM developing T2DN in the Asian population. However, more studies should be performed in the future.

Keywords

Type-2 diabetic nephropathy (T2DN), type-2 diabetes mellitus (T2DM), angiotensin-converting enzyme (ACE), insertion/deletion (I/D) gene polymorphism, meta-analysis

Date received: 27 October 2014; accepted: 29 November 2014

Introduction

Diabetes mellitus (DM), a multifactorial metabolic disease characterized by post-prandial hyperglycemia, is the most common cause of chronic kidney disease and end-stage renal disease (ESRD).¹ DM includes type-1 diabetes mellitus (T1DM) and type-2 diabetes mellitus (T2DM), and the incidence of DM has increased dramatically over the last several decades.² Diabetic nephropathy (DN), a serious complication of DM, includes type-1 diabetic nephropathy (T1DN) due to type-1 DM and type-2 diabetic nephropathy (T2DN) due to type-2 DM.^{2,3} DN as a cause of ESRD is associated with a poor life expectancy, causing serious socioeconomic problems.⁴

The angiotensin-converting enzyme gene (ACE) insertion/deletion (I/D) gene polymorphism is a 287-bp sequence of DNA in the intron 16 of the ACE gene.⁵ The ACE gene consists of either an insertion (I) allele or a deletion (D) allele that forms three possible genotypes: II, ID or DD.⁶ *ACE*, directly involved in the process of cell proliferation, differentiation, apoptosis and angiogenesis,⁷ can convert angiotensin I into angiotensin II, and angiotensin II is the main effector molecule of the renin-angiotensin system, is pleiotropic, and is a mediator of the

WZ and ZJ contributed equally to this work.

Corresponding author:

Tian-Biao Zhou, Department of Nephrology, the Sixth Affiliated Hospital, Sun Yat-Sen University, Yuancunerheng Road, No. 26, Guangdong, Guangzhou 510655, China. Email: tianbiaozhou@163.com or a126tianbiao@126.com

Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (http://www.uk.sagepub.com/aboutus/openaccess.htm).

¹Department of Nephrology, Central Hospital of Huizhou, China ²Department of Nephrology, the Sixth Affiliated Hospital, Sun Yat-Sen University, China

development and progression of diseases.⁸ When compared with II homozygotes, circulating *ACE* levels in plasma were nearly 30% and 60% higher in ID heterozygotes and DD homozygotes, respectively.⁶ Moreover, DD homozygotes also have been associated with higher tissue levels of *ACE*. The *ACE* I/D gene polymorphism, correlating with circulating *ACE* concentration, might be implicated in the etiology of T2DN and has been investigated in numerous epidemiologic studies.

Present epidemiologic studies show that the ACE I/D gene polymorphism has been implicated in the etiology of T2DN and the risk of patients with T2DM developing T2DN. However, the available evidence reported to date is weak, owing to sparseness of data or disagreements among studies. We performed this meta-analysis to investigate the relation between the ACE I/D gene polymorphism and T2DN susceptibility and the risk of patients with T2DM developing T2DN in the Asian population.

Materials and methods

Search strategy

The relevant studies were searched from the electronic databases of PubMed and Cochrane Library on March 1, 2014. The terms "(diabetic nephropathy) AND (angiotensin-converting enzyme) AND (polymorphism OR variant)" were entered into PubMed and Cochrane Library for search. The search in PubMed was limited to humans and the English language. We also extended the search spectrum to the "related articles" and the bibliographies of all recruited studies.

Inclusion and exclusion criteria

Inclusion criteria. The inclusion criteria were: (1) a casecontrol study or a prospective study; (2) the outcome had to be T2DN; (3) there had to be at least two comparison groups (T2DN group vs control group); and (4) the study should be conducted in the Asian population.

Exclusion criteria. The exclusion criteria were: (1) review articles, editorials and case reports; (2) articles did not provide detailed genotype data; (3) investigating the association of other genes with T2DN; (4) investigating the role of *ACE* in diseases; and (5) multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study independently by two investigators: first author's surname, year of publication, ethnicity of study population, and the number of cases and controls for the *ACE* I/D genotype. Frequencies of the D allele were calculated for the case group and control group, from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data were entered into Cochrane Review Manager (RevMan, version 5, Oxford, UK) and analyzed. The pooled statistic was counted using the fixed-effects model, but a random-effects model was conducted when the p value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. P < 0.05 was required for the overall OR to be deemed statistically significant. I^2 was used to test the heterogeneity between the included studies. Sensitivity analysis was performed according to sample size of each case (< 100 vs \geq 100). The Begg adjusted rank correlation test⁹ and the Egger regression asymmetry test¹⁰ were used for exploring publication bias (p < 0.1 was considered significant).

Results

Study characteristics

The search yielded 261 references, 260 from PubMed, and one from Cochrane Library. According to the inclusion and exclusion criteria, 29 articles^{11–39} were identified for the analysis of the association between the *ACE* I/D gene polymorphism and T2DN susceptibility and the risk of T2DM developing into T2DN in the Asian population in our review. Fourteen studies^{11–24} were conducted on the relationship between the *ACE* I/D gene polymorphism and T2DN susceptibility (Table 1), and 27 reports^{11–17,20–39} were conducted on the relationship between the *ACE* I/D gene polymorphism and the susceptibility of T2DM developing into T2DN (Table 2).

Association of the ACE I/D gene polymorphism with T2DN risk

In this meta-analysis, the *ACE* I/D gene polymorphism was associated with T2DN risk in the Asian population (D allele: OR = 1.32, 95% CI: 1.13–1.54, p = 0.0006; DD genotype: OR = 1.44, 95% CI: 1.04–1.98, p = 0.03; II genotype: OR = 0.74, 95% CI: 0.65–0.85, p < 0.0001; Figure 1 and Table 3).

Sensitivity analysis for the relationship between the *ACE* I/D gene polymorphism and T2DN risk in the Asian population was also performed according to case sample size (< 100 vs \ge 100). In the sensitivity analysis according to case sample size \ge 100, we found that the results were also similar with the non-sensitivity analysis, except for DD genotype. Furthermore, the *ACE* I/D gene polymorphism was associated with T2DN risk in the Asian

												_
First author, year	T2DN	1					Contr	ol				
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	П	Total	D allele	Total (allele)
Mizuiri 199511	19	50	11	80	88	160	14	37	25	76	65	152
Doi 1996 ¹²	14	30	20	64	58	128	15	42	48	105	72	210
Ohno 1996 ¹³	15	38	26	79	68	158	8	34	32	74	50	148
Hanyu 1998¹⁴	4	13	7	24	21	48	13	27	17	57	53	114
Wu 1998 ¹⁵	12	18	21	51	42	102	23	44	43	110	90	220
Hsieh 2000 ¹⁶	40	59	80	179	139	358	24	106	133	263	154	526
Lee 200217	40	137	117	294	217	588	66	277	330	673	409	1346
Chang 2003 ¹⁸	13	60	56	129	86	258	14	42	60	116	70	232
Park 2005 ¹⁹	27	49	27	103	103	206	7	51	30	88	65	176
Movva 2007 ²⁰	39	88	47	174	166	348	24	52	35		100	222
Naresh 2009 ²¹	15	11	4	30	41	60	I	17	12	30	19	60
Jayapalan 2010 ²²	21	77	77	175	119	350	20	56	61	137	96	274
Al-Harbi 2011 ²³	59	39	12	110	157	220	142	160	58	360	444	720
Kumar 2013 ²⁴	98	170	139	407	366	814	72	77	83	232	221	464

Table I.	Characteristics o	f the studies	evaluating the	e effects of the	e ACE I/D gei	ne polymor	phism on [.]	T2DN risk
----------	-------------------	---------------	----------------	------------------	---------------	------------	-----------------------	-----------

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T2DN: type-2 diabetic nephropathy.

Table 2. Characteris	tics of the studies evalua	ing the effects of the AC	E I/D gene polymoi	rphism on T2DM (developing into T2DN.
----------------------	----------------------------	---------------------------	--------------------	------------------	-----------------------

First author, year	T2DI	N					T2DI	1					
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total (allele)	
Mizuiri 1995 ¹¹	19	50	11	80	88	160	9	11	11	31	29	62	
Panagiotopoulos 1995 ²⁵	30	50	20	100	110	200	37	38	25	100	112	200	
Doi 1996 ¹²	14	30	20	64	58	128	12	56	56	124	80	248	
Ohno 1996 ¹³	15	38	26	79	68	158	5	15	33	53	25	106	
Nakajima 1996 ²⁶	6	25	16	47	37	94	4	19	18	41	27	82	
Yoshida 1996 ²⁷	I	_	-	36	-	-	6	_	_	60	-	_	
Hanyu 1998 ¹⁴	4	13	7	24	21	48	2	5	7	14	9	28	
Wu 1998 ¹⁵	12	18	21	51	42	102	I.	11	6	18	13	36	
Kuramoto 1999 ²⁸	3	13	13	29	19	58	9	16	8	33	34	66	
Tomino 1999 ²⁹	93	337	311	741	523	1482	54	190	163	407	298	814	
Wong 1999 ³⁰	8	38	54	100	54	200	14	45	41	100	73	200	
Hsieh 2000 ¹⁶	40	59	80	179	139	358	21	50	86	157	92	314	
Gohda 2001 ³¹	85	222	229	536	392	1072	31	92	89	212	154	424	
Viswanathan 2001 ³²	24	45	17	86	93	172	5	8	10	23	18	46	
Lee 2002 ¹⁷	40	137	117	294	217	588	39	170	208	417	248	834	
Okuno 2003 ³³	5	12	21	38	22	76	3	8	I	12	14	24	
Prasad 2006 ³⁴	55	75	66	196	185	392	52	97	76	225	201	450	
So 2006 ³⁵	93	364	407	864	550	1728	150	526	549	1225	826	2450	
Movva 2007 ²⁰	39	88	47	174	166	348	27	74	74	175	128	350	
Naresh 2009 ²¹	15		4	30	41	60	7	11	12	30	25	60	
Tien 2009 ³⁶	132	64	44	240	328	480	89	117	49	255	295	510	
Jayapalan 2010 ²²	21	77	77	175	119	350	19	31	31	81	69	162	
Al-Harbi 201123	59	39	12	110	157	220	96	75	25	196	267	392	
Felehgari 2011 ³⁷	32	30	6	68	94	136	26	32	14	72	84	144	
Rahimi 2011 ³⁸	23	36	13	72	82	144	26	32	14	72	84	144	
Rahimi 2012 ³⁹	55	66	19	140	176	280	26	32	14	72	84	144	
Kumar 2013 ²⁴	98	170	139	407	366	814	56	68	61	185	180	370	

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T2DM: type-2 diabetes mellitus; T2DN: type-2 diabetic nephropathy.



Figure 1. Association of the ACE I/D gene polymorphism on T2DN susceptibility (T2DN vs control).

ACE: angiotensin-converting enzyme; I: insertion; D: deletion; T2DN: type-2 diabetic nephropathy; CI: confidence interval; M-H: Mantel-Haenszel test.

Genetic contrasts	Number of	Q test	Model	OR	Þ	
	studies	p value	selected	(95% CI)	7	
T2DN vs control						
D vs I	14	0.002	Random	1.32 (1.13, 1.54)	0.0006	
DD vs (ID+II)	14	<0.0001	Random	1.44 (1.04, 1.98)	0.03	
II vs (ID+DD)	14	0.38	Fixed	0.74 (0.65, 0.85)	<0.0001	
T2DN vs control (sensi	tivity analysis: \geq 100)					
D vs I	7	0.02	Random	1.20 (1.01, 1.42)	0.04	
DD vs (ID+II)	7	0.0004	Random	1.22 (0.82, 1.80)	0.32	
II vs (ID+DD)	7	0.77	Fixed	0.79 (0.68, 0.92)	0.002	
T2DN vs control (sensi	tivity analysis: < 100)					
D vs I	7	0.03	Random	1.55 (1.16, 2.07)	0.003	
DD vs (ID+II)	7	0.03	Random	1.89 (1.08, 3.33)	0.03	
II vs (ID+DD)	7	0.21	Fixed	0.62 (0.47, 0.82)	0.0007	
T2DN vs T2DM						
D vs I	26	<0.00001	Random	1.61 (1.02, 1.32)	0.03	
DD vs (ID+II)	27	<0.0001	Random	1.14 (0.94, 1.38)	0.18	
ll vs (ID+DD)	26	<0.00001	Random	0.81 (0.68, 0.96)	0.02	
T2DN vs T2DM (sensiti	vity analysis: \geq 100)					
D vs I	12	<0.0001	Random	1.11 (0.96, 1.27)	0.16	
DD vs (ID+II)	12	0.0002	Random	1.15 (0.91, 1.45)	0.23	
ll vs (ID+DD)	12	0.01	Random	0.92 (0.78, 1.07)	0.28	
T2DN vs T2DM (sensiti	ivity analysis: < 100)					
D vs I	14	<0.0001	Random	1.24 (0.94, 1.64)	<0.0001	
DD vs (ID+II)	15	0.02	Random	1.13 (0.78, 1.63)	0.53	
II vs (ID+DD)	14	0.0007	Random	0.66 (0.44, 0.99)	0.04	

Table 3. Meta-analysis of the association of the ACE I/D gene polymorphism with risk of T2DN and the T2DM developing into T2DN.

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T2DM: type-2 diabetes mellitus; T2DN: type-2 diabetic nephropathy; OR: odds ratio; CI: confidence interval.

population in the sensitivity analysis according to case sample size < 100 (Table 3), and the results were similar to those in the nonsensitivity analysis.

Association of the ACE I/D gene polymorphism with the risk of T2DM patients developing T2DN

In this meta-analysis, the *ACE* D allele and II genotype were associated with the risk of T2DM patients developing T2DN in the Asian population (D allele: OR = 1.61, 95% CI: 1.02–1.32, p = 0.03; II genotype: OR = 0.81, 95% CI: 0.68–0.96, p = 0.02; Figure 2 for the D allele, and Figure 3 for the II genotype; Table 3), but this association was not found for the DD genotype (OR = 1.06, 95% CI: 0.90–1.24, p = 0.52; Figure 4 for the DD genotype).

Sensitivity analysis for the relationship between the *ACE* I/D gene polymorphism and the risk of T2DM patients developing into T2DN in the Asian population was also performed according to case sample size (< 100 vs \geq 100). In the sensitivity analysis according to case sample size \geq 100, we found that *ACE* I/D gene polymorphism were not associated with the risk of T2DM patients developing into

T2DN in Asian population (Table 3). However, in the sensitivity analysis according to case sample size <100, the results were similar to those in the nonsensitivity analysis (Table 3).

Evaluation of publication bias

No significant publication bias was shown in the comparison of T2DN vs T2DM (Begg p = 0.967, Egger p = 0.600; Figure 5 for Begg test).

Discussion

Some meta-analyses reported that the *ACE* I/D gene polymorphism was associated with the risk of some renal diseases.^{5,40–42} Dysfunction of *ACE* generation brought by the *ACE* I/D gene polymorphism is considered to be the important deterioration factor associated with the T2DN susceptibility and the risk of patients with T2DM developing T2DN in the Asian population. There was a rare genetic molecular marker to predict the onset of T2DN and the risk of patients with T2DM developing T2DN in Asian population. This study using a meta-analysis

	T2D	N	T2D	N		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Panagiotopoulos 1995	110	200	112	200	4.1%	0.96 [0.65, 1.42]	1995	
Mizuiri 1995	88	160	29	62	2.8%	1.39 [0.77, 2.50]	1995	+
Nakajima 1996	37	94	27	82	2.7%	1.32 [0.71, 2.46]	1996	+- /
Doi 1996	58	128	80	248	3.8%	1.74 [1.12, 2.70]	1996	
Ohno 1996	68	158	25	106	3.1%	2.45 [1.42, 4.23]	1996	
Hanyu 1998	21	48	9	28	1.4%	1.64 [0.62, 4.36]	1998	
Wu 1998	42	102	13	36	2.0%	1.24 [0.56, 2.72]	1998	
Wong 1999	54	200	73	200	3.9%	0.64 [0.42, 0.98]	1999	
Kuramoto 1999	19	58	34	66	2.2%	0.46 [0.22, 0.95]	1999	
Tomino 1999	523	1482	298	814	5.9%	0.94 [0.79, 1.13]	1999	+
Hsieh 2000	139	358	92	314	4.7%	1.53 [1.11, 2.12]	2000	y
Gohda 2001	392	1072	154	424	5.4%	1.01 [0.80, 1.28]	2001	~ +
Viswanathan 2001	93	172	18	46	2.5%	1.83 [0.94, 3.56]	2001	<u> </u>
Lee 2002	217	588	248	834	5.5%	1.38 [1.10, 1.73]	2002	-
Okuno 2003	22	76	14	24	1.5%	0.29 [0.11, 0.75]	2003	
Prasad 2006	185	392	201	450	5.1%	1.11 [0.84, 1.45]	2006	
So 2006	550	1728	826	2450	6.2%	0.92 (0.80, 1.05)	2006	
Mowa 2007	166	348	128	350	4.9%	1.58 [1.17, 2.14]	2007	/ -
Tien 2009	328	480	295	510	5.2%	1.57 [1.21, 2.04]	2009	-
Naresh 2009	41	60	25	60	2.1%	3.02 [1.43, 6.38]	2009	——
Jayapalan 2010	119	350	69	162	4.2%	0.69 (0.47, 1.02)	2010	-
Rahimi 2011	82	144	84	144	3.6%	0.94 [0.59, 1.51]	2011	+
Al-Harbi 2011	157	220	267	392	4.4%	1.17 [0.81, 1.67]	2011	+-
Felehgari 2011	94	136	84	144	3.4%	1.60 [0.98, 2.61]	2011	
Rahimi 2012	176	280	84	144	4.0%	1.21 [0.80, 1.82]	2012	
Kumar 2013	366	814	180	370	5.3%	0.86 [0.67, 1.10]	2013	-
Total (95% CI)		9848		8660	100.0%	1.16 [1.02, 1.32]		•
Total events	4147		3469					
Heterogeneity: Tau ² = 0.0)7; Chi² =	86.56,	df = 25 (P	< 0.00	001); l ² =	71%		
Test for overall effect: Z =	2.19 (P =	0.03)						

Figure 2. Association of the ACE D allele on the risk of T2DM developing into T2DN (T2DN vs T2DM). ACE: angiotensin-converting enzyme; type-2 diabetes mellitus; l: insertion; D: deletion; T2DN: type-2 diabetic nephropathy; CI: confidence interval; M-H: Mantel-Haenszel test.

method was performed to explore whether the *ACE* I/D gene polymorphism could predict the susceptibility of T2DN susceptibility and the risk of patients with T2DM developing T2DN in the Asian population.

In this meta-analysis, the association between the *ACE* I/D gene polymorphism and T2DN susceptibility in the Asian population was assessed using a meta-analysis method. We found that the *ACE* I/D gene polymorphism was associated with T2DN susceptibility in the Asian population. Furthermore, sensitivity analysis was performed according to sample size of case (< 100 vs \geq 100), and the results from the sensitive analysis according to case sample size < 100 were similar to those from the nonsensitive analysis. In the sensitivity analysis according to case sample size \geq 100, we found that the results were also similar to the nonsensitivity analysis, except for the DD genotype. The small sample size in some included studies might draw a more positive result. More studies should be performed in the future.

The relationship between the ACE I/D gene polymorphism and the risk of patients with T2DM developing T2DN in the Asian population was also assessed in this meta-analysis. The results indicated that the ACE D allele and II genotype were associated with the risk of T2DM patients developing T2DN in the Asian population, but

this association was not found for the DD genotype. Furthermore, sensitivity analysis was performed according to case sample size (< 100 vs \geq 100), and the results from the sensitive analysis according to case sample size < 100were similar to those from the non-sensitive analysis. However, in the sensitivity analysis according to case sample size ≥ 100 , we found that the ACE I/D gene polymorphism was not associated with the risk of patients with T2DM developing T2DN in the Asian population, and the result for the D allele and II genotype were not similar to those in the nonsensitive analysis. There was no significant publication bias among the studies on the relationship between the ACE I/D gene polymorphism and the risk of patients with T2DM developing T2DN in the Asian population, and the results might be more robust. However, the small sample size in some included studies might draw a more positive result, and more studies should be performed in the future.

In this meta-analysis, we found that the ACE D allele, DD genotype and II genotype were associated with T2DN susceptibility and the ACE D allele and II genotype were associated with the risk of patients with T2DM developing T2DN in the Asian population. However, these findings should be regarded cautiously because many other factors, such as heterogeneity of enrolled cases, limited statistical

~ . ~ .	120	N	T2DI	VI		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% CL
Mizuiri 1995	11	80	11	31	2.3%	0.29 [0.11, 0.77]	1995	
Panagiotopoulos 1995	20	100	25	100	3.7%	0.75 [0.38, 1.46]	1995	- T
Doi 1996	20	64	56	124	3.9%	0.55 [0.29, 1.04]	1996	
Nakajima 1996	16	47	18	41	2.7%	0.66 [0.28, 1.56]	1996	
Ohno 1996	26	79	33	53	3.4%	0.30 [0.14, 0.62]	1996	
Hanyu 1998	7	24	7	14	1.4%	0.41 [0.10, 1.62]	1998	
Wu 1998	21	51	6	18	1.9%	1.40 [0.45, 4.32]	1998	
Tomino 1999	311	741	163	407	6.9%	1.08 [0.85, 1.38]	1999	
Wong 1999	54	100	41	100	4.4%	1.69 [0.97, 2.96]	1999	
Kuramoto 1999	13	29	8	33	2.0%	2.54 [0.86, 7.49]	1999	
Hsieh 2000	80	179	86	157	5.4%	0.67 [0.43, 1.03]	2000	
Gohda 2001	229	536	89	212	6.3%	1.03 [0.75, 1.42]	2001	+
Viswanathan 2001	17	86	10	23	2.3%	0.32 [0.12, 0.85]	2001	
Lee 2002	117	294	208	417	6.4%	0.66 [0.49, 0.90]	2002	 →
Okuno 2003	21	38	1	12	0.6%	13.59 [1.59, 116.03]	2003	
So 2006	407	864	549	1225	7.3%	1.10 [0.92, 1.31]	2006	+
Prasad 2006	66	196	76	225	5.6%	1.00 [0.66, 1.49]	2006	+
Mowa 2007	47	174	74	175	5.2%	0.51 [0.32, 0.79]	2007	
Naresh 2009	4	30	12	30	1.5%	0.23 [0.06, 0.83]	2009	
Tien 2009	44	240	49	255	5.2%	0.94 [0.60, 1.48]	2009	7+
Jayapalan 2010	77	175	31	81	4.5%	1.27 [0.74, 2.17]	2010	/ -
Felehgari 2011	6	68	14	72	2.1%	0.40 [0.14, 1.11]	2011	
Rahimi 2011	13	72	14	72	2.8%	0.91 [0.40, 2.11]	2011	
Al-Harbi 2011	12	110	25	196	3.3%	0.84 [0.40, 1.74]	2011	
Rahimi 2012	19	140	14	72	3.2%	0.65 (0.30, 1.39)	2012	
Kumar 2013	139	407	61	185	5.9%	1.05 (0.73, 1.52)	2013	+
Total (95% CI)		4924		4330	100.0%	0.81 [0.68, 0.96]		•
Total events	1797		1681					
Heterogeneity: Tau ² = 0.1	0: Chi ² = 1	67.68	df = 25 (F	, < U UU	001) 12 =	63%	\vdash	

Figure 3. Association of the ACE II genotype on the risk of T2DM developing into T2DN (T2DN vs T2DM). ACE: angiotensin-converting enzyme; type-2 diabetes mellitus; I: insertion; D: deletion; T2DN: type-2 diabetic nephropathy; CI: confidence interval; M-H: Mantel-Haenszel test.

	T2D	1	T2DN	1		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Panagiotopoulos 1995	30	100	37	100	4.6%	0.73 [0.40, 1.32]	1995	
Mizuiri 1995	19	80	9	- 31	2.8%	0.76 [0.30, 1.93]	1995	
Nakajima 1996	6	47	4	41	1.6%	1.35 [0.35, 5.17]	1996	
Doi 1996	14	64	12	124	3.2%	2.61 [1.13, 6.05]	1996	 →→
Ohno 1996	15	79	5	53	2.3%	2.25 [0.76, 6.62]	1996	
Yoshida 1996	1	36	6	60	0.7%	0.26 [0.03, 2.23]	1996	
Hanyu 1998	4	24	2	14	1.0%	1.20 [0.19, 7.57]	1998	
Wu 1998	12	51	1	18	0.8%	5.23 [0.63, 43.49]	1998	
/Vong 1999	8	100	14	100	2.8%	0.53 [0.21, 1.34]	1999	
Kuramoto 1999	3	29	9	33	1.5%	0.31 [0.07, 1.27]	1999	
Tomino 1999	93	741	54	407	6.2%	0.94 [0.65, 1.34]	1999	+
Hsieh 2000	40	179	21	157	4.6%	1.86 [1.04, 3.32]	2000	
∕iswanathan 2001	24	86	5	23	2.2%	1.39 [0.47, 4.17]	2001	
Gohda 2001	85	536	31	212	5.6%	1.10 [0.70, 1.72]	2001	+-
_ee 2002	40	294	39	417	5.4%	1.53 [0.96, 2.44]	2002	
Okuno 2003	5	38	3	12	1.2%	0.45 [0.09, 2.27]	2003	
Prasad 2006	55	196	52	225	5.6%	1.30 [0.84, 2.01]	2006	+
Bo 2006	93	864	150	1225	6.8%	0.86 [0.66, 1.14]	2006	-
Mowa 2007	39	174	27	175	4.9%	1.58 [0.92, 2.73]	2007	
Naresh 2009	15	30	7	30	2.2%	3.29 [1.08, 9.95]	2009	
Tien 2009	132	240	89	255	6.2%	2.28 [1.59, 3.27]	2009	
Javapalan 2010	21	175	19	81	4.0%	0.44 [0.22, 0.88]	2010	
N-Harbi 2011	59	110	96	196	5.4%	1.21 [0.75, 1.92]	2011	
elehoari 2011	32	68	26	72	4.0%	1.57 (0.80, 3.09)	2011	
Rahimi 2011	23	72	26	72	3.9%	0.83 [0.42, 1.66]	2011	_ _
Rahimi 2012	55	140	26	72	4.6%	1.14 [0.64, 2.06]	2012	_ - _
<umar 2013<="" td=""><td>98</td><td>407</td><td>56</td><td>185</td><td>6.0%</td><td>0.73 [0.50, 1.08]</td><td>2013</td><td>-</td></umar>	98	407	56	185	6.0%	0.73 [0.50, 1.08]	2013	-
Fotal (95% CI)	4	4960		4390	100.0%	1.14 [0.94, 1.38]		•
Total events	1021		826					
Heterogeneity: Tau ² = 0.1	1.2. Chi ² = 6	61.96.	df = 26 (P	< 0.00	01): I ² = 5	8%		
Test for overall effect: Z =	1.34 (P =	0.18)						0.01 0.1 1 10 10
Contrast Construction 2 -		/						Favours T2DN Favours T2DM

Figure 4. Association of the ACE DD genotype on the risk of T2DM developing into T2DN (T2DN vs T2DM). ACE: angiotensin-converting enzyme; type-2 diabetes mellitus; l: insertion; D: deletion; T2DN: type-2 diabetic nephropathy; CI: confidence interval; M-H: Mantel-Haenszel test.



Figure 5. Begg's funnel plots with pseudo 95% confidence limits. Evaluation of publication bias for the association of the ACE I/D gene polymorphism with the risk of T2DM developing into T2DN. ACE: angiotensin-converting enzyme; type-2 diabetes mellitus; I: insertion; D: deletion; T2DN: type-2 diabetic nephropathy.

power, variable study designs and different interventions, were closely related to affect the results. Undoubtedly, the limitations mentioned above might affect our final conclusions.

In conclusion, the results in our study support that the *ACE* I/D gene polymorphism was associated with T2DN susceptibility and the *ACE* D allele and II genotype were associated with the risk of patients with T2DM developing T2DN in the Asian population. However, more association investigations on larger, stratified populations are required to further clarify the role of the *ACE* I/D gene polymorphism in T2DN susceptibility and the risk of patients with T2DM developing T2DN in the Asian population.

Conflict of interest

None declared.

Funding

This work was supported by the sub-item of 985 Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation; No. 88000-3311300).

References

- Peev V, Reiser J and Alachkar N. Diabetes mellitus in the transplanted kidney. *Front Endocrinol (Lausanne)* 2014; 5: 141.
- Yu ZY, Chen LS, Zhang LC, et al. Meta-analysis of the relationship between ACE I/D gene polymorphism and endstage renal disease in patients with diabetic nephropathy. Nephrology (Carlton) 2012; 17: 480–487.
- 3. Hussain H, Ramachandran V, Ravi S, et al. *TCF7L2* rs7903146 polymorphism and diabetic nephropathy association is not independent of type 2 diabetes—a study in a

south Indian population and meta-analysis. *Endokrynol Pol* 2014; 65: 298–305.

- Kaur M, Bedi O, Sachdeva S, et al. Rodent animal models: From mild to advanced stages of diabetic nephropathy. *Inflammopharmacology* 2014; 22: 279–293.
- Zhou TB, Qin YH, Su LN, et al. The association between angiotensin-converting enzyme insertion/deletion gene variant and risk of focal segmental glomerulosclerosis: A systematic review and meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 624–633.
- Zhou TB, Yin SS and Qin YH. Association between angiotensin-converting enzyme insertion/deletion gene polymorphism and end-stage renal disease susceptibility. *J Renin Angiotensin Aldosterone Syst* 2014; 15: 22–31.
- 7. Zha Y, Gan P, Liu Q, et al. Relationship between polymorphism of angiotensin-converting enzyme gene insertion/ deletion and risk of hepatocellular carcinoma in a Chinese Dai population. *J Renin Angiotensin Aldosterone Syst*. Epub ahead of print 10 September 2014.
- 8. Song GG and Lee YH. The insertion/deletion polymorphism in the angiotensin-converting enzyme and susceptibility to schizophrenia or Parkinson's disease: A meta-analysis. *J Renin Angiotensin Aldosterone Syst*. Epub ahead of print 20 August 2014.
- Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
- Egger M, Davey Smith G, Schneider M, et al. Bias in metaanalysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
- Mizuiri S, Hemmi H, Inoue A, et al. Angiotensin-converting enzyme polymorphism and development of diabetic nephropathy in non-insulin-dependent diabetes mellitus. *Nephron* 1995; 70: 455–459.
- 12. Doi Y, Yoshizumi H, Yoshinari M, et al. Association between a polymorphism in the angiotensin-converting

enzyme gene and microvascular complications in Japanese patients with NIDDM. *Diabetologia* 1996; 39: 97–102.

- 13. Ohno T, Kawazu S and Tomono S. Association analyses of the polymorphisms of angiotensin-converting enzyme and angiotensinogen genes with diabetic nephropathy in Japanese non-insulin-dependent diabetics. *Metabolism* 1996; 45: 218–222.
- Hanyu O, Hanawa H, Nakagawa O, et al. Polymorphism of the angiotensin I-converting enzyme gene in diabetic nephropathy in type II diabetic patients with proliferative retinopathy. *Ren Fail* 1998; 20: 125–133.
- 15. Wu S, Xiang K, Weng Q, et al. Relationship between angiotensin I converting enzyme gene polymorphism and diabetic nephropathy. *Chin Med J (Engl)* 1998; 111: 478–479.
- Hsieh MC, Lin SR, Hsieh TJ, et al. Increased frequency of angiotensin-converting enzyme DD genotype in patients with type 2 diabetes in Taiwan. *Nephrol Dial Transplant* 2000; 15: 1008–1013.
- Lee YJ and Tsai JC. ACE gene insertion/deletion polymorphism associated with 1998 World Health Organization definition of metabolic syndrome in Chinese type 2 diabetic patients. Diabetes Care 2002; 25: 1002–1008.
- Chang HR, Cheng CH, Shu KH, et al. Study of the polymorphism of angiotensinogen, anigiotensin-converting enzyme and angiotensin receptor in type II diabetes with end-stage renal disease in Taiwan. J Chin Med Assoc 2003; 66: 51–56.
- Park HC, Choi SR, Kim BS, et al. Polymorphism of the ACE gene in dialysis patients: Overexpression of DD genotype in type 2 diabetic end-stage renal failure patients. Yonsei Med J 2005; 46: 779–787.
- Movva S, Alluri RV, Komandur S, et al. Relationship of angiotensin-converting enzyme gene polymorphism with nephropathy associated with Type 2 diabetes mellitus in Asian Indians. *J Diabetes Complications* 2007; 21: 237–241.
- Naresh VV, Reddy AL, Sivaramakrishna G, et al. Angiotensin converting enzyme gene polymorphism in type II diabetics with nephropathy. *Indian J Nephrol* 2009; 19: 145–148.
- 22. Jayapalan JJ, Muniandy S and Chan SP. Null association between *ACE* gene I/D polymorphism and diabetic nephropathy among multiethnic Malaysian subjects. *Indian J Hum Genet* 2010; 16: 78–86.
- Al-Harbi EM, Farid EM, Gumaa KA, et al. Angiotensinconverting enzyme gene polymorphisms and T2DM in a case-control association study of the Bahraini population. *Mol Cell Biochem* 2011; 350: 119–125.
- Kumar R, Sharma RK and Agarwal S. Genetic predisposition for development of nephropathy in type 2 diabetes mellitus. *Biochem Genet* 2013; 51: 865–875.
- Panagiotopoulos S, Smith TJ, Aldred GP, et al. Angiotensinconverting enzyme (ACE) gene polymorphism in type II diabetic patients with increased albumin excretion rate. J Diabetes Complications 1995; 9: 272–276.
- Nakajima S, Baba T and Yajima Y. Is ACE gene polymorphism a useful marker for diabetic albuminuria in Japanese NIDDM patients? *Diabetes Care* 1996; 19: 1420–1422.
- 27. Yoshida H, Kuriyama S, Atsumi Y, et al. Angiotensin I converting enzyme gene polymorphism in non-insulin dependent diabetes mellitus. *Kidney Int* 1996; 50: 657–664.

- 28. Kuramoto N, Iizuka T, Ito H, et al. Effect of *ACE* gene on diabetic nephropathy in NIDDM patients with insulin resistance. *Am J Kidney Dis* 1999; 33: 276–281.
- Tomino Y, Makita Y, Shike T, et al. Relationship between polymorphism in the angiotensinogen, angiotensin-converting enzyme or angiotensin II receptor and renal progression in Japanese NIDDM patients. *Nephron* 1999; 82: 139–144.
- Wong TY, Chan JC, Poon E, et al. Lack of association of angiotensin-converting enzyme (DD/II) and angiotensinogen M235T gene polymorphism with renal function among Chinese patients with type II diabetes. *Am J Kidney Dis* 1999; 33: 1064–1070.
- Gohda T, Makita Y, Shike T, et al. Association of the DD genotype and development of Japanese type 2 diabetic nephropathy. *Clin Nephrol* 2001; 56: 475–480.
- Viswanathan V, Zhu Y, Bala K, et al. Association between ACE gene polymorphism and diabetic nephropathy in South Indian patients. JOP 2001; 2: 83–87.
- Okuno S, Utsugi T, Ohno T, et al. Angiotensin-converting enzyme gene polymorphism as a potent risk factor for developing microalbuminuria in Japanese patients with type 2 diabetes mellitus: A 9-year follow-up study. *J Int Med Res* 2003; 31: 290–298.
- Prasad P, Tiwari AK, Kumar KM, et al. Chronic renal insufficiency among Asian Indians with type 2 diabetes: I. Role of RAAS gene polymorphisms. *BMC Med Genet* 2006; 7: 42.
- 35. So WY, Ma RC, Ozaki R, et al. Angiotensin-converting enzyme (*ACE*) inhibition in type 2, diabetic patients—interaction with *ACE* insertion/deletion polymorphism. *Kidney Int* 2006; 69: 1438–1443.
- Tien KJ, Hsiao JY, Hsu SC, et al. Gender-dependent effect of ACE I/D and AGT M235T polymorphisms on the progression of urinary albumin excretion in Taiwanese with type 2 diabetes. Am J Nephrol 2009; 29: 299–308.
- Felehgari V, Rahimi Z, Mozafari H, et al. ACE gene polymorphism and serum ACE activity in Iranians type II diabetic patients with macroalbuminuria. Mol Cell Biochem 2011; 346: 23–30.
- 38. Rahimi Z, Felehgari V, Rahimi M, et al. The frequency of factor V Leiden mutation, ACE gene polymorphism, serum ACE activity and response to ACE inhibitor and angiotensin II receptor antagonist drugs in Iranians type II diabetic patients with microalbuminuria. Mol Biol Rep 2011; 38: 2117–2123.
- Rahimi Z, Vaisi-Raygani A and Parsian A. Concomitant presence of endothelial nitric oxide 894T and angiotensin II-converting enzyme D alleles are associated with diabetic nephropathy in a Kurdish population from Western Iran. *Nephrology (Carlton)* 2012; 17: 175–181.
- 40. Zhou TB, Yin SS and Liang R. A meta-analysis of the association between angiotensin-converting enzyme insertion/deletion gene polymorphism and end-stage renal disease risk in IgA nephropathy patients. *J Renin Angiotensin Aldosterone Syst* 2013; 14: 235–241.
- Zhou TB, Yin SS and Qin YH. Association between angiotensin-converting enzyme insertion/deletion gene polymorphism and end-stage renal disease susceptibility. *J Renin Angiotensin Aldosterone Syst* 2014; 15: 22–31.
- Zhou TB, Liu YG, Lin N, et al. Relationship between angiotensin-converting enzyme insertion/deletion gene polymorphism and systemic lupus erythematosus/lupus nephritis: A systematic review and metaanalysis. *J Rheumatol* 2012; 39: 686–693.

Retraction notice

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP45 © The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314566221 jra.sagepub.com SAGE

This article has been included in a multiple retraction: Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

This article has been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System (JRAAS)* (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System Septembr 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011

Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage). Original Article

jraas

RETRACTED: Relationship between the angiotensinogen AII66C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP46–NP50 © The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314566221 ira.sagepub.com

SAGE

Chun-Hua Yang¹ and Tian-Biao Zhou²

Abstract

Aim: The relationship between the angiotensinogen (AGT) A1166C gene polymorphism and the risk of diabetes mellitus (DM) developing into diabetic nephropathy (DN) is still controversial. This study was performed to evaluate the association of the AGT A1166C gene polymorphism with susceptibility of the subject's DM developing into DN, using a meta-analysis method.

Methods: We performed a predefined literature search and selection of eligible relevant studies, to collect data from electronic databases.

Results: Nine articles were identified for the analysis of the association of the AGT A1166C gene polymorphism with the subject's susceptibility of DM to develop into DN. The AGT CC genotype was associated with the susceptibility of DM to develop into DN in the overall population, but the C allele and AA genotype were not. Furthermore, the AGT C allele and CC genotype were associated with the risk of DM developing into DN in the Asian population, but the AA genotype was not; however, the AGT A1166C gene polymorphisms were not associated with susceptibility of DM developing into DN, in the Caucasian population.

Conclusions: The AGT CC genotype was associated with the susceptibility of DM developing into DN in the overall population and in the Asian population, and the C allele was associated with the susceptibility of DM to develop into DN, in Asians; however, more studies should be performed.

Keywords

Angiotensinogen, diabetes mellitus, diabetic nephropathy, gene polymorphisms, meta-analysis, racial differences

Introduction

Diabetes mellitus (DM), an important public health problem, is a chronic disease with high morbidity and mortality among patients, which impair their health and quality of life.¹ Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes; and it can lead to end-stage renal disease.² DN includes Type-1 diabetic nephropathy (T1DN), due to Type-1 diabetes mellitus, and Type-2 diabetic nephropathy (T2DN) due to Type-2 diabetes mellitus.^{3,4} Some investigations suggest that genetic factors might act with a key role in the susceptibility of DM developing into DN.

The renin-angiotensin system is a major determinant of blood pressure regulation and it is associated with the risk of renal diseases.⁵ The angiotensinogen (AGT) gene, located on chromosome 1q41-qter, regulates the expression of

angiotensinogen; its cleavage by renin liberates angiotensin I, which is converted into angiotensin II by the angiotensinconverting enzyme. The AGT A1166C gene polymorphism, correlated with circulating and cellular AGT concentration, has been implicated in the etiology of DM developing into DN and has been investigated in numerous epidemiologic

²Department of Nephrology, Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

Corresponding author:

Tian-Biao Zhou, Department of Nephrology, Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510655, China. Email: tianbiaozhou@163.com

Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (http://www.uk.sagepub.com/aboutus/openaccess.htm).

¹Department of Emergency, First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

studies at present; however, the available evidence reported to date is weak, due to a sparseness of data or disagreements among studies. We performed this meta-analysis to investigate the relationship between the AGT A1166C gene polymorphism and the susceptibility for DM developing into DN.

Materials and methods

Search strategy

Relevant studies were screened from the search engines of PubMed and Cochrane Library on 1 August 2014. We used '(angiotensinogen OR AGT) AND (diabetic nephropathy)' in PubMed and the Cochrane Library to complete the search. We also extended the search spectrum to 'related articles' and the bibliographies of all retrieved studies. If multiple publications of the same data from the same study group occurred, we only recruited the later paper for analysis.

Inclusion criteria

- A case–control study;
- The outcome had to be DN; and
- There had to be at least two comparison groups (DN group versus DM group).

Exclusion criteria

- Review articles, editorials and case reports;
- Articles that did not provide the detailed genotype data of A1166C;
- Investigations of the association of other genes with DN;
- Investigations of the role of drugs to diseases; and
- Multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study, independently, by two investigators: First author's surname, year of publication, ethnicity of study population, the number of cases and controls for the A1166C genotype. Frequencies of the C allele were calculated for the case group and control group, from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data was entered into the Cochrane Review Manager (RevMan, version 5) and analyzed. The pooled statistic was counted using the fixed effects model, but a random effects model was conducted when the *p* value of the heterogeneity test was < 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% CI were also calculated; *p* < 0.05 was required for the overall OR to

be deemed statistically significant I^2 was used to test the heterogeneity between the included studies. We classified the investigations into studies for Asians and for Caucasians, because genotype frequencies and prevalence of DN were different among ethnic groups. We used the Begg adjusted rank correlation test⁶ and the Egger regression asymmetry test⁷ to explore publication bias p < 0.1 was considered significant), when the sample number was more than five.

Results

Study characteristics

The search yielded 162 references: 162 from PubMed and 0 from the Cochrane Library. According to the inclusion and exclusion criteria, nine articles^{8–16} were identified for the analysis of the between AGT A1166C gene polymorphism and the susceptibility of DM developing into DN, in our review (Table 1).

Association of the AGT A1166C gene polymorphism with the risk of DM patients developing into DN

In this meta-analysis, the AGT CC genotype was associated with the susceptibility of DM developing into DN in the overall population, but the C allele and AA genotype were not (CC genotype: OR = 1.42; 95% CI 0.97–2.08; p = 0.07 and C allele: OR = 1.26; 95% CI 0.96–1.65; p = 0.10; and AA genotype: OR = 0.81; 95% CI 0.56–1.18, p = 0.28; with Figure 1 for the C allele, Figure 2 for the CC genotype and Figure 3 for the AA genotype; and Table 2).

In the meta-analysis according to ethnicity, we found that the AGT C allele and CC genotype were associated with the risk of DM developing into DN in the Asian population, but the AA genotype was not (Table 2); however, the AGT A1166C gene polymorphisms were not associated with the susceptibility of DM developing into DN in the Caucasian population (Table 2).

A sensitivity analysis for the relationship between the AGT A1166C gene polymorphism and the susceptibility of DM developing into DN was also performed according to the types of DM. In the sensitivity analysis, the AGT A1166C gene polymorphisms were not associated with the susceptibility of T1DM developing into T1DN in the overall population (Table 2); however, the AGT CC genotype was associated with the susceptibility of T2DM developing into T2DN in the overall population, while the C allele and AA genotype were not (Table 2).

Evaluation of publication bias

No significant publication bias was shown in this metaanalysis (Begg p = 1.000, Egger p = 0.826; Figure 4 has the Begg test results).

First author, year	Ethnicity	Туре	DN						DM					
		of DM	сс	AC	AA	Total	C allele	Total (allele)	СС	AC	AA	Total	C allele	Total (allele)
Doria, 1997	Caucas	TIDM	9	29	35	73	47	146	7	25	47	79	39	158
Tomino, 1999	Asian	T2DM	_	_	128	745	_	-	_	-	61	407	_	-
Van Ittersum, 2000	Caucas	TIDM	21	88	91	200	130	400	10	53	37	100	73	200
Fradin, 2002	Caucas	T2DM	12	31	74	117	55	234	5	52	61	118	62	236
Prasad, 2006	Asian	T2DM	5	22	169	196	32	392	2	29	194	225	33	450
Möllsten, 2008	Caucas	TIDM	Ι	20	52	73	22	146	5	56	136	197	66	394
Gallego, 2008	Caucas	TIDM	5	21	15	41	31	82	32	183	196	411	247	822
Ahluwalia, 2009	Asian	T2DM	24	112	104	240	160	480	5	119	131	255	129	510
Yin, 2013	Asian	T2DM	Ι	20	131	152	22	304	0	8	133	141	8	282

Table I. Characteristics of the studies evaluating the effects of AGT AII66C gene polymorphism on DM developing into DN.

AGT: angiotensinogen; Caucas : caucasian; DM: diabetes mellitus; DN: diabetic nephropathy

	DN		DM			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl,	Year	M-H, Random, 95% Cl
Doria,1997	47	146	39	158	11.5%	1.45 [0.88, 2.39]	1997) +
VAN Ittersum, 2000	130	400	73	200	15.8%	0.84 [0.59, 1.20]	2000	-
Fradin,2002	55	234	62	236	13.8%	0.86 (0.57, 1.31)	2002	∕ →
Prasad,2006	32	392	33	450	11.3%	1.12 [0.68, 1.86]	2006	+-
Gallego,2008	31	82	247	822	12.3%	1.42 [0.88, 2.27]	2008	+-
Möllsten,2008	22	146	66	394	10.9%	0.88 [0.52, 1.49]	2008	-
Ahluwalia,2009	160	480	129	510	18.7%	1.48 [1.12, 1.95]	2009	-
Yin,2013	22	304	8	282	5.9%	2.67 [1.17, 6.10]	2013	
Total (95% CI)		2184		3052	100.0%	1.18 [0.94, 1.48]		•
Total events	499		657					
Heterogeneity: Tau ² =	= 0.05; Ch	i ^z = 14.	46, df = 7	(P = 0.	.04); l² = 5	2%		
Test for overall effect:	Z=1.43	(P = 0.1	15)					Favours DN Favours DM

Figure 1. Association of the AGT C allele regarding the risk of DM developing into DN. AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy

Discussion

We included nine studies into this meta-analysis and we found that the AGT CC genotype was associated with the susceptibility of DM developing into DN in the overall population, but the C allele and AA genotype were not. Furthermore, the AGT C allele and CC genotype were associated with the risk of DM developing into DN in the Asian population, but the AA genotype was not; however, the AGT A1166C gene polymorphisms were not associated with the susceptibility of DM developing into DN in the Caucasian population. There was no publication bias in this meta-analysis and the results for overall populations might be robust to some extent; however, the number of included studies for the Asian and Caucasian populations were small, so more studies in these populations should be performed in the future.

In the sensitivity analysis, the relationship between the AGT A1166C gene polymorphism and the susceptibility of DM developing into DN was also performed according to the types of DM. We found that the AGT A1166C gene polymorphism was not associated with the susceptibility of T1DM developing into T1DN, in the overall population; however, the AGT CC genotype was associated with the

susceptibility of T2DM developing into T2DN in the overall population, but the C allele and AA genotype were not.

In our investigation, we found that the AGT CC genotype was associated with the susceptibility of DM to develop into DN in the overall population, and the AGT C allele and CC genotype were associated with the risk of DM developing into DN in the Asian population. Furthermore, the AGT CC genotype was associated with the susceptibility of T2DM developing into T2DN in overall population; however, these findings should be regarded cautiously, because many other ingredients, such as the heterogeneity of the enrolled cases, limited statistical power, variable study designs and different interventions, were closely related to affecting the results. Furthermore, whether the AGT A1166C polymorphism is just linked with other discrete loci involved in the susceptibility of DM developing into DN is not clear at the moment.

Conclusions

In conclusion, the results in our study support that the AGT CC genotype was associated with the susceptibility of DM developing into DN in the overall population, and the AGT

	DN		DM			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl,	Year	M-H, Fixed, 95% Cl
Doria,1997	9	73	7	79	16.0%	1.45 [0.51, 4.11]	1997	
VAN Ittersum, 2000	21	200	10	100	32.5%	1.06 [0.48, 2.34]	2000	-
Fradin,2002	12	117	5	118	12.2%	2.58 [0.88, 7.58]	2002	—
Prasad,2006	5	196	2	225	4.9%	2.92 [0.56, 15.22]	2006	/
Möllsten, 2008	1	73	5	197	7.3%	0.53 [0.06, 4.64]	2008	
Gallego,2008	5	41	32	411	13.9%	1.64 [0.60, 4.48]	2008	
Ahluwalia,2009	24	240	5	255	11.9%	5.56 [2.08, 14.81]	2009	
Yin,2013	1	152	0	141	1.4%	2.80 [0.11, 69.35]	2013	
Total (95% CI)		1092		1526	100.0%	2.00 [1.35, 2.95]		•
Total events	78		66					
Heterogeneity: Chi ² =	9.06, df =	7 (P =	0.25); l² =	: 23%				
Test for overall effect:	Z = 3.48 ((P = 0.0	005)					Favours DN Favours DM

Figure 2. Association of the AGT CC genotype regarding the risk of DM developing into DN. AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy

	DN		DM			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl,	Year	M-H, Random, 95% Cl
Doria,1997	35	73	47	79	9.3%	0.63 (0.33, 1.19)	1997	
Tomino,1999	128	745	61	407	15.7%	1.18 [0.84, 1.64]	1999	
VAN Ittersum,2000	91	200	37	100	12.0%	1,42 [0.87, 2.33]	2000	+- -
Fradin,2002	74	117	61	118	11.5%	1.61 [0.95, 2.71]	2002	
Prasad,2006	169	196	194	225	10.8%	1.00 [0.57, 1.74]	2006	+
Möllsten, 2008	52	73	136	197	10.2%	1.11 [0.62, 2.00]	2008	- - -
Gallego,2008	15	41	196	411	8.9%	0.63 [0.33, 1.23]	2008	
Ahluwalia,2009	104	240	131	255	15.2%	0.72 [0.51, 1.03]	2009	
Yin,2013	131	152	133	141	6.5%	0.38 [0.16, 0.88]	2013	
T-4-1 (05%) OD		4007		4000	100.00			
Total (95% CI)		1837		1933	100.0%	0.94 [0,72, 1.22]		T
Total events	799		996					
Heterogeneity: Tau ² =	0.08; Chi	i ^z = 18.	23, df = 8	(P = 0.	02); l² = 5	6%		
Test for overall effect:	Z=0.48	(P = 0.6)	(3)					

Figure 3. Association of the AGT AA genotype on the risk of DM developing into DN. AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy

Genetic contrasts	Group and subgroups	studies	Q test (P value)	Model selected	OR (95%CI)	Р
C vs A	Overall	8	0.04	Random	1.18 (0.94, 1.48)	0.15
	Asian	3	0.21	Fixed	1.47 (1.17, 1.85)	0.001
	Caucas	5	0.21	Fixed	1.01 (0.83, 1.23)	0.91
CC vs (AC + AA)	Overall	8	0.25	Fixed	2.00 (1.35, 2.95)	0.0005
	Asian	3	0.77	Fixed	4.63 (2.06, 10.41)	0.0002
	Caucas	5	0.63	Fixed	1.41 (0.89, 2.25)	0.14
AA vs (AC + CC)	Overall	9	0.02	Random	0.94 (0.72, 1.22)	0.63
	Asian	4	0.04	Random	0.83 (0.56, 1.23)	0.35
	Caucas	5	0.07	Random	1.04 (0.71, 1.52)	0.83
TIDN						
C vs A	Overall	4	0.17	Fixed	1.06 (0.85, 1.32)	0.62
CC vs (AC + AA)	Overall	4	0.77	Fixed	1.21 (0.72, 2.04)	0.48
AA vs (AC + CC)	Overall	4	0.12	Fixed	0.96 (0.72, 1.29)	0.80
T2DN					· · · ·	
C vs A	Overall	4	0.05	Random	1.29 (0.89, 1.87)	0.17
CC vs (AC + AA)	Overall	4	0.75	Fixed	3.81 (2.00, 7.25)	<0.0001
AA vs (AC + CC)	Overall	5	0.01	Random	0.94 (0.64, 1.37)	0.74

Table 2. Meta-analysis of the association of AGT AI166C gene polymorphism with risk of DM developing into DN.

AGT: angiotensinogen; Caucas : caucasian; DM: diabetes mellitus; DN: diabetic nephropathy ; vs: versus



Figure 4. Begg's funnel plots with pseudo 95% confidence limits. Evaluation of publication bias for the association of AGT A1166C gene polymorphism with the risk of DM developing into DN.

AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy; logor : loglinear-odds ratio; s.e.: standard error.

C allele and CC genotype were associated with the risk of DM developing into DN in the Asian population. Furthermore, the AGT CC genotype was associated with the susceptibility of T2DM to develop into T2DN in the overall population; however, more case-control association investigations on larger, stratified populations are required to further clarify the role of this AGT A1166C gene polymorphism in the susceptibility of DM developing into DN.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This work was supported by a sub-item of the 985 Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation, grant number 88000-3311300).

References

- Lemes Dos Santos PF, Dos Santos PR, Ferrari GS, et al. Knowledge of diabetes mellitus: Does gender make a difference? Osong Public Health Res Perspect 2014; 5: 199–203.
- Zhou TB, Xu HL and Yin SS. Association between endothelial nitric oxide synthase Glu298Asp gene polymorphism and diabetic nephropathy susceptibility. *Ren Fail* 2013; 35: 173–178.
- 3. Yu ZY, Chen LS, Zhang LC, et al. Meta-analysis of the relationship between ACE I/D gene polymorphism and endstage renal disease in patients with diabetic nephropathy. *Nephrology* 2012; 17: 480–487.
- Hussain H, Ramachandran V, Ravi S, et al. TCF7L2 rs7903146 polymorphism and diabetic nephropathy association is not independent of Type 2 diabetes: A study in a south Indian population and meta-analysis. *Endokrynol Pol* 2014; 65: 298–305.
- 5. Qi Y, Zhang K, Wu Y, et al. Novel mechanism of blood pressure regulation by forkhead box class o1-mediated transcriptional control of hepatic angiotensinogen. *Hypertension* 2014; 64: 1131–1140.

- Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
- Egger M, Davey Smith G, Schneider M, et al. Bias in metaanalysis detected by a simple, graphical test. *Brit Med J* 1997; 315: 629–634.
- Doria A, Onuma T, Warram JH, et al. Synergistic effect of angiotensin II Type 1 receptor genotype and poor glycaemic control on risk of nephropathy in IDDM. *Diabetologia* 1997; 40: 1293–1299.
- Tomino Y, Makita Y, Shike T, et al. Relationship between polymorphism in the angiotensinogen, angiotensin-converting enzyme or angiotensin II receptor and renal progression in Japanese NIDDM patients. *Nephron* 1999; 82: 139–144.
- Van Ittersum FJ, De Man AM, Thijssen S, et al. Genetic polymorphisms of the renin-angiotensin system and complications of insulin-dependent diabetes mellitus. *Nephrol Dial Transplant* 2000; 15: 1000–1007.
- 11. Fradin S, Goulet-Salmon B, Chantepie M, et al. Relationship between polymorphisms in the renin-angiotensin system and nephropathy in Type 2 diabetic patients. *Diab Metab* 2002; 28: 27–32.
- Prasad P, Tiwari AK, Kumar KM, et al. Chronic renal insufficiency among Asian Indians with Type 2 diabetes: I. Role of RAAS gene polymorphisms. *BMC Med Genet* 2006; 7: 42.
- Mollsten A, Kockum I, Svensson M, et al. The effect of polymorphisms in the renin-angiotensin-aldosterone system on diabetic nephropathy risk. *J Diab Complicat* 2008; 22: 377–383.
- Gallego PH, Shephard N, Bulsara MK, et al. Angiotensinogen gene T235 variant: A marker for the development of persistent microalbuminuria in children and adolescents with Type 1 diabetes mellitus. *J Diabetes Complicat* 2008; 22: 191–198.
- Ahluwalia TS, Ahuja M, Rai TS, et al. ACE variants interact with the RAS pathway to confer risk and protection against Type 2 diabetic nephropathy. DNA Cell Biol 2009; 28: 141–150.
- Yin X, Li H, Xuan J, et al. AGTR1 A1166C polymorphism is associated with risk of diabetic nephropathy. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2013; 42: 45–51.

Retraction notice

The following article has been included in a multiple retraction:

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System (JRAAS) 1470320314563424, first published 18 December 2014. DOI: 10.1177/1470320314563424.

This article has been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the JRAAS (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer-review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online-first articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

JRAAS 1470320314563426, first published 18 December 2014. DOI: 10.1177/1470320314563426.

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

JRAAS 1470320314563424, first published 18 December 2014. DOI:10.1177/1470320314563424.

Weiqiang Zhong, Zongpei Jiang and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

JRAAS1470320314566019, first published 26 January 2015. DOI: 10.1177/1470320314566019.

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

JRAAS 1470320314563425, first published 1 February 2015. DOI:10.1177/1470320314563425.

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

JRAAS 1470320314566221, first published 1 February 2015. DOI: 10.1177/1470320314566221.

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

JRAAS 1470320314568521, first published 3 February 2015. DOI: 10.1177/1470320314568521.

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

JRAAS March 2015; 16: 165-171, first published 14 November 2014. DOI: 10.1177/1470320314557849.

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

JRAAS September 2015; 16: 660–665, first published 20 August 2014. DOI: 10.1177/1470320314524011.



Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Aldosterone System 2015, Vol. 16(4) NP11 © The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314563424

jra.sagepub.com **SAGE**

Journal of the Renin-Angiotensin-

RETRACTED: Role of renin-angiotensinaldosterone system inhibitors in radiation nephropathy

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP12–NP17 © The Author(s) 2014 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314563424 jra.sagepub.com

(S)SAGE

Tian-Biao Zhou¹, Hong-Yan Li², Zong-Pei Jiang¹, Jia-Fan Zhou¹, Miao-Fang Huang¹ and Zhi-Yang Zhou³

Abstract

Background and objective: The purpose of this study is to explore the effects of renin-angiotensin-aldosterone system (RAAS) inhibitors in radiation nephropathy (RD) diseases.

Method: Studies including randomized studies comparing treatment with RAAS inhibitors versus without RAAS inhibitors in patients/animals with RD disease were identified using a predefined search strategy. Data of blood urea nitrogen (BUN), serum creatinine (Scr), blood pressure (BP), ratio of urine protein to urine creatinine (UP/UC), and time to develop renal failure (TDRF) were extracted and compared by RevMan 5.1 (The Cochrane Collaboration, Oxford, UK).

Results: Seven studies were identified, and all the studies were conducted in rats. Meta-analysis showed that RAAS inhibitors treatment resulted in lower levels of BUN, Scr, BP, UP/UC when compared to treatment without RAAS inhibitors, and RAAS inhibitors resulted in a longer TDRF for RD rats.

Conclusions: RAAS inhibitors treatment might achieve a protective role in RD diseases. However, more well-designed, randomized, controlled trails should be performed to confirm it in the future.

Keywords

Radiation nephropathy (RD), renin-angiotensin-aldosterone system (RAAS) inhibitors, BUN, Scr, meta-analysis

Introduction

Radiation nephropathy (RD) occurs reliably after sufficient exposure of kidneys to ionizing radiation, and singlefraction total-body irradiation (TBI) of 10 Gy will cause radiation nephropathy in humans and in rats within six months after TBI.¹ Proteinuria, azotemia and hypertension are the main characteristics of RD. RD has emerged as a significant complication of hematopoietic stem cell transplantation when TBI is used in the conditioning regimen, and after internal radionuclide cancer therapy in current medical practice, and is a potential sequela of radiological terrorism and radiation accidents.^{1,2}

The renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathogenesis and progression of chronic kidney disease. Activation of the intra-renal RAAS contributes to glomerular hypertrophy, mesangial expansion and glomerulosclerosis in various renal diseases. Previous clinical and experimental studies have demonstrated that inhibition of the RAAS using angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) results in the reduction of proteinuria and retards progression of renal disease in addition to lowering blood pressure.³

Currently available evidence indicates that RAAS inhibitors might play a protective role in RD. However, the available evidence is weak owing to sparseness of data or disagreements among the reported investigations. The

²Department of Nephrology, Huadu District People's Hospital, Southern Medical University, China

³Department of Radiology, the Sixth Affiliated Hospital, Sun Yat-Sen University, China

T.B.Z. and H.Y.L. contributed equally to this work.

Corresponding author:

Zhi-Yang Zhou, Department of Radiology, the Sixth Affiliated Hospital, Sun Yat-Sen University, Yuancun Erheng Road No.26, Guangzhou, 510655, China. Email: zhiyangzhou@yeah.net

Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (http://www.uk.sagepub.com/aboutus/openaccess.htm).

Department of Nephrology, the Sixth Affiliated Hospital, Sun Yat-Sen University, China

Author, year	Age/weight of rats	Dose of radiation	RAAS inhibitors	Outcome	Reference (PMID)
Cohen, 1992⁴	26 weeks old	15–27 Gy	Captopril	BUN	1475357
Moulder, 1993 ⁵	7 to 9 weeks old	14–18.5 Gy	Captopril	BUN, Scr, BP, UP/UC	8278583
Juncos, 1 993 6	150–200 g	NC	Enalapril	Scr, BP	8321359
Moulder, 1993 ⁷	5 to 26 weeks old	17–27 Gy	Captopril, enalapril	BUN, Scr, UP/UC	8365947
Cohen, 1 996 ⁸	5 to 7 weeks old	I7 Gy	Captopril	BUN, BP, UP/UC	8804358
Moulder, 1998 ⁹	15 weeks old	26 Gy	Captopril	BUN, BP, UP/UC	9806595
Moulder, 2007 ¹⁰	NC	18.5 Gy	Captopril, ATI blocker (L-158,809), AT2 blocker (PD123319)	BUN, BP, UP/UC, TDRF	17506717

Table I. The detailed characteristics of included studies.

BUN: blood urea nitrogen; Scr: serum creatinine; BP: blood pressure; UP/UC: ratio of urine protein to urine creatinine; TDRF: time to develop renal failure; NC: not clear.

evidence from meta-analysis might be powerful compared with individual investigations. This study was performed to assess the role of RAAS inhibitors in RD using the meta-analysis method.

Materials and methods

Search strategy

The relevant studies were screened from the search engines of PubMed, Embase, and Cochrane Library as of June 31, 2014. The search terms "(renin-angiotensin-aldosterone system OR RAAS OR angiotensin-converting enzyme inhibitor OR ACEI OR angiotensin type 1 OR AT1 OR angiotensin type 2 OR AT2) AND (radiation nephropathy)" were used in PubMed, Embase, and Cochrane Library without language limitation. We also extended the search spectrum to the "related articles" and the bibliographies of all retrieved studies. If multiple publications from the same study group occurred, we recruited only the most complete paper for analysis.

Inclusion and exclusion criteria

Inclusion criteria. The inclusion criteria for the study are given below: (1) Study type: randomized, controlled study, including RAAS inhibitors + RD group (RAAS group) vs RD group. (2) Object of the study met the diagnostic criteria for RD. (3) Interventions: using ACEI, AT1 or AT2 for treatment. (4) Baseline information: comparable.

Exclusion criteria. The exclusion criteria for the study are given below: (1) used only ACEI, AT1 or AT2 for the treatment. (2) The data were not clear.

Outcome measures

Blood urea nitrogen (BUN), serum creatinine (Scr), blood pressure (BP), ratio of urine protein to urine creatinine (UP/UC), and time to develop renal failure (TDRF) were used for the outcome measures.

Data collection

Method of agreeing on inclusion of studies was performed by two observers independently according to predetermined inclusion criteria. Titles and abstracts were scanned first to make a list of possibly related literature, and then full texts were obtained for those articles identified as either relevant or not clear; only randomized, controlled study fitting predefined inclusion criteria were included. Disagreements were resolved by other reviewers.

Statistical analysis

Statistical analysis was performed by RevMan 5.1. The pooled statistics were calculated using the fixed-effects model, but a random-effects model was conducted if the p value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data and weighted mean differences (WMD) for continuous data, and 95% confidence intervals (CI) were also counted. Heterogeneity between included studies was tested using the X²-test.

Results

Search results

In this meta-analysis, seven studies^{4–10} were included (Table 1). All the studies were conducted in rats, and there was no clinical trial.

BUN level between RAAS inhibitors group and RD group

Six reports^{4,5,7–10} including 20 comparisons were included in this meta-analysis for the BUN level between the RAAS inhibitors group and the RD group. The *p* value of heterogeneity test was less than 0.00001 and a random-effects model was conducted. The pooled mean difference was -38.80 (95% CI: -50.43 to -27.16). The difference in

		Case		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Cohen 1992a	14	5	15	33	28	18	7.1%	-19.00 [-32.18, -5.82]	
Cohen 1992b	29	15	18	27	10	20	7.5%	2.00 [-6.20, 10.20]	+
Cohen 1992c	46	19	14	98	80	4	1.7%	-52.00 [-131.03, 27.03]	← / /
Cohen 1996a	60	16	5	94	47	5	3.7%	-34.00 [-77.52, 9.52]	
Cohen 1996b	61	6	5	94	47	5	3.9%	-33.00 [-74.53, 8.53]	
Cohen 1996c	44	6	5	94	47	5	3.9%	-50.00 [-91.53, -8.47]	
Cohen 1996d	38	5	5	94	47	5	3.9%	-56.00 [-97.43, -14.57]	
Moulder 1993a	29	3	11	44	5.5	11	7.7%	-15.00 [-18.70, -11.30]	-
Moulder 1993b	38	7.5	11	131	57	10	4.5%	-93.00 [-128.61, -57.39]	←
Moulder 1993c	47	13.5	19	47	12	18	7.5%	0.00 [-8.22, 8.22]	+
Moulder 1993d	46	12.5	19	47	12	18	7.5%	-1.00 [-8.89, 6.89]	+
Moulder 1998a	26	2.5	16	122	33	12	6.5%	-96.00 [-114.71, -77,29]	→
Moulder 1998b	86	16.5	15	122	33	12	6.3%	-36.00 [-56.45, -15.55]	
Moulder 2007a	80	7.5	7	190	85.5	7	2.3%	-110.00 [-173.58, -46.42]	←
Moulder 2007b	71	25.5	7	190	85.5	7	2.2%	-119.00 [-185.10, -52.90]	←
Moulder 2007c	64	3	7	190	85.5	7	2.4%	-126.00 [-189.38, -62.62]	
Moulder 2007d	59	22.5	7	190	85.5	7	2.2%	-131.00 [-196.49, -65.51]	
Moulder 2007e	41	13.5	12	74	29	12	6.5%	-33.00 [-51.10, -14.90]	/
Moulder 2007f	58	21.5	12	74	29	12	6.3%	-16.00 [-36.43, 4.43]	
Moulder 2007g	45	12.5	11	74	29	12	6.5%	-29.00 [-46.99, -11.01]	
Total (95% CI)			221			207	100.0%	-38.80 [-50.43, -27.16]	•
Heterogeneity: Tau ² =	= 454.68;	Chi ² =	= 192.9	6. df = 1	9 (P <	0.0000	$(1): ^2 = 90$	1%	
Test for overall effect	Z = 6.53	(P < 1	1.00001	0	- •				-100 -50 0 50 10

Figure 1. Blood urea nitrogen (BUN) level between the RAAS inhibitors group and the RD group. RAAS: renin-angiotensin-aldosterone system; RD: radiation nephropathy.

		Case		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Juncos 1993a	0.75	0.01	6	0.78	0.1	5	17.9%	40.03 [-0.12, 0.06]	+
Juncos 1993b	0.87	0.07	5	1.18	0.05	5	18.2%	-0.31 [-0.39, -0.23]	•
Moulder 1993a	0.39	0.04	11	0.53	0.12	11	18.2%	-0.14 [-0.21, -0.07]	+
Moulder 1993b	0.44	0.09	11	1.36	0.45	10	11.2%	-0.92 [-1.20, -0.64]	1
Moulder 1993c	0.5	0.14	19	0.5	-0.2	18	17.2%	0.00 [-0.11, 0.11]	+
Moulder 1993d	0.47	0.13	19	0.5	0.2	18	17.3%	-0.03 [-0.14, 0.08]	t
lotal (95% CI)			71			67	100.0%	-0.20 [-0.34, -0.05]	
Heterogeneity: Tau ² :	= 0.03: C	hi ² = 6	4.29. df	= 5 (P	< 0.000	001); I ^a	= 92%		

Figure 2. Serum creatinine (Scr) level between the RAAS inhibitors group and the RD group. RAAS: renin-angiotensin-aldosterone system; RD: radiation nephropathy.

BUN level was statistically significant between the RAAS inhibitors group and the RD group (p < 0.00001; Figure 1).

Scr level between RAAS inhibitors group and RD group

Three reports^{5–7} including six comparisons were included in this meta-analysis of the Scr level between the RAAS inhibitors group and the RD group. The *p* value of heterogeneity test was less than 0.00001 and a random-effects model was conducted. The pooled mean difference was -0.20 (95% CI: -0.34 to -0.05). The difference in Scr level was statistically significant between the RAAS inhibitors group and the RD group (p = 0.01; Figure 2).

Ratio of UP/UC between RAAS inhibitors group and RD group

Five reports^{5,7–10} including 17 comparisons were included in this meta-analysis of the UP/UC between the RAAS inhibitors group and the RD group. The *p* value of heterogeneity test was less than 0.00001 and a random-effects model was conducted. The pooled mean difference was -7.70 (95% CI: -11.03 to -4.36). The difference in UP/UC

	(Case		С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Cohen 1996a	18	2	5	18	4	5	6.0%	0.00 [-3.92, 3.92]	
Cohen 1996b	18	3	5	18	4	5	5.9%	0.00 [-4.38, 4.38]	+
Cohen 1996c	8	6	5	18	4	5	5.3%	-10.00 [-16.32, -3.68]	-
Cohen 1996d	2	1	5	18	4	5	6.1%	-16.00 [-19.61, -12.39]	
Moulder 1993a	1.63	0.27	11	16.6	3.4	11	6.4%	-14.97 [-16.99, -12.95]	•
Moulder 1993b	2.45	1.2	11	24.9	13.7	10	4.6%	-22.45 [-30.97, -13.93]	
Moulder 1993c	23.5	6.5	19	26.1	6.5	18	5.9%	-2.60 [-6.79, 1.59]	
Moulder 1993d	25.2	14.5	19	26.1	6.5	18	5.0%	-0.90 [-8.08, 6.28]	
Moulder 1998a	0.9	0.2	16	20	9.5	12	5.6%	-19.10 [-24.48, -13.72]	-
Moulder 1998b	17	13.5	15	20	9.5	12	4.5%	-3.00 [-11.69, 5.69]	
Moulder 2007a	6	1	7	19	2.5	7	6.4%	-13.00 [-14.99, -11.01]	7
Moulder 2007b	9	2	7	19	2.5	7	6.3%	-10.00 [-12.37, -7.63]	~-
Moulder 2007c	13	3	7	19	2.5	7	6.3%	-6.00 [-8.89, -3.11]	-
Moulder 2007d	8	2	7	19	2.5	7	6.3%	-11.00 [-13.37, -8.63]	•
Moulder 2007e	13	4	12	18	2	12	6.3%	-5.00 [-7.53, -2.47]	•
Moulder 2007f	18	2	12	18	2	12	6.5%	0.00 [-1.60, 1.60]	†
Moulder 2007g	19	2.5	11	18	2	12	6.4%	1.00 [-0.86, 2.86]	t t
									//
Total (95% CI)			174			165	100.0%	-7.70 [-11.03, -4.36]	•
Heterogeneity: Tau ² =	: 44.11; (Chi² =	345.25	, df = 16	(P < 0	0.00001); l² = 959	8	-100 -50 0 50 100
Test for overall effect:	Z = 4.52	? (P < (0.00001	0					Favours case Favours control

Figure 3. Ratio of urine protein to urine creatinine (UP/UC) between the RAAS inhibitors group and the RD group. RAAS: renin-angiotensin-aldosterone system; RD: radiation nephropathy.

	(Case		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Cohen 1996a	171	13	5	175	16	5	5.2%	-4.00 [-22.07, 14.07]	
Cohen 1996b	165	17	5	175	16	5	4.9%	-10.00 [-30.46, 10.46]	
Cohen 1996c	154	18	5	175	16	5	4.9%	-21.00 [-42.11, 0.11]	
Cohen 1996d	137	9	5	175	16	5	5.4%	-38.00 [-54.09, -21.91]	_ _
Juncos 1993a	66.7	5.4	6	128	7.3	5	6.2%	261.30 [-69.02, -53.58]	-
Juncos 1993b	90	4	5	152	8.6	5	6.2%	-62.00 [-70.31, -53.69]	
Moulder 1993a	137	17.5	11	179	21.5	11	5.4%	-42.00 [-58.38, -25.62]	
Moulder 1993b	124	17	11	199	13	10	5.8%	-75.00 [-87.88, -62.12]	
Moulder 1998a	110	4.5	16	161	10	12	6.3%	-51.00 [-57.07, -44.93]	+
Moulder 1998b	153	13	15	161	10	12	6.1%	-8.00 [-16.68, 0.68]	
Moulder 2007a	152	7.5	7	180	7.5	7	6.2%	-28.00 [-35.86, -20.14]	
Moulder 2007b	144	5.5	7	180	7.5	7	6.3%	-36.00 [-42.89, -29.11]	-
Moulder 2007c	139	7.5	7	180	7.5	7	6.2%	-41.00 [-48.86, -33.14]	
Moulder 2007d	150	15	7	180	7.5	7	5.8%	-30.00 [-42.42, -17.58]	
Moulder 2007e	151	6.5	12	181	7	12	6.3%	-30.00 [-35.40, -24.60]	-
Moulder 2007f	172	5.5	12	181	7	12	6.4%	-9.00 [-14.04, -3.96]	-
Moulder 2007a	153	9.5	11	181	7	12	6.3%	-28.00 [-34.87, -21.13]	-
-									
Total (95% CI)			147			139	100.0%	-34.26 [-43.61, -24.91]	◆
Heterogeneity: Tau ² =	= 350.89;	Chi ² =	319.0	6. df = 1	6 (P <	0.0000	1); I ² = 95	5%	
Test for overall effect	Z=7.18) (P < (0.00001)	- •				-100 -50 0 50 10 Favours case Favours control

Figure 4. Blood pressure (BP) level between the RAAS inhibitors group and the RD group. RAAS: renin-angiotensin-aldosterone system; RD: radiation nephropathy.

level was statistically significant between the RAAS inhibitors group and the RD group (p < 0.00001; Figure 3).

BP level between RAAS inhibitors group and RD group

Five reports^{5,6,8–10} including six comparisons were included in this meta-analysis of the BP level between the RAAS inhibitors group and the RD group. The p value of heterogeneity test was less than 0.00001 and a random-effects model was conducted. The pooled mean difference was -34.26 (95% CI: -43.61 to -24.91). The difference in BP level was statistically significant between the RAAS inhibitors group and the RD group (p < 0.00001; Figure 4).

TDRF between RAAS inhibitors group and RD group

One report¹⁰ including seven comparisons were included in this meta-analysis for the TDRF between the RAAS inhibitors group and the RD group. The p value of heterogeneity test was 0.16 and a random-effects model was

	(Case		Co	ontro	I		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CL
Moulder 2007a	38	7.5	7	21	8	7	15.2%	17.00 [8.88, 25.12]	· · · · · · · · · · · · · · · · · · ·
Moulder 2007b	36	9.5	7	21	8	7	11.9%	15.00 [5.80, 24.20]	+
Moulder 2007c	42	12	7	21	8	7	8.8%	21.00 [10.32, 31.68]	- /
Moulder 2007d	34	21.5	7	21	8	7	3.5%	13.00 [-3.99, 29.99]	
Moulder 2007e	28	12	12	22	7.5	12	15.7%	6.00 [-2.01, 14.01]	
Moulder 2007f	30	8	12	22	7.5	12	26.1%	8.00 [1.80, 14.20]	
Moulder 2007g	30	10	11	22	7.5	12	19.0%	8.00 [0.72, 15.28]	
Total (95% CI)			63			64	100.0%	11.20 [8.03, 14.37]	
Heterogeneity: Chi ² =	= 9.27, df	= 6 (P	= 0.16)); l ² = 35	%				
Test for overall effect:	: Z = 6.93	(P < 0	0.00001	0					-100 -50 0 50 100
		-							Favours case Favours control

Figure 5. Time to develop renal failure (TDRF) between RAAS inhibitors group and RD group. RAAS: renin-angiotensin-aldosterone system; RD: radiation nephropathy.

conducted. The pooled mean difference was 11.20 (95% CI: 8.03 to 14.37). The difference in TDRF was statistically significant between the RAAS inhibitors group and the RD group (p < 0.00001; Figure 5).

Discussion

In this meta-analysis, the difference in BUN level between the RAAS inhibitors group and the RD group was significant, and the pooled mean difference was -38.80. It indicated that the RAAS inhibitors group could achieve a lower BUN level than the RD group. When the fixedmodel was chosen, we also found the result was similar to this. It indicated that using the RAAS inhibitors in rats with RD might achieve a better benefit.

The Scr level between the RAAS inhibitors group and the RD group was also assessed. In this study, we found that the pooled mean difference was -0.20. It indicated that RAAS inhibitors treatment might obtain a lower Scr than in RD rats without treatment. When the fixed-model was used to assess this relationship, it also showed that RAAS treatment might get a lower Scr level when compared with without treatment.

The ratio of UP/UC between the RAAS inhibitors group and the RD group in this meta-analysis was also detected, and we found that the pooled mean difference was -7.70. It indicated that RAAS inhibitors treatment might achieve a lower UP/UC.

Increased BP level was one of the most important risk factors for the RD patients. In this meta-analysis, we found that the RAAS inhibitors treatment could obtain a lower BP level than those without treatment, and the pooled mean difference was -34.26.

In this meta-analysis, TDRF between the RAAS inhibitors group and the RD group was also detected. The pooled mean difference was 11.20, and the difference of TDRF between the RAAS inhibitors group and RD group was significant. It indicated that the RAAS inhibitors could achieve a longer TDRF. As those mentioned above, we might draw a conclusion that RAAS inhibitors treatment in RD rats might achieve more benefit when compared to those without treatment, such as lowers level of BUN, Scr, UP/UC, BP, and RAAS treatment could achieve a longer TDRF than without RAAS treatment.

In conclusion, the evidence in this meta-analysis indicates that RAAS inhibitors could get a protective role in rats with RD. However, more well-designed, randomized, controlled trails should be performed to confirm it in the future.

Conflict of interest

None declared.

Funding

This study was supported by the Nature Science Foundation of China (no. 81400719), the sub-item of 985 Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation; No. 88000-3311300), Department of Social Development and Basic Research Project of Guangdong Provincial Science and Technology (2011A030400003) and Cooperative Technology Innovation Platform Project (2012B090600044).

References

- Cohen EP, Fish BL and Moulder JE. Mitigation of radiation injuries via suppression of the renin-angiotensin system: Emphasis on radiation nephropathy. *Curr Drug Targets* 2010; 11: 1423–1429.
- Liu DG and Wang TM. Role of connective tissue growth factor in experimental radiation nephropathy in rats. *Chin Med J (Engl)* 2008; 121: 1925–1931.
- Lee JH, Kwon YE, Park JT, et al. The effect of renin-angiotensin system blockade on renal protection in chronic kidney disease patients with hyperkalemia. *J Renin Angiotensin Aldosterone Syst*. Epub ahead of print 20 August 2014. DOI: 10.1177/1470320313507122.
- Cohen EP, Fish BL and Moulder JE. Treatment of radiation nephropathy with captopril. *Radiat Res* 1992; 132: 346–350.

- Moulder JE, Cohen EP, Fish BL, et al. Prophylaxis of bone marrow transplant nephropathy with captopril, an inhibitor of angiotensin-converting enzyme. *Radiat Res* 1993; 136: 404–407.
- Juncos LI, Carrasco Dueñas S, Cornejo JC, et al. Long-term enalapril and hydrochlorothiazide in radiation nephritis. *Nephron* 1993; 64: 249–255.
- Moulder JE, Fish BL and Cohen EP. Treatment of radiation nephropathy with ACE inhibitors. *Int J Radiat Oncol Biol Phys* 1993; 27: 93–99.
- Cohen EP, Molteni A, Hill P, et al. Captopril preserves function and ultrastructure in experimental radiation nephropathy. *Lab Invest* 1996; 75: 349–360.
- 9. Moulder JE, Fish BL and Cohen EP. Brief pharmacological intervention in experimental radiation nephropathy. *Radiat Res* 1998; 150: 535–541.
- Moulder JE, Fish BL and Cohen EP. Treatment of radiation nephropathy with ACE inhibitors and AII type-1 and type-2 receptor antagonists. *Curr Pharm Des* 2007; 13: 1317–1325.

Retraction notice

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP18 © The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314563425 jra.sagepub.com SAGE

The following article has been included in a multiple retraction:

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

This article has been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System (JRAAS)* (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System September 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011

Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

<u>jraas</u>

RETRACTED: Relationship between the ACE I/D gene polymorphism and TIDN susceptibility/risk of TIDM developing into TIDN in the Caucasian population

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP19-NP26 © The Author(s) 2014 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314563425 jra.sagepub.com

(S)SAGE

Tian-Biao Zhou¹, Xue-Feng Guo², Zongpei Jiang¹ and Hong-Yan Li³

Abstract

Background and objective: The relationship between the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism and type I diabetic nephropathy (TIDN) susceptibility/risk of type I diabetes mellitus (TIDM) developing into TIDN in the Caucasian population is still controversial. This study was performed to evaluate the association of the ACE I/D gene polymorphism with TIDN susceptibility and the risk of TIDM developing into TIDN in the Caucasian population.

Method: A predefined literature search and selection of eligible relevant studies were performed to collect data from electronic databases.

Results: Twenty-one articles were identified for the analysis of the association of the ACE I/D gene polymorphism with TIDN susceptibility and the risk of TIDM developing into TIDN in the Caucasian population. The ACE I/D gene polymorphism was not associated with TIDN susceptibility and the risk of patients with TIDM developing TIDN in the Caucasian population. Sensitivity analysis according to a sample size of cases (< 100 vs \geq 100) was also performed, and the results were also similar with the non-sensitivity analysis.

Conclusions: The ACE I/D gene polymorphism was not associated with TIDN susceptibility and the risk of patients with TIDM developing TIDN in the Caucasian population. However, more studies should be performed in the future.

Keywords

Type I diabetic nephropathy (TIDN), type I diabetes mellitus (TIDM), angiotensin-converting enzyme (ACE), insertion/deletion (I/D) gene polymorphism, meta-analysis

Introduction

Diabetes mellitus is a multifactorial metabolic disease characterized by post-prandial hyperglycemia, and it is associated with significant morbidity and mortality and its prevalence is increasing worldwide.^{1,2} Diabetes mellitus includes type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), and the incidence of diabetes mellitus has increased dramatically over the last several decades.³ Diabetic nephropathy (DN) is a serious complication of diabetes mellitus, and it includes type 1 diabetic nephropathy (T1DN) due to T1DM and type-2 diabetic nephropathy (T2DN) due to T2DM.^{3,4} DN as a cause of end-stage renal disease (ESRD) is associated with a poor life expectancy, causing serious socioeconomic problems.⁵ The angiotensin-converting enzyme gene (ACE) is directly involved in the process of cell proliferation,

²Department of Colorectal Surgery, the Sixth Affiliated Hospital, Sun Yat-Sen University, China

³Department of Nephrology, Huadu District People's Hospital, Southern Medical University, China

T.B.Z. and X.F.G. contributed equally to this manuscript.

Corresponding author:

Hong-Yan Li, Department of Nephrology, Huadu District People's Hospital, Southern Medical University, Baohua Road No. 22, Guangzhou, China. Email: hongyli@yeah.net

Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (http://www.uk.sagepub.com/aboutus/openaccess.htm).

¹Department of Nephrology, the Sixth Affiliated Hospital, Sun Yat-Sen University, China

differentiation, apoptosis and angiogenesis.⁶ ACE can convert angiotensin I into angiotensin II, and inactivate bradykinin via the kallikrein-kininogen system, and angiotensin II is the main effector molecule of the reninangiotensin system, is pleiotropic, and is a mediator of the development and progression of diseases.⁷ The ACE insertion/deletion (I/D) gene polymorphism is a 287-bp sequence of DNA in the intron 16 of the ACE gene.⁸ The ACE gene consists of either an insertion (I) allele or a deletion (D) allele that form three possible genotypes: II, ID or DD.⁹ In adults plasma ACE does not change with age and is only to a minor extent influenced by environmental or lifestyle factors.8 When compared with II homozygotes, circulating ACE levels in plasma were nearly 30% and 60% higher in ID heterozygotes and DD homozygotes, respectively.9 Moreover, DD homozygotes also have been associated with higher tissue levels of ACE. The ACE I/D gene polymorphism, correlating with circulating ACE concentration, might be implicated in the etiology of T1DN and has been investigated in numerous epidemiologic studies.

The present epidemiologic studies show that the *ACE* I/D gene polymorphism has been implicated in the etiology of T1DN and the risk of patients with T1DM developing T1DN. However, the available evidence reported to date is weak, owing to sparseness of data or disagreements among studies. We performed this meta-analysis to investigate the relation between the *ACE* I/D gene polymorphism and T1DN susceptibility and the risk of patients with T1DM developing T1DN in the Caucasian population, with the intention of providing a much more reliable finding on the significance of the association.

Materials and methods

Search strategy

The relevant studies were searched from the electronic databases of PubMed and Cochrane Library on March 1, 2014. The terms "(diabetic nephropathy) AND (angiotensin converting enzyme) AND (polymorphism OR variant)" were entered into PubMed and Cochrane Library for the search. The search in PubMed was limited to studies of humans written in the English language. We also extended the search spectrum to "related articles" and the bibliographies of all recruited studies. If multiple publications from the same study group occurred, we recruited only the most complete paper for our analysis.

Inclusion and exclusion criteria

Inclusion criteria. (1) A case-control study; (2) the outcome had to be T1DN; (3) there had to be at least two comparison groups (T1DN group vs control group); (4) the study should

be conducted in the Caucasian population.

Exclusion criteria. (1) Review articles, editorials and case reports; (2) articles did not provide the detailed genotype data; (3) investigating the association of other genes with T1DN; (4) investigating the role of *ACE* in diseases; (5) multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study independently by two investigators: first author's surname, year of publication, ethnicity of the study population, and the number of cases and controls for the *ACE* I/D genotype. Frequencies of the D allele were calculated for the case group and the control group from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data were entered into Cochrane Review Manager (RevMan, version 5, Oxford, UK) and analyzed. The pooled statistics were counted using the fixed-effects model, but a random-effects model was conducted when the *p* value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. p < 0.05 was required for the overall OR to be deemed statistically significant. I^2 was used to test the heterogeneity between the included studies. Sensitivity analysis was performed according to sample size of case (< 100 vs \geq 100). The Begg adjusted rank correlation test¹⁰ and the Egger regression asymmetry test¹¹ were used for exploring publication bias (p < 0.1 was considered significant).

Results

Study characteristics

The search yielded 261 references, 260 from PubMed, and one from Cochrane Library. According to the inclusion and exclusion criteria, 21 articles were identified for the analysis between the *ACE* I/D gene polymorphism and T1DN susceptibility and the risk of T1DM developing into T1DN in the Caucasian population in our review. Six studies^{12–17} were conducted on the relationship between the *ACE* I/D gene polymorphism and T1DN susceptibility (Table 1), and 21 reports^{12–32} were conducted on the relationship between the *ACE* I/D gene polymorphism and the susceptibility of T1DM developing into T1DN (Table 2).

NP21

First author, year	TIDN	1				Contr	rol					
· · · · · · · · , , · · ·	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total (allele)
Powrie, 1994	7	8	4	19	22	38	112	168	84	364	392	728
Schmidt, 1995	52	38	24	114	142	228	49	63	22	134	161	268
Chowdhury, 1996	78	124	40	242	280	484	58	91	38	187	207	374
Demurov, 1997	24	29	3	56	77	112	40	43	13	96	123	192
Pfohl, 1998	17	15	8	40	49	80	46	90	43	179	182	358
De Cosmo, 1999	73	79	23	175	225	350	86	88	26	200	260	400

Table I. Characteristics of the studies evaluating the effects of the ACE I/D gene polymorphism on TIDN risk.

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; TIDN: type I diabetic nephropathy.

Table 2. Characteristics of the studies evaluating the effects of ACE I/D gene polymorphism on TIDM developing into TIDN.

First author, year	TIDN	TIDN TIDM												
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total (allele)		
Powrie, 1994	7	8	4	19	22	38	24	37	24	85	85	170		
Doria, 1994	78	19	51	148	175	296	87	7	60	154	181	308		
Tarnow, 1995	63	95	40	198	221	396	67	77	46	190	211	380		
Schmidt, 1995	52	38	24	114	142	228	55	55	23	133	165	266		
Chowdhury, 1996	78	124	40	242	280	484	55	79	32	166	189	332		
Hibberd, 1997	21	42	9	72	84	144	16	43	27	86	75	172		
Ringel, 1997	35	68	31	134	138	268	57	130	39	226	244	452		
Barnas, 1997	4	21	15	40	29	80	14	27	9	50	55	100		
Marre, 1997	119	168	50	337	406	674	48	69	40	157	165	314		
Demurov, 1997	24	29	3	56	77	112	24	32	20	76	80	152		
Pfohl, 1998	17	15	8	40	49	80	15	18	7	40	48	80		
Freire, 1998	33	32	12	77	98	154	34	45	10	89	113	178		
Bouhanick, 1999	4	20	5	29	28	58	19	19	9	47	57	94		
De Cosmo, 1999	73	79	23	175	225	350	65	53	18	136	183	272		
Vleming, 1999	39	24	16	79	102	158	26	34	22	82	86	164		
van Ittersum, 2000	40	94	66	200	174	400	26	46	28	100	98	200		
Hadjadj, 2007	-	-	_	-	990	2084	-	-	-	-	1208	2246		
Möllsten, 2008	16	45	12	73	77	146	48	113	36	197	209	394		
Gallego, 2008	15	17	9	41	47	82	102	204	103	409	408	818		
Currie, 2010	211	335	134	680	757	1360	186	392	152	730	764	1460		
llić, 2014	10	23	13	46	43	92	10	12	11	33	32	66		

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; TIDM: type I diabetes mellitus; TIDN: type I diabetic nephropathy.

Association of the ACE I/D gene polymorphism with TIDN risk

In this meta-analysis, the *ACE* I/D gene polymorphism was not associated with T1DN risk in the Caucasian population (D allele: OR = 1.12, 95% CI: 0.96–1.30, p = 0.16; DD genotype: OR = 1.17, 95% CI: 0.94–1.45, p = 0.16; II genotype: OR = 0.89, 95% CI: 0.67–1.18, p = 0.42; Figure 1 and Table 3).

Sensitivity analysis for the relationship between the *ACE* I/D gene polymorphism and T1DN risk in the Caucasian population was also performed according to

sample size of case (< 100 vs \ge 100). We found that the results were also similar with the non-sensitivity analysis. The *ACE* I/D gene polymorphism was not associated with T1DN risk in the Caucasian population (Table 3).

Association of ACE I/D gene polymorphism with the risk of TIDM patients developing TIDN

In this meta-analysis, the ACE I/D gene polymorphism was also not associated with the risk of T1DM patients developing T1DN in the Caucasian population (D allele: OR =

D vs I								
	T1DN	N N	Contr	ol		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Powrie 1994	22	38	392	728	5.3%	1.18 [0.61, 2.28]	1994	
Schmidt 1995	142	228	161	268	17.9%	1.10 (0.76, 1.58)	1995	+ /
Chowdhury 1996	280	484	207	374	31.6%	1.11 [0.84, 1.45]	1996	▶ +
Demurov 1997	77	112	123	192	9.1%	1.23 [0.75, 2.03]	1997	
Pfohl 1998	49	80	182	358	8.3%	1.53 [0.93, 2.51]	1998	
De Cosmo 1999	225	350	260	400	27.8%	0.97 [0.72, 1.31]	1999	+
Total (95% CI)		1292		2320	100.0%	1.12 [0.96, 1.30]		
Total events	795		1325					
Heterogeneity: Chi ² =	2.59, df =	5 (P =	0.76); l ^z :	= 0%				
Test for overall effect:	Z=1.42 (P = 0.1	6)					70.01 0.1 1 10 100
								Favors ITDN Favors control
DD vs ID+II								
DD VOID II	T1DM	u l	Contr	ol		Odds Ratio		Odds Ratio
Study or Subaroup	Events	- Total	Events	Total	Weight	M-H. Fixed. 95% Cl	Year	M-H. Fixed, 95% Cl
Powrie 1994	7	19	112	364	4.7%	1.31 [0.50, 3.42]	1994	
Schmidt 1995	52	114	49	134	16.4%	1.45 [0.872.42]	1995	
Chowdhury 1996	78	242	58	187	29.7%	1.06 (0.70, 1.60)	1996	+
Demurov 1997	24	56	40	96	11.3%	1.05 [0.54, 2.05]	1997	、 +
Pfohl 1998	17	40	46	179	6.5%	2.14 [1.05, 4.35]	1998	
De Cosmo 1999	73	175	86	200	31.4%	0.95 [0.63, 1.43]	1999) +
Total (95% CI)		646		1160	100.0%	1.17 [0.94, 1.45]		∕ ♦
Total events	251		391					
Heterogeneity: Chi ² =	4.85, df =	5 (P =	0.43); l² :	= 0%				
Test for overall effect:	Z=1.41 (P = 0.1	6)					Eavere T1DN Eavere control
								Favors IIDN Favors control
II vs ID+DD								
	T1DN	N N	Contr	ol		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Powrie 1994	4	19	84	364	6.5%	0.89 [0.29, 2.75]	1994	
Schmidt 1995	24	114	22	134	15.8%	1.36 [0.71, 2.58]	1995	
Chowdhury 1996	40	242	38	187	35.4%	0.78 [0.47, 1.27]	1996	
Demurov 1997	3	56	13	96	9.0%	0.36 [0.10, 1.33]	1997	
Pfohl 1998	8	40	43	179	12.4%	0.79 [0.34, 1.84]	1998	
De Cosmo 1999	23	175	26	200	20.9%	1.01 [0.55, 1.85]	1999	
Total (95% CI)		646		1160	100.0%	0.89 [0.67, 1.18]		•
Total events	102		226					
Heterogeneity: Chi ² =	4.05, df=	5 (P =	0.54); l² =	= 0%				
Test for overall effect:	Z=0.81 (P = 0.4	2)		7			Eavors T1DN Eavors control
					4			Favors FIDIN Favors conttol

Figure I. Association of the ACE I/D gene polymorphism on TIDN susceptibility (TIDN vs controls). ACE: angiotensin-converting enzyme; I/D: insertion/deletion; TIDN: type-I diabetic nephropathy; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

1.04, 95% CI: 0.92–1.18, p = 0.50; DD genotype: OR = 1.06, 95% CI: 0.90–1.24, p = 0.52; II genotype: OR = 0.88, 95% CI: 0.72–1.06, p = 0.18; Figure 2 for D allele, Figure 3 for DD genotype and Figure 4 for II genotype; Table 3).

Sensitivity analysis for the relationship between the *ACE* I/D gene polymorphism and the risk of T1DM patients developing into T1DN in the Caucasian population was also performed according to sample size of case (< 100 vs \geq 100). We found that the results were also similar with the non-sensitivity analysis. The *ACE* I/D gene polymorphism was not associated with the risk of T1DM patients developing T1DN in the Caucasian population (Table 3).

Evaluation of publication bias

No significant publication bias appeared in the comparison of T1DN vs T1DM (Begg p = 0.833, Egger p = 0.231; Figure 5 for Begg test).

Discussion

Dysfunction of *ACE* generation brought about by the *ACE* I/D gene polymorphism is considered the important deterioration factor associated with T1DN susceptibility and the risk for patients with T1DM developing T1DN in the Caucasian population. There was a rare genetic molecular

Genetic contrasts	Number of studies	Q test	Model	OR	Þ
		þ value	selected	(95% CI)	
TIDN vs control					
D vs I	6	0.76	Fixed	1.12 (0.96, 1.30)	0.16
DD vs (ID+II)	6	0.43	Fixed	1.17 (0.94, 1.45)	0.16
II vs (ID+DD)	6	0.54	Fixed	0.89 (0.67, 1.18)	0.42
TIDN vs control (sensi	itivity analysis: \geq 100)				
D vs I	3	0.79	Fixed	1.06 (0.88, 1.26)	0.55
DD vs (ID+II)	3	0.43	Fixed	1.10 (0.85, 1.41)	0.47
ll vs (ID+DD)	3	0.39	Fixed	0.97 (0.70,1.35)	0.87
TIDN vs control (sensi	itivity analysis: < 100)				
D vs I	3	0.77	Fixed	1.33 (0.98, 1.81)	0.07
DD vs (ID+II)	3	0.35	Fixed	1.42 (0.92, 2.19)	0.11
ll vs (ID+DD)	3	0.54	Fixed	0.68 (0.37, 1.23)	0.20
TIDN vs TIDM			~		
D vs I	21	<0.0001	Random	1.04 (0.92, 1.18)	0.50
DD vs (ID+II)	20	0.03	Random	1.06 (0.90, 1.24)	0.52
ll vs (ID+DD)	20	0.03	Random	0.88 (0.72, 1.06)	0.18
TIDN vs TIDM (sensit	ivity analysis: \geq 100)				
D vs I	10	0.002	Random	0.98 (0.86, 1.12)	0.79
DD vs (ID+II)	9	0.28	Fixed	1.06 (0.93, 1.21)	0.41
II vs (ID+DD)	9	0.15	Fixed	0.92 (0.79, 1.07)	0.26
TIDN vs TIDM (sensit	ivity analysis: < 100)				
D vs I	11	0.005	Random	1.14 (0.89, 1.46)	0.31
DD vs (ID+II)	10	0.02	Random	1.10 (0.77, 1.57)	0.59
II vs (ID+DD)	10	0.03	Random	0.79 (0.53, 1.18)	0.25

 Table 3. Meta-analysis of the association of ACE I/D gene polymorphism with risk of TIDN and the TIDM developing into TIDN.

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; TIDM: type I diabetes mellitus; TIDN: type I diabetic nephropathy; OR: odds ratio; CI: confidence interval.

	T1D	N	T1DN	1		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Doria 1994	175	296	181	308	5.6%	1.01 [0.73, 1.40]	1994	+
Powrie 1994	22	38	85	170	2,3%	1.38 [0.68, 2.80]	1994	+
Tarnow 1995	221	396	211	380	6.1%	1.01 [0.76, 1.34]	1995	+
Schmidt 1995	142	228	165	266	5.1%	1.01 [0.70, 1.46]	1995	+
Chowdhury 1996	280	484	189	332	6.1%	1.04 [0.78, 1.38]	1996	+
Hibberd 1997	84	144	75	172	4.2%	1.81 [1.16, 2.83]	1997	
Marre 1997	406	674	165	314	6.3%	1.37 [1.04, 1.79]	1997	+
Barnas 1997	-29	80	55	100	2.9%	0.47 [0.25, 0.85]	1997	
Demurov 1997	77	112	80	152	3.6%	1.98 [1.19, 3.30]	1997	
Ringel 1997	138	268	244	452	5.8%	0.90 [0.67, 1.22]	1997	+
Freire 1998	98	154	113	178	4.2%	1.01 [0.64, 1.58]	1998	+
Pfohl 1998	49	80	48	80	2.7%	1.05 [0.56, 1.99]	1998	+
Bouhanick 1999	28	58	57	94	2.6%	0.61 [0.31, 1.17]	1999	
De Cosmo 1999	225	350	183	272	5.4%	0.88 [0.63, 1.22]	1999	-+
Vieming 1999	102	158	86	164	4.2%	1.65 [1.06, 2.58]	1999	—
van Ittersum 2000	174	400	98	200	5.4%	0.80 [0.57, 1.13]	2000	
Hadjadj 2007	990	2084	1208	2246	8.2%	0.78 [0.69, 0.88]	2007	•
Gallego 2008	47	82	408	818	4.1%	1.35 [0.85, 2.13]	2008	+
Möllsten 2008	77	146	209	394	4.9%	0.99 [0.68, 1.45]	2008	+
Currie 2010	757	1360	764	1460	7.9%	1.14 [0.99, 1.33]	2010	+
Ilić 2014	43	92	32	66	2.7%	0.93 [0.50, 1.76]	2014	
Total (95% CI)		7684		8618	100.0%	1.04 [0.92, 1.18]		•
Total events	4164		4656					
Heterogeneity: Tau ² =	0.05; Chi	² = 57.3	22, df = 20) (P < I	0.0001); P	²= 65%		
Test for overall effect:	Z=0.67 ((P = 0.5	0)					Favors T1DN Favors T1DM

Figure 2. Association of ACE D allele on the risk of TIDM developing into TIDN (TIDN vs TIDM). ACE: angiotensin-converting enzyme; I/D: insertion/deletion; TIDN: type-I diabetic nephropathy; TIDM: type-I diabetes mellitus; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

	T1D	N	T1DI	N		Odds Ratio		Odds Ratio
tudy or Subgroup	Events	Total	Events	Total	Weight I	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
oria 1994	78	148	87	154	6.8%	0.86 [0.55, 1.35]	1994	
owrie 1994	7	19	24	85	2.1%	1.48 [0.52, 4.22]	1994	+
chmidt 1995	52	114	55	133	6.1%	1.19 [0.72, 1.97]	1995	
arnow 1995	63	198	67	190	7.3%	0.86 [0.56, 1.31]	1995	► +
howdhury 1996	78	242	55	166	7.3%	0.96 [0.63, 1.46]	1996	
emurov 1997	24	56	24	76	3.8%	1.63 [0.79, 3.33]	1997	
libberd 1997	21	72	16	86	3.6%	1.80 [0.86, 3.79]	1997	
larre 1997	119	337	48	157	7.6%	1.24 [0.83, 1.86]	1997	
tingel 1997	35	134	57	226	6.3%	1.05 [0.64, 1.71]	1997	+
arnas 1997	4	40	14	50	1.6%	0.29 [0.09, 0.95]	1997	
reire 1998	33	77	34	89	4.7%	1.21 [0.65, 2.26]	1998	
fohl 1998	15	40	15	40	2.7%	1.00 [0.40, 2.47]	1998	·
leming 1999	39	79	26	82	4.5%	2.10 [1.11, 3.99]	1999	- - -
e Cosmo 1999	73	175	65	136	6.8%	0.78 [0.50, 1.23]	1999	-+
ouhanick 1999	4	29	19	47	1.6%	0.24 [0.07, 0.79]	1999	
an Ittersum 2000	40	200	26	100	5.3%	0.71 [0.40, 1.25]	2000	-+
allego 2008	15	41	102	409	4.2%	1.74 [0.89, 3.41]	2008	7 +
löllsten 2008	16	73	48	197	4.5%	0.87 [0.46, 1.66]	2008	· -
urrie 2010	211	680	186	730	11.0%	1.32 [1.04, 1.66]	2010	-
ić 2014	10	46	10	33	2.2%	0.64 [0.23, 1.77]	2014	
								l
otal (95% CI)		2800		3186	100.0%	1.06 [0.90, 1.24]		•
otal events	937		978					
leterogeneity: Tau ² =	0.05; Chi	² = 31.	75, df = 1	9 (P = 0	0.03); I ² = 4	0%	L L	

Figure 3. Association of ACE DD genotype on the risk of TIDM developing into TIDN (TIDN vs TIDM). ACE: angiotensin-converting enzyme; I/D: insertion/deletion; TIDN: type-1 diabetic nephropathy; TIDM: type-1 diabetes mellitus; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

	T1DN	1	T1D	NI .		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Powrie 1994	4	19	24	85	2.2%	0.68 [0.20, 2.25]	1994	
Doria 1994	51	148	60	154	7.5%	0.82 [0.52, 1.32]	1994	
Schmidt 1995	24	114	23	133	5.5%	1.28 [0.68, 2.41]	1995	
Tarnow 1995	40	198	46	190	7.4%	0.79 [0.49, 1.28]	1995	-+
Chowdhury 1996	40	242	32	166	6.9%	0.83 [0.50, 1.39]	1996	
Demurov 1997	3	56	20	76	2.0%	0.16 [0.04, 0.56]	1997	
Ringel 1997	31	134	39	226	6.7%	1.44 [0.85, 2.45]	1997	+
Marre 1997	50	337	40	157	7.5%	0.51 [0.32, 0.81]	1997	
Barnas 1997	15	40	9	50	3.1%	2.73 [1.04, 7.17]	1997	<u> </u>
Hibberd 1997	9	72	27	86	3.8%	0.31 [0.14, 0.72]	1997	
Freire 1998	12	77	10	89	3.4%	1.46 [0.59, 3.59]	1998	
Pfohl 1998	8	40	7	40	2.4%	1.18 [0.38, 3.63]	1998	
Vleming 1999	16	79	22	82	4.6%	0.69 [0.33, 1.44]	1999	
Bouhanick 1999	5	29	9	47	2.1%	0.88 [0.26, 2.94]	1999	
De Cosmo 1999	23	175	18	136	5.2%	0.99 [0.51, 1.92]	1999	
van Ittersum 2000	66	200	28	100	6.7%	1.27 [0.75, 2.14]	2000	+
Gallego 2008	9	41	103	409	4.3%	0.84 [0.39, 1.81]	2008	
Möllsten 2008	12	73	36	197	4.7%	0.88 [0.43, 1.80]	2008	
Currie 2010	134	680	152	730	10.9%	0.93 [0.72, 1.21]	2010	+
Ilić 2014	13	46	11	33	3.1%	0.79 [0.30, 2.07]	2014	
Total (95% CI)		2800		3186	100.0%	0.88 [0.72, 1.06]		•
Total events	565		716	5.00		000 [0112, 100]		
Heterogeneity: Tau² =	0.07 [.] Chi	² = 32 3	74 df = 1	9 (P = (1 03) [,] I ^z =	42%		
Test for overall effect:	7 = 1.34 (P = 0.1	8)	50-0		12.00		0.01 0.1 1 10 10

Figure 4. Association of ACE II genotype on the risk of TIDM developing into TIDN (TIDN vs TIDM).

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; TIDN: type-1 diabetic nephropathy; TIDM: type-1 diabetes mellitus; OR: odds ratio; Cl: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.



Figure 5. Begg's funnel plots with pseudo 95% confidence limits. Evaluation of publication bias for the association of ACE I/D gene polymorphism with the risk of TIDM developing into TIDN.

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; TIDN: type-1 diabetic nephropathy; TIDM: type-1 diabetes mellitus.

marker to predict the onset of T1DN and the risk of patients with T1DM developing T1DN in Caucasian population. This study using the meta-analysis method was performed to explore whether the *ACE* I/D gene polymorphism could predict the susceptibility of T1DN susceptibility and the risk of patients with T1DM developing T1DN in Caucasian population.

In this study, the relationship between the *ACE* I/D gene polymorphism and T1DN susceptibility in the Caucasian population was assessed using the meta-analysis method. We found that the *ACE* I/D gene polymorphism was not associated with T1DN susceptibility in the Caucasian population. Furthermore, sensitivity analysis was performed according to sample size of case (< 100 vs \geq 100), and the results from the sensitivity analysis. However, the number of included studies was small (only six included studies for meta-analysis), and the evidence was less robust. More studies should be performed in the future.

The relationship between the ACE I/D gene polymorphism and the risk of patients with T1DM developing T1DN in the Caucasian population was also assessed in this meta-analysis. The results indicated that the ACE I/D gene polymorphism was not associated with T1DN susceptibility. Furthermore, sensitivity analysis was performed according to sample size of case (< 100 vs \geq 100), and the results from the sensitivity analysis, and there was no significant publication bias. The number of included studies was large, and the evidence might be robust to some extent.

In this meta-analysis, we found that the *ACE* I/D gene polymorphism was not associated with T1DN susceptibility and the risk of patients with T1DM developing T1DN. However, these findings should be regarded cautiously

because many other factors, such as heterogeneity of enrolled cases, limited statistical power, variable study designs and different interventions, were closely related to affect the results. Undoubtedly, the limitations mentioned above might affect our final conclusions.

In conclusion, the results in our study support that the *ACE* I/D gene polymorphism was not associated with T1DN susceptibility and the risk of patients with T1DM developing T1DN in the Caucasian population. However, more association investigations on larger, stratified populations are required to further clarify the role of the *ACE* I/D gene polymorphism in T1DN susceptibility and the risk of patients with T1DM developing T1DN in the Caucasian population.

Conflict of interest

None declared.

Funding

This study was supported by the sub-item of 985 Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation, no. 88000-3311300), and the Guangzhou Medical Key Subject Construction Project (2013–2015).

References

- Ghosh S, More P, Derle A, et al. Diosgenin from *Dioscorea* bulbifera: Novel hit for treatment of type II diabetes mellitus with inhibitory activity against alpha-amylase and alphaglucosidase. *PLoS One* 2014; 9: e106039.
- Akash MS, Rehman K and Chen S. Spice plant *Allium cepa*: Dietary supplement for treatment of type 2 diabetes mellitus. *Nutrition* 2014, 30: 1128–1137.
- 3. Yu ZY, Chen LS, Zhang LC, et al. Meta-analysis of the relationship between *ACE* I/D gene polymorphism and

end-stage renal disease in patients with diabetic nephropathy. *Nephrology (Carlton)* 2012; 17: 480–487.

- Hussain H, Ramachandran V, Ravi S, et al. *TCF7L2* rs7903146 polymorphism and diabetic nephropathy association is not independent of type 2 diabetes—a study in a south Indian population and meta-analysis. *Endokrynol Pol* 2014; 65: 298–305.
- Kaur M, Bedi O, Sachdeva S, et al. Rodent animal models: From mild to advanced stages of diabetic nephropathy. *Inflammopharmacology* 2014; 22: 279–293.
- Zha Y, Gan P, Liu Q, et al. Relationship between polymorphism of angiotensin-converting enzyme gene insertion/ deletion and risk of hepatocellular carcinoma in a Chinese Dai population. *J Renin Angiotensin Aldosterone Syst.* Epub ahead of print 10 September 2014.
- Song GG and Lee YH. The insertion/deletion polymorphism in the angiotensin-converting enzyme and susceptibility to schizophrenia or Parkinson's disease: A meta-analysis. J Renin Angiotensin Aldosterone Syst. Epub ahead of print 20 August 2014.
- Zhou TB, Qin YH, Su LN, et al. The association between angiotensin-converting enzyme insertion/deletion gene variant and risk of focal segmental glomerulosclerosis: A systematic review and meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 624–633.
- Zhou TB, Yin SS and Qin YH. Association between angiotensin-converting enzyme insertion/deletion gene polymorphism and end-stage renal disease susceptibility. *J Renin Angiotensin Aldosterone Syst* 2014; 15: 22–31.
- Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
- 11. Egger M, Davey Smith G, Schneider M, et al. Bias in metaanalysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
- Powrie JK, Watts GF, Ingham JN, et al. Role of glycaemic control in development of microalbuminuria in patients with insulin dependent diabetes. *BMJ* 1994; 309: 1608–1612.
- Schmidt S, Schöne N and Ritz E. Association of ACE gene polymorphism and diabetic nephropathy? The Diabetic Nephropathy Study Group. *Kidney Int* 1995; 47: 1176–1181.
- Chowdhury TA, Dronsfield MJ, Kumar S, et al. Examination of two genetic polymorphisms within the renin-angiotensin system: No evidence for an association with nephropathy in IDDM. *Diabetologia* 1996; 39: 1108–1114.
- Demurov LM, Chistiakov DA, Chugunova LA, et al. Polymorphism of the insertion/deletion type in the angiotensin-converting enzyme gene in normal subjects and among patients with vascular complications [article in Russian]. *Mol Biol (Mosk)* 1997; 31: 59–62.
- Pfohl M, Frost D, Koch M, et al. Lack of association between the insertion/deletion polymorphism of the angiotensin-converting-enzyme gene and diabetic nephropathy in IDDM patients. *Horm Metab Res* 1998; 30: 276–280.
- De Cosmo S, Margaglione M, Tassi V, et al. ACE, PAI-1, decorin and Werner helicase genes are not associated with the development of renal disease in European patients with type 1 diabetes. *Diabetes Metab Res Rev* 1999; 15: 247–253.
- Doria A, Warram JH and Krolewski AS. Genetic predisposition to diabetic nephropathy. Evidence for a role of the angiotensin I-converting enzyme gene. *Diabetes* 1994; 43: 690–695.

- Tarnow L, Cambien F, Rossing P, et al. Lack of relationship between an insertion/deletion polymorphism in the angiotensin I-converting enzyme gene and diabetic nephropathy and proliferative retinopathy in IDDM patients. *Diabetes* 1995; 44: 489–494.
- Hibberd ML, Millward BA and Demaine AG. The angiotensin I-converting enzyme (ACE) locus is strongly associated with age and duration of diabetes in patients with type I diabetes. *J Diabetes Complications* 1997; 11: 2–8.
- Ringel J, Beige J, Kunz R, et al. Genetic variants of the renin-angiotensin system, diabetic nephropathy and hypertension. *Diabetologia* 1997; 40: 193–199.
- 22. Barnas U, Schmidt A, Illievich A, et al. Evaluation of risk factors for the development of nephropathy in patients with IDDM: Insertion/deletion angiotensin converting enzyme gene polymorphism, hypertension and metabolic control. *Diabetologia* 1997; 40: 327–331.
- Marre M, Jeunemaitre X, Gallois Y, et al. Contribution of genetic polymorphism in the renin-angiotensin system to the development of renal complications in insulin-dependent diabetes: Genetique de la Nephropathie Diabetique (GENEDIAB) study group. J Clin Invest 1997; 99:1585–1595.
- Freire MB, van Dijk DJ, Erman A, et al. DNA polymorphisms in the ACE gene, serum ACE activity and the risk of nephropathy in insulin-dependent diabetes mellitus. Nephrol Dial Transplant 1998; 13: 2553–2558.
- 25. Bouhanick B, Gallois Y, Hadjadj S, et al. Relationship between glomerular hyperfiltration and *ACE* insertion/deletion polymorphism in type 1 diabetic children and adolescents. *Diabetes Care* 1999; 22: 618–622.
- 26. Vleming LJ, van der Pijl JW, Lemkes HH, et al. The DD genotype of the *ACE* gene polymorphism is associated with progression of diabetic nephropathy to end stage renal failure in IDDM. *Clin Nephrol* 1999; 51: 133–140.
- van Ittersum FJ, de Man AM, Thijssen S, et al. Genetic polymorphisms of the renin-angiotensin system and complications of insulin-dependent diabetes mellitus. *Nephrol Dial Transplant* 2000; 15: 1000–1007.
- Hadjadj S, Tarnow L, Forsblom C, et al. Association between angiotensin-converting enzyme gene polymorphisms and diabetic nephropathy: Case-control, haplotype, and family-based study in three European populations. *J Am Soc Nephrol* 2007; 18: 1284–1291.
- Möllsten A, Kockum I, Svensson M, et al. The effect of polymorphisms in the renin-angiotensin-aldosterone system on diabetic nephropathy risk. *J Diabetes Complications* 2008; 22: 377–383.
- Gallego PH, Shephard N, Bulsara MK, et al. Angiotensinogen gene *T235* variant: A marker for the development of persistent microalbuminuria in children and adolescents with type 1 diabetes mellitus. *J Diabetes Complications* 2008; 22: 191–198.
- Currie D, McKnight AJ, Patterson CC, et al. Investigation of ACE, ACE2 and AGTR1 genes for association with nephropathy in Type 1 diabetes mellitus. *Diabet Med* 2010; 27: 1188–1194.
- 32. Ilić V, Ilić M, Soldatović I, et al. Association of reninangiotensin system genes polymorphism with progression of diabetic nephropathy in patients with type 1 diabetes mellitus. *Vojnosanit Pregl* 2014; 71: 627–633.

Retraction notice

jraas

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP27 © The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314563426 jra.sagepub.com SAGE

This article has been included in a multiple retraction:

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

This article has been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System (JRAAS)* (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou Association between the ACE I/D gene polymorphism

and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System September 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011

Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

j<u>raas</u>

RETRACTED: Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP28–NP34 © The Author(s) 2014 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314563426 ira.sagepub.com

SAGE

Wenzhuang Tang¹, Tian-Biao Zhou² and Zongpei Jiang²

Abstract

Aim: The association between angiotensinogen (*AGT*) M235T gene polymorphism and the risk of diabetes mellitus (DM) developing into diabetic nephropathy (DN) is still controversial. This meta-analysis was performed to evaluate the association of *AGT* M235T gene polymorphism with the susceptibility of DM developing into DN.

Methods: A predefined literature search and selection of eligible relevant studies were performed to collect data from electronic databases.

Results: Nineteen articles were identified for analysis of the association of the AGT M235T gene polymorphism with the susceptibility of DM developing into DN. The AGT M235T gene polymorphism was not associated with the susceptibility of DM developing into DN in overall populations, in Asians and in the Caucasian population. Furthermore, the AGT M235T gene polymorphism was not associated with the susceptibility of DM developing into DN in overall with the susceptibility of DM developing into DN in the TIDM population and T2DM population.

Conclusions: The AGT M235T gene polymorphism was not associated with the susceptibility of DM developing into DN. However, more studies should be performed in the future.

Keywords

Diabetes mellitus (DM), diabetic nephropathy (DN), angiotensinogen, M235T, gene polymorphism, meta-analysis

Introduction

Diabetes mellitus (DM) is a major public health problem worldwide.¹ It is associated with endothelial dysfunction, reducing nitric oxide (NO)-dependent vasodilation and increasing production of pro-inflammatory factors, leading to increased long-term cardiovascular and kidney risk.² Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes and the leading cause of end-stage renal disease.³ DN includes type 1 diabetic nephropathy (T1DN) due to type 1 DM and type 2 diabetic nephropathy (T2DN) due to type 2 DM.^{4,5} Some investigations suggested that genetic factors might play a key role in the risk of DM developing into DN.

The angiotensinogen (*AGT*) gene is located on chromosome 1q41-qter, and regulates the expression of angiotensinogen, a glycoprotein produced by the liver. Its cleavage by renin liberates angiotensin I, which is converted into angiotensin II by the angiotensin-converting enzyme.^{6–8} The M235T variant of the *AGT* gene has been associated with higher plasma AGT levels in patients homozygous for the T allele and occurs among various ethnic populations.⁹ The *AGT* M235T gene polymorphism, correlating with circulating and cellular AGT concentration, has been implicated in the etiology of DM developing into DN and has been investigated in numerous epidemiologic studies at present. However, the available evidence reported to date is

W.T. and T.B.Z. contributed equally to this manuscript.

Corresponding author:

Zongpei Jiang, Department of Nephrology, the Sixth Affiliated Hospital, Sun Yat-Sen University, Yuancunerheng Road No.26, Guangzhou, 510655, China. Email: zongpeijiang@yeah.net

Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (http://www.uk.sagepub.com/aboutus/openaccess.htm).

Department of Nephrology, the Affiliated Hospital of Hainan Medical College, China

²Department of Nephrology, the Sixth Affiliated Hospital, Sun Yat-Sen University, China

weak, due to sparseness of data or disagreements among studies. There was rare meta-analysis to explore the association of *AGT* M235T gene polymorphism with risk of DM developing into DN. We performed this meta-analysis to investigate the relation between AGT M235T gene polymorphism and risk of DM developing into DN.

Materials and methods

Search strategy

The relevant studies were screened from the search engines of PubMed, Cochrane Library on August 1, 2014. The terms "(angiotensinogen OR AGT) AND (diabetic nephropathy)" were used in PubMed and Cochrane Library to complete the search. We also extended the search spectrum to the "related articles" and the bibliographies of all retrieved studies. If multiple publications of the same data from the same study group occurred, we recruited only the later paper for analysis.

Inclusion criteria. (1) A case-control study; (2) the outcome had to be DN; (3) there had to be at least two comparison groups (DN group vs DM group).

Exclusion criteria. (1) Review articles, editorials and case reports; (2) articles did not provide the detail genotype data; (3) investigating the association of other genes with DN; (4) investigating the role of drugs on diseases; (5) multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study independently by at least two investigators: first author's surname, year of publication, ethnicity of study population, and the number of cases and controls for the M235T genotype. Frequencies of T allele were calculated for case group and control group, from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data were entered into Cochrane Review Manager (RevMan, version 5) and analyzed. The pooled statistic was counted using the fixed-effects model, but a random-effects model was conducted when the *p* value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. *p* < 0.05 was required for the overall OR to be deemed statistically significant. *I*² was used to test the heterogeneity between the included studies. We classified the investigations into studies for Asians, Caucasians and African populations because genotype frequencies and prevalence of DN were different among ethnic

groups. The Begg adjusted rank correlation test¹⁰ and the Egger regression asymmetry test¹¹ were used for exploring publication bias (p < 0.1 was considered significant) when the sample number was more than five.

Results

Study characteristics

The search yielded 162 references: 162 from PubMed, and 0 from Cochrane Library. According to the inclusion and exclusion criteria, nineteen articles^{12–30} were identified for the analysis of the between the *AGT* M/T gene polymorphism and the susceptibility of DM developing into DN in our review (Table 1).

Association of AGT M/T gene polymorphism with the risk of DM patients developing into DN

In this meta-analysis, the *AGT* M/T gene polymorphism was not associated with the susceptibility of DM developing into DN in the overall population (T allele: OR = 1.26, 95% CI: 0.96–1.65, p = 0.10; TT genotype: OR = 1.42, 95% CI: 0.97– 2.08, p = 0.07; MM genotype: OR = 0.81, 95% CI: 0.56–1.18, p = 0.28; Figure 1 for T allele, and Figure 2 for TT genotype and Figure 3 for MM genotype; Table 2). Furthermore, the *AGT* M/T gene polymorphism was not associated with the susceptibility of DM developing into DN in Asians and the Caucasian population (Table 2).

Sensitivity analysis for the relationship between the *AGT* M/T gene polymorphism and the susceptibility of DM developing into DN was also performed according to types of DM. In the sensitivity analysis, the *AGT* M/T gene polymorphism was not associated with the susceptibility of T1DM developing into T1DN in the overall population (T allele: OR = 1.26, 95% CI: 0.94–1.70, p = 0.12; TT genotype: OR = 1.41, 95% CI: 0.76–2.63, p = 0.28; MM genotype: OR = 0.76, 95% CI: 0.55–1.04, p = 0.09; Table 2). Furthermore, the *AGT* M/T gene polymorphism was not associated with the susceptibility of T2DM developing into T2DN in the overall population (T allele: OR = 1.17, 95% CI: 0.78–1.76, p = 0.45; TT genotype: OR = 1.31, 95% CI: 0.79–2.15, p = 0.29; MM genotype: OR = 0.89, 95% CI: 0.54–1.47, p = 0.65; Table 2).

Evaluation of publication bias

No significant publication bias was shown in this metaanalysis (Begg P=0.596, Egger P=0.416; Figure 4 for Begg test).

Discussion

In this investigation, 19 studies were included into this meta-analysis, and we found that the *AGT* M/T gene polymorphism was not associated with the susceptibility of

First author, year	Ethnicity	Type of	DN						DM					
		DIT	TT	MT	MM	Total	T allele	Total (allele)	TT	MT	MM	Total	T allele	Total (allele)
Rogus, 1998	Caucasian	TIDM	_	_	_	_	76	143	_	-	-	_	32	70
Miura, 1999	Asian	TIDM	61	34	3	98	156	196	69	32	2	103	170	206
Tomino, 1999	Asian	T2DM	507	-	_	745	-	-	277	4	-	407	-	-
van Ittersum, 2000	Caucasian	TIDM	13	37	19	69	63	138	21	96	71	188	138	376
Zychma, 2000	Caucasian	T2DM	106	228	116	450	440	900	64	116	63	243	244	486
Lovati, 2001	Caucasian	TIDM	5	18	9	32	28	64	I	16	20	37	18	74
Fradin, 2002	Caucasian	T2DM	25	44	49	118	94	236	19	59	40	118	97	236
Prasad, 2006	Asian	T2DM	86	86	24	196	258	392	45	85	95	225	175	450
Osawa, 2007	Asian	T2DM	22	209	504	735	253	1470	15	195	341	551	225	1102
Eroglu, 2008	Caucasian	T2DM	10	24	12	46	44	92	9	32	15	56	50	112
Möllsten, 2008	Caucasian	TIDM	7	40	26	73	54	146	35	104	58	197	174	394
Gallego, 2008	Caucasian	TIDM	10	23	8	41	43	82	77	23)	136	444	385	888
Tien, 2009	Asian	T2DM	17	_	-	93	-	-	97	_	-	432	-	_
Ahluwalia, 2009	Asian	T2DM	82	104	54	240	268	480	27	120	108	255	174	510
Manea, 2011	Caucasian	T2DM	17	60	30	107	94	214	41	92	10	143	174	286
Mtiraoui, 2011	Caucasian	T2DM	73	138	118	329	284	658	20	176	209	405	216	810
Reis, 2011	Caucasian	T2DM	17	68	23	108	102	216	41	51	19	111	133	222
Shaikh, 2014	Asian	NC	62	47	I	110	171	220	35	77	3	115	147	230
llić, 2014	Caucasian	TIDM	15	23	8	46	53	92	3	23	7	33	29	66

Table I	 Characteristics 	of the studies	evaluating the e	effects of the A	ATG M235T	gene polymo	rphism on D	M developing into DN
---------	-------------------------------------	----------------	------------------	------------------	-----------	-------------	-------------	----------------------

DM: diabetes mellitus; DN: diabetic nephropathy; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; NC: Not clear.

		Cas	е	Contr	ol		Odds Ratio		Odds Ratio
5	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
F	Rogus 1998	76	143	32	70	5.2%	1,35 [0.76, 2.39]	1998	+
N	vliura 1999	156	196	170	206	5.6%	0.83 [0:50, 1.36]	1999	
٧	an Ittersum 2000	63	138	138	376	6.0%	1.45 [0.98, 2.15]	2000	
Z	Zychma 2000	440	900	244	486	6.5%	0.95 (0.76, 1.18)	2000	+
L	ovati 2001	28	64	18	74	4.6%	2.42 [1.17, 5.00]	2001	
F	radin 2002	94	236	97	236	6.1%	0.95 [0.66, 1.37]	2002	+
F	Prasad 2006	258	392	175	450	6.4%	3.03 [2.28, 4.01]	2006	-
0	Osawa 2007	253	1470	225	1102	6.6%	0.81 [0.66, 0.99]	2007	-
E	Eroglu 2008	44	92	50	112	5.3%	1.14 [0.65, 1.98]	2008	+
0	Gallego 2008	43	82	385	888	5.7%	1.44 [0.92, 2.27]	2008	+
N	/löllsten 2008	54	146	174	394	6.0%	0.74 [0.50, 1.10]	2008	-+
P	Ahluwalia 2009	268	480	174	510	6.4%	2.44 [1.89, 3.16]	2009	-
N	/lanea 2011	94	214	174	286	6.1%	0.50 [0.35, 0.72]	2011	
N	Atiraoui 2011	284	658	216	810	6.5%	2.09 [1.68, 2.60]	2011	-
F	Reis 2011	102	216	133	222	6.0%	0.60 [0.41, 0.87]	2011	
	lić 2014	53	92	29	66	5.0%	1.73 [0.92, 3.28]	2014	
8	Shaikh 2014	171	220	147	230	5.9%	1.97 [1.30, 2.99]	2014	-
		- 4							
1	otal (95% CI)		5739		6518	100.0%	1.26 [0.96, 1.65]		•
٦	Fotal events	2481		2581					
H	Heterogeneity: Tau ² = 0).28; Chi	² = 169	.46, df=	16 (P <	0.00001)); I ² = 91%		
٦	Fest for overall effect; Z	= 1.63 ((P = 0.1	0)					0.01 0.1 1 10 100 Eavara DN Eavara DM
				-					Favors DIV Favors DM

Figure 1. Association of AGTT allele on the risk of DM developing into DN.

AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

DM developing into DN in the overall population. Furthermore, the *AGT* M/T gene polymorphism was not associated with the susceptibility of DM developing into DN in Asians and the Caucasian population. There was no publication bias in this meta-analysis, and the results might be robust to some extent. In the sensitivity analysis, the relationship between the AGT M/T gene polymorphism and the susceptibility of DM developing into DN was also performed according to types of DM. We found that the AGT M/T gene polymorphism was not associated with the susceptibility of T1DM developing into T1DN in the overall population.

	DN		DM			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year M-H, Random, 95% Cl
Tomino 1999	507	745	277	407	6.7%	1.00 [0.77, 1.30]	1999
Miura 1999	61	98	69	103	6.0%	0.81 [0.46, 1.45]	1999 -
van Ittersum 2000	13	69	21	188	5.5%	1.85 [0.87, 3.93]	2000
Zychma 2000	106	450	64	243	6.5%	0.86 [0.60, 1.23]	2000
Lovati 2001	5	32	1	37	2.1%	6.67 [0.74, 60.42]	2001
Fradin 2002	25	118	19	118	5.8%	1.40 [0.72, 2.71]	2002
Prasad 2006	86	196	45	225	6.4%	3.13 [2.03, 4.82]	2006
Osawa 2007	22	735	15	551	5.7%	1.10 [0.57, 2.15]	2007
Gallego 2008	10	41	77	444	5.5%	1.54 [0.72, 3.27]	2008
Eroglu 2008	10	46	9	56	4.7%	1.45 [0.53, 3.94]	2008
Möllsten 2008	7	73	35	197	5.1%	0.49 [0.21, 1.16]	2008
Ahluwalia 2009	82	240	27	255	6.3%	4.38 [2.71, 7.08]	2009
Tien 2009	17	93	97	432	6.0%	0.77 [0.44, 1.37]	2009
Manea 2011	17	107	41	143	5.8%	0.47 [0.25, 0.88]	2011
Reis 2011	17	108	41	111	5.8%	0.32 [0.17, 0.61]	2011
Mtiraoui 2011	73	329	20	405	6.2%	5.49 [3.27, 9.23]	2011
llić 2014	15	46	3	33	3.8%	4.84 [1.27, 18.43]	2014
Shaikh 2014	62	110	35	115	6.1%	2.95 [1.71, 5.10]	2014
Total (95% CI)		3636		4063	100.0%	1.42 [0.97, 2.08]	*
Total events	1135		896				
Heterogeneity: Tau ² =	0.55; Ch	i ² = 133	.28, df =	17 (P <	0.00001); I ² = 87%	
Test for overall effect:	Z=1.79	(P = 0.0	(7)				Eavors DN Eavors DM
							ravois DIN Pavois DIN

Figure 2. Association of *AGT* TT genotype on the risk of DM developing into DN. *AGT*: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

	DN		DM			Odds Ratio		Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Rando	m, 95% Cl
Miura 1999	3	98	2	103	2.8%	1.59 [0.26, 9.75]	1999		-
Zychma 2000	116	450	63	243	7.9%	0.99 [0.69, 1.42]	2000	-+	-
van Ittersum 2000	19	69	71	188	6.9%	0.63 [0.34, 1.15]	2000		
Lovati 2001	9	32	20	37	5.2%	0.33 [0.12, 0.91]	2001		
Fradin 2002	49	118	40	118	7.2%	1.38 [0.82, 2.35]	2002	+	•
Prasad 2006	24	196	95	225	7.3%	0.19 [0.12, 0.32]	2006	-	
Osawa 2007	504	735	341	551	8.2%	1.34 [1.07, 1.69]	2007	ŀ	•-
Möllsten 2008	26	73	58	197	7.1%	1.33 [0.75, 2.34]	2008	+	•
Gallego 2008	8	41	136	444	6.1%	0.55 [0.25, 1.22]	2008		
Eroglu 2008	12	46	15	56	5.7%	0.96 [0.40, 2.34]	2008	-+	
Ahluwalia 2009	54	240	108	255	7.7%	0.40 [0.27, 0.58]	2009		
Reis 2011	23	108	19	111	6.6%	1.31 [0.67, 2.57]	2011	+	-
Mtiraoui 2011	118	329	209	405	8.0%	0.52 [0.39, 0.71]	2011	-	
Manea 2011	30	107	10	143	6.2%	5.18 [2.40, 11.18]	2011		
Shaikh 2014	1	110	3	115	2.0%	0.34 [0.04, 3.34]	2014		
llić 2014	8	46	7	33	4.8%	0.78 [0.25, 2.42]	2014		
Total (95% CI)		2798		3224	100.0%	0.81 [0.56, 1.18]		•	
Total events	1004		1197					-	
Heterogeneity: Tau ² =	0.43; Chi	² = 109	.35, df =	15 (P <	0.00001); I² = 86%			10 10
Test for overall effect:	Z = 1.08 (P = 0.2	8)					0.01 0.1 1	10 10

Figure 3. Association of *AGT* MM genotype on the risk of DM developing into DN. *AGT*: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

Furthermore, the *AGT* M/T gene polymorphism was not associated with the susceptibility of T2DM developing into T2DN in the overall population.

As those mentioned above, this study indicated that the AGT M/T gene polymorphism might not be associated with the susceptibility of DM developing into DN. However, more studies should be conducted in further to

confirm it. However, when the fixed model was used for this meta-analysis, we found that the *AGT* M/T gene polymorphism was associated with the susceptibility of DM developing into DN (data not shown).

In our investigation, we found that the *AGT* M235T gene polymorphism was not associated with the susceptibility of DM developing into DN in overall populations, in

Genetic contrasts	Group and	Studies	Q test	Model	OR	Þ
	subgroups		p value	Selected	(95% CI)	
T vs M	Overall	17	<0.00001	Random	I.26 (0.96, I.65)	0.10
	Asian	5	<0.00001	Random	1.59 (0.87,2.90)	0.13
	Caucasian	12	<0.00001	Random	1.13 (0.84, 1.51)	0.43
TT vs (TM+MM)	Overall	18	<0.00001	Random	1.42 (0.97, 2.08)	0.07
	Asian	7	<0.00001	Random	1.62 (0.94, 2.79)	0.08
	Caucasian	11	<0.00001	Random	1.31 (0.73, 2.34)	0.37
MM vs (TM+TT)	Overall	16	<0.00001	Random	0.81 (0.56, 1.18)	0.28
	Asian	5	<0.00001	Random	0.54 (0.20, 1.46)	0.23
	Caucasian	11	<0.00001	Random	0.96 (0.66, 1.41)	0.84
TIDN						
T vs M	Overall	7	0.02	Random	1.26 (0.94, 1.70)	0.12
TT vs (TM+MM)	Overall	6	0.02	Random	1.41 (0.76, 2.63)	0.28
MM vs (TM+TT)	Overall	6	0.16	Fixed	0.76 (0.55, 1.04)	0.09
T2DN						
T vs M	Overall	9	<0.00001	Random	1.17 (0.78, 1.76)	0.45
TT vs (TM+MM)	Overall	11	<0.00001	Random	1.31 (0.79, 2.15)	0.29
MM vs (TM+TT)	Overall	9	<0.00001	Random	0.89 (0.54, 1.47)	0.65

Table 2. Meta-analysis of the association of the ATG M235T gene polymorphism with risk of DM developing into DN.

DM: diabetes mellitus; DN: diabetic nephropathy.



Figure 4. Begg's funnel plots with pseudo 95% confidence limits. Evaluation of publication bias for the association of the AGT M/T gene polymorphism with the risk of DM developing into DN. DM: diabetes mellitus; DN: diabetic nephropathy.

Asians and in the Caucasian population. Furthermore, the *AGT* M235T gene polymorphism was not associated with the susceptibility of DM developing into DN in the T1DM population and T2DM populations. However, these findings should be regarded cautiously because many other factors, such as heterogeneity of enrolled cases, limited statistical power, variable study designs and different interventions, were closely related to affect the results. Furthermore, whether the **AGT** M235T polymorphism

is just linked with other discrete loci involved in the susceptibility of DM developing into DN is not clear at the moment.

Conclusions

In conclusion, the results in our study support that the *AGT* M235T gene polymorphism was not associated with the susceptibility of DM developing into DN. However, more

case-control association investigations on larger, stratified populations are required to further clarify the role of this *AGT* M235T gene polymorphism in the susceptibility of DM developing into DN.

Conflict of interest

None declared.

Funding

This study was supported by the sub-item of 985 Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation, no. 88000-3311300).

References

- Abbas S, Goyal S and Cornelius T. Presence of diabetes mellitus in the 'Dawoodi Bohra youth community' in Udaipur, Rajasthan. *Indian J Med Res* 2014; 140: 302–306.
- Santi D, Giannetta E, Isidori AM, et al. Therapy of endocrine disease: Effects of chronic use of phosphodiesterase inhibitors on endothelial markers in type 2 diabetes mellitus: A meta-analysis. *Eur J Endocrinol*. Epub ahead of print 2 October 2014.
- Zhou TB, Xu HL and Yin SS. Association between endothelial nitric oxide synthase Glu298Asp gene polymorphism and diabetic nephropathy susceptibility. *Ren Fail* 2013; 35: 173–178.
- Yu ZY, Chen LS, Zhang LC, et al. Meta-analysis of the relationship between ACE I/D gene polymorphism and endstage renal disease in patients with diabetic nephropathy. Nephrology (Carlton) 2012; 17: 480–487.
- Hussain H, Ramachandran V, Ravi S, et al. TCF7L2 rs7903146 polymorphism and diabetic nephropathy association is not independent of type 2 diabetes—a study in a south Indian population and meta-analysis. *Endokrynol Pol* 2014; 65: 298–305.
- Polugari Prem Kumar Manohar Rao, Munshi A, Mullapudi R, et al. The M235T polymorphism of the angiotensinogen gene in South Indian patients of hypertrophic cardiomyopathy. J Renin Angiotensin Aldosterone Syst 2011; 12: 238–242.
- MtiraouiN, EzzidiI, TurkiA, etal. Renin-angiotensin-aldosterone system genotypes and haplotypes affect the susceptibility to nephropathy in type 2 diabetes patients. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 572–580.
- Mendizábal-Ruiz AP, Morales J, Castro Martinez X, et al. RAS polymorphisms in cancerous and benign breast tissue. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 85–92.
- Mehri S, Mahjoub S, Farhati A, et al. Angiotensinogen gene polymorphism in acute myocardial infarction patients. J Renin Angiotensin Aldosterone Syst 2011; 12: 42–47.
- Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
- Egger M, Davey Smith G, Schneider M, et al. Bias in metaanalysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
- 12. Rogus JJ, Moczulski D, Freire MB, et al. Diabetic nephropathy is associated with *AGT* polymorphism T235: results of a family-based study. *Hypertension* 1998; 31: 627–631.

- 13. Miura J, Uchigata Y, Yokoyama H, et al. Genetic polymorphism of renin-angiotensin system is not associated with diabetic vascular complications in Japanese subjects with long-term insulin dependent diabetes mellitus. *Diabetes Res Clin Pract* 1999; 45: 41–49.
- Tomino Y, Makita Y, Shike T, et al. Relationship between polymorphism in the angiotensinogen, angiotensin-converting enzyme or angiotensin II receptor and renal progression in Japanese NIDDM patients. *Nephron* 1999; 82: 139–144.
- van Ittersum FJ, de Man AM, Thijssen S, et al. Genetic polymorphisms of the renin-angiotensin system and complications of insulin-dependent diabetes mellitus. *Nephrol Dial Transplant* 2000; 15: 1000–1007.
- Zychma MJ, Zukowska-Szczechowska E, Lacka BI, et al. Angiotensinogen M235T and chymase gene CMA/B polymorphisms are not associated with nephropathy in type II diabetes. *Nephrol Dial Transplant* 2000; 15: 1965–1970.
- Lovati E, Richard A, Frey BM, et al. Genetic polymorphisms of the renin-angiotensin-aldosterone system in endstage renal disease. *Kidney Int* 2001; 60: 46–54.
- 18. Fradin S, Goulet-Salmon B, Chantepie M, et al. Relationship between polymorphisms in the renin-angiotensin system and nephropathy in type 2 diabetic patients. *Diabetes Metab* 2002; 28: 27–32.
- Prasad P, Tiwari AK, Kumar KM, et al. Chronic renal insufficiency among Asian Indians with type 2 diabetes: I. Role of RAAS gene polymorphisms. *BMC Med Genet* 2006; 7: 42.
- Osawa N, Koya D, Araki S, et al. Combinational effect of genes for the renin-angiotensin system in conferring susceptibility to diabetic nephropathy. *J Hum Genet* 2007; 52: 143–151.
- Eroglu Z, Cetinkalp S, Erdogan M, et al. Association of the angiotensinogen M235T and angiotensin-converting enzyme insertion/deletion gene polymorphisms in Turkish type 2 diabetic patients with and without nephropathy. J Diabetes Complications 2008; 22: 186–190.
- Möllsten A, Kockum I, Svensson M, et al. The effect of polymorphisms in the renin-angiotensin-aldosterone system on diabetic nephropathy risk. *J Diabetes Complications* 2008; 22: 377–383.
- Gallego PH, Shephard N, Bulsara MK, et al. Angiotensinogen gene T235 variant: A marker for the development of persistent microalbuminuria in children and adolescents with type 1 diabetes mellitus. *J Diabetes Complications* 2008; 22: 191–198.
- Tien KJ, Hsiao JY, Hsu SC, et al. Gender-dependent effect of ACE I/D and AGT M235T polymorphisms on the progression of urinary albumin excretion in Taiwanese with type 2 diabetes. Am J Nephrol 2009; 29: 299–308.
- 25. Ahluwalia TS, Ahuja M, Rai TS, et al. *ACE* variants interact with the RAS pathway to confer risk and protection against type 2 diabetic nephropathy. *DNA Cell Biol* 2009; 28: 141–150.
- 26. Manea SA, Robciuc A, Guja C, et al. Identification of gene variants in NOS3, ET-1 and RAS that confer risk and protection against microangiopathy in type 2 diabetic obese subjects. *Biochem Biophys Res Commun* 2011; 407: 486–490.

- 27. Mtiraoui N, Ezzidi I, Turki A, et al. Renin-angiotensinaldosterone system genotypes and haplotypes affect the susceptibility to nephropathy in type 2 diabetes patients. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 572–580.
- Reis KA, Ebinç FA, Koç E, et al. Association of the angiotensinogen M235T and APO E gene polymorphisms in Turkish type 2 diabetic patients with and without nephropathy. *Ren Fail* 2011; 33: 469–474.
- 29. Shaikh R, Shahid SM, Mansoor Q, et al. Genetic variants of *ACE* (Insertion/Deletion) and *AGT* (M268T) genes in patients with diabetes and nephropathy. *J Renin Angiotensin Aldosterone Syst* 2014; 15: 124–130.
- Ilić V, Ilić M, Soldatović I, et al. Association of reninangiotensin system genes polymorphism with progression of diabetic nephropathy in patients with type 1 diabetes mellitus. *Vojnosanit Pregl* 2014; 71: 627–633.

Retraction notice

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(4) NP10 © The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320315623881 jra.sagepub.com **SAGE**

The following articles have been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the Journal of the Renin-Angiotensin Aldosterone System (JRAAS) (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System September 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011



Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Retraction notice

The following articles have been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the Journal of the Renin-Angiotensin Aldosterone System (JRAAS) (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

raas

Journal of the Renin-Angiotensin-Aldosterone System

© The Author(s) 2015 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314524011 jra.sagepub.com (\$)SAGE

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System September 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011



Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

<u>jraas</u>

RETRACTED: Association of aldosterone synthase (CYPIIB2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of the Renin-Angiotensin-Aldosterone System 2015, Vol. 16(3) 660–665 © The Author(s) 2014 Reprints and permissions: sagepub.co.uk/journalsPermissions.nav DOI: 10.1177/1470320314524011 jra.sagepub.com

SAGE

Weiqiang Zhong¹, Zhongliang Huang¹, Yong Wu¹, Zongpei Jiang² and Tian-Biao Zhou²

Abstract

Objective: This meta-analysis was conducted to assess the association of aldosterone synthase (CYP11B2) gene polymorphism with the risk of immunoglobulin A (IgA) nephropathy (IgAN) and the progression of IgAN. **Methods:** The literature on associations was identified from PubMed and the Cochrane Library on 1 October 2013, and eligible reports were synthesized.

Results: Eligible reports were recruited into this meta-analysis for the association of *CYP11B2-344C/T* (rs1799998) gene polymorphism with IgAN risk, and the progression of IgAN. In this meta-analysis, the association of *CYP11B2-344C/T* (rs1799998) gene polymorphism with IgAN risk was not found in overall populations and in Asians. Interestingly, the C allele and CC genotype were associated with the risk of IgAN in Caucasians, but the TT genotype was not.

Conclusion: CYP11B2-344C/T gene polymorphism is not associated with IgAN risk and IgAN progression in overall populations and in Asians, but CYP11B2 C allele and CC genotype were associated with the risk of IgAN in Caucasians. However, more studies should be performed in the future to confirm this association.

Keywords

IgA nephropathy, aldosterone synthase, CYP11B2, gene polymorphism, meta-analysis

Date received: 9 November 2013; accepted: 15 January 2014

Introduction

Immunoglobulin A (IgA) nephropathy (IgAN), the most prevalent glomerular disease in the world and characterized by predominant IgA deposition in the mesangium, requires a renal biopsy for diagnosis.¹ It is initially regarded as a disease with a favorable prognosis but data from longterm follow-up studies have revealed that IgAN may progress to end-stage renal failure in up to 30% of patients with a follow up period of 20 years.^{2,3} There is a lack of a well-documented diagnostic approach for IgAN risk; and reliable biomarkers are needed for the non-invasive diagnosis of this disease and to more fully delineate its natural history and risk for progression. Current evidence indicates that gene polymorphism of some genes is associated with the susceptibility of IgAN.^{4,6}

Aldosterone, one of the main effectors of the renin-angiotensin system, has classically been thought to act as a regulator for the absorption of sodium and water, as well as the excretion of potassium in normal physiology, and as a mediator of edema in numerous disease states.⁷ Aldosterone secretion is regulated largely by the expression level of the final enzyme required for its biosynthesis, aldosterone synthase (CYP11B2). Expression of CYP11B2 is regulated by angiotensin II through cyclic adenosine monophosphate (cAMP) dependent modulation of the gene promoter region, which contains a variety of control factors.⁷ Therefore, genetic variants in CYP11B2, which may be associated with the biosynthesis of aldosterone in local tissue, may also affect the progression of renal dysfunction in primary glomerulonephritis. Aldosterone, via its

Corresponding author:

Zongpei Jiang, Department of Nephrology, the Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510655, China. Email: zongpeijiang@yeah.net

Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (http://www.uk.sagepub.com/aboutus/openaccess.htm).

¹Department of Nephrology, Central Hospital of Huizhou, China ²Department of Nephrology, Sixth Affiliated Hospital of Sun Yat-Sen University, China

binding to and activation of the mineralocorticoid receptors, is a main regulator of blood pressure by controlling renal sodium reabsorption.⁸

Gene polymorphism is one of the most important factors taking part in the etiology of some diseases. The evidence from meta-analysis might be powerful compared with the individual investigation. There was no meta-analysis to evaluate the association of the *CYP11B2*-344C/T gene polymorphism with the risk of IgAN and progression of IgAN. This meta-analysis was conducted to investigate whether the *CYP11B2*-344C/T gene polymorphism was associated with the risk of IgAN and the progression of IgAN, by widely collecting reported studies.

Materials and methods

Search strategy

The relevant studies were sought from the electronic databases of PubMed and the Cochrane Library on 1 October 2013. The retrieval strategy of '(IgA nephropathy OR IgA renal disease OR IgAN) AND (aldosterone synthase OR *CYP11B2*) AND (polymorphism OR variant)' was entered into these databases. Additional reports were identified through references cited in recruited articles.

Inclusion and exclusion criteria

Inclusion criteria: (a) The outcome had to be IgAN; (b) there had to be at least two comparison groups (case group vs control group); (c) investigation should provide data on *CYP11B2* genotype distribution.

Exclusion criteria: (a) Review articles and editorials; (b) case reports; (c) preliminary result not on *CYP11B2*-344C/T gene polymorphism or outcome; (d) investigating the role *CYP11B2* gene expression in disease; (e) if multiple publications for the same data from the same study group occurred, we only recruited the later paper into our final analysis.

Data extraction and synthesis

The following information from each eligible study was extracted independently by two investigators: first author's surname, year of publication, ethnicity, genotyping methods, control source of the control group, and the number of cases and controls for *CYP11B2*-344C/T genotypes. The results were compared and disagreement was resolved by discussion.

Statistical analysis

Cochrane Review Manager Version 5 (Cochrane Library, UK) was used to calculate the available data from each study. The pooled statistic was counted using the fixed effects model, but a random effects model was conducted when the *p* value of heterogeneity test was less than $0.1.^{9-11}$ Results were expressed with odds ratios (ORs) for dichotomous data, and 95% confidence intervals (CIs) were also calculated.^{12,13} The value of *p*<0.05 was required for the pooled OR to be statistically significant.¹⁴ *I*² was used to test the heterogeneity among the included studies. Sensitivity analysis was also performed according to source of the controls (healthy vs hospital) and sample size of case (<100 vs ≥100).

Results

Study characteristics

Four studies^{15–18} reporting the relationship between *CYP11B2*-344C/T gene polymorphism and IgAN susceptibility/IgAN progression were included into this metaanalysis. Four investigations^{15–18} were conducted for the association of *CYP11B2*-344C/T gene polymorphism and IgAN risk, and two studies^{15,16} were performed for the relationship between *CYP11B2*-344C/T gene polymorphism and IgAN progression (Table 1). Those four investigations contained 542 IgAN patients and 707 controls. The average distribution frequency of C allele of *CYP11B2*-344C/T in the IgAN group was 32.57% and the average frequency in the control group was 39%. The average distribution frequency of the case group for C allele was lower than that in the control group (case/ control=0.84).

Table I. General characteristics of the included studies in this meta-analysis.

Authors, year	Country/	Ethnicity	Genotyping	Source of	Case				Control			
	District		methods	control	сс	СТ	TT	total	сс	СТ	TT	Total
lgAN risk		7										
Kim et al., 2009 ¹⁵	Asian	Korea	TaqMan	Healthy	26	90	122	238	31	124	145	300
Huang et al., 2010 ¹⁶	Asian	Chinese	PCR-RFLP	Healthy	14	52	64	130	13	52	55	120
Bantis et al., 201117	Caucasian	Germany	PCR-RFLP	Healthy	-	-	48	143	-	_	31	100
Pawlik et al., 2013 ¹⁸	Caucasian	Poland	PCR-RFLP	Healthy	4	15	12	31	48	104	35	187
IgAN progression				-								
Kim et al., 2009 ¹⁵	Asian	Korea	TaqMan	Healthy	-	-	34	66	-	_	88	172
Huang et al., 2010 ¹⁶	Asian	Chinese	PCR-RFLP	Healthy	5	17	25	47	9	35	39	83

IGAN: IgA nephropathy; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

(a)							
(4)	Cae	0	Contr	lo		Odde Ratio	Odde Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% Cl	M-H. Fixed, 95% Cl
Huang 2010	80	260	78	240	27.1%	0.92 [0.63 1.35]	
Kim 2009	142	476	186	600	55.7%	0.95 (0.73, 1.23)	
Pawlik 2013	23	62	200	374	17 3%	0.51 [0.79, 0.89]	
1 411111 2010	20	02	200	014	11.0 %	0.01 [0.20, 0.00]	
Total (95% CI)		798		1214	100.0%	0.87 [0.71, 1.06]	
Total events	245		464				
Heterogeneity: Chi ² =	3.98. df =	2 (P =	0.14); 2:	= 50%			
Test for overall effect	Z=1.42	(P = 0.1)	6)				0.01 0.1 1 10 100
							Favours case Favours control
(b)							
							Partner astron
	Cas	е	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Huang 2010	14	130	13	120	28.3%	0.99 [0.45, 2.21]	7 -
Kim 2009	26	238	31	300	57.4%	1.06 [0.61, 1.85]	
Pawlik 2013	12	31	35	187	14.3%	2.74 [1.22, 6.17]	
Total (95% CI)		399		607	100.0%	1.28 (0.86, 1.91)	·
Total events	52		79				
Heterogeneity Chi ² =	: 4 21 df=	2 (P =	0 12)· ₽:	= 52%			+ + + + + + + + + + + + + + + + + + + +
Test for overall effect	7=1 24	(P = 0.2)	22)	02.10			0.01 0.1 1 10 100
			/				Favours case Favours control
(c)							
	Cae	0	Contr	ol		Odde Patio	Odde Patio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H Fixed 95% CL	MLH Fixed 95% Cl
Bantis 2011	48	143	31	100	19.9%	1 1 2 10 65 1 941	
Huang 2010	64	130	55	120	23.8%	1 15 [0 70 1 88]	-
Kim 2009	122	238	145	300	51.3%	1 12 [0 80 1 58]	+
Pawlik 2013	12	31	36	187	5.0%	2 74 [1 22 6 17]	T
1 GWIR 2015	12	51	55	107	5.0 %	2.04 [1.22, 0.17]	
Total (95% CI)		542		707	100.0%	1.21 [0.95, 1.54]	•
Total events	246		266				
Heterogeneity; Chi ² =	4.21. df =	3 (P =	0.24); 12:	= 29%			
Test for overall effect	Z=1.57	(P = 0.1)	2)				0.01 0.1 1 10 100
			-				Favours case Favours control

Figure 1. Association of aldosterone synthase CYP11B2-344C/T gene polymorphism with IgA nephropathy (IgAN) risk in overall populations. (a) C vs T; (b) CC vs CT + TT; (c) TT vs CT + CC.

Association of CYPIIB2-344C/T gene polymorphism with IgAN susceptibility

The *CYP11B2*-344C/T gene polymorphism was not associated with IgAN risk for overall populations and Asians in this meta-analysis, (overall populations: C allele: OR=0.87, 95% CI: 0.71-1.06, p=0.16; CC: OR=1.28, 95% CI: 0.86-1.91, p=0.22; TT: OR=1.21, 95% CI: 0.95-1.54, p=0.12; Asians: C allele: OR=0.94, 95% CI: 0.76-1.16, p=0.56; CC: OR=1.04, 95% CI: 0.66-1.64, p=0.86; TT: OR=1.13, 95% CI: 0.85-1.50, p=0.39; Figure 1 for overall populations, Table 2). Interestingly, C allele and CC genotype were associated with the risk of IgAN in Caucasians, but not the TT genotype (C allele: OR=0.51, 95% CI: 0.29-0.89, p=0.02; CC: OR=2.74, 95% CI: 1.22-6.17, p=0.01; TT: OR=1.67, 95% CI: 0.70-3.98, p=0.25; Table 2).

Association of CYPIIB2-344C/T gene polymorphism with IgAN progression

In this meta-analysis, all the included studies were from the Asian population, and *CYP11B2*-344C/T gene polymorphism was not associated with IgAN progression in overall populations and Asians (overall populations: C allele: OR=0.86, 95% CI: 0.49–1.49, p=0.59; CC: OR=0.98, 95% CI: 0.31–3.11, p=0.97; TT: OR=1.11, 95% CI: 0.71–1.73, p=0.65; Asians: C allele: OR=0.86, 95% CI: 0.49–1.49, p=0.59; CC: OR=0.98, 95% CI: 0.31–3.11, p=0.97; TT: OR=1.11, p=0.97; CI: 0.71–1.73, p=0.65; Figure 2 and Table 2).

Sensitivity analysis

Sensitivity analysis for the relationship between *CYP11B2* -344C/T gene polymorphism and IgAN risk was also

Genetic contrasts	Group and subgroups	Studies number	Q test p value	Model selected	OR (95% CI)	Þ
lgAN risk						
C vs T	Overall	3	0.14	Fixed	0.87(0.71-1.06)	0.16
	Asian	2	0.92	Fixed	0.94(0.76-1.16)	0.56
	Caucasian	I	-	Fixed	0.51 (0.29-0.89)	0.02
CC vs CT+TT	Overall	3	0.12	Fixed	1.28(0.86-1.91)	0.22
	Asian	2	0.89	Fixed	1.04(0.66-1.64)	0.86
	Caucasian	I	-	Fixed	2.74(1.22-6.17)	0.01
TT vs CT+CC	Overall	4	0.24	Fixed	1.21 (0.95-1.54)	0.12
	Asian	2	0.95	Fixed	1.13(0.85-1.50)	0.39
	Caucasian	2	0.07	Random	1.67(0.70-3.98)	0.25
IgAN progression						
C vs T	Overall	I	_	Fixed	0.86(0.49-1.49)	0.59
	Asian	I	_	Fixed	0.86(0.49-1.49)	0.59
CC vs CT+TT	Overall	I	-	Fixed	0.98(0.31-3.11)	0.97
	Asian	I	-	Fixed	0.98(0.31-3.11)	0.97
TT vs CT+CC	Overall	2	0.62	Fixed	1.11(0.71–1.73)	0.65
	Asian	2	0.62	Fixed	1.11(0.71–1.73)	0.65

 Table 2.
 Meta-analysis of the association of CYPI IB2-344C/T gene polymorphism with IgA nephropathy (IgAN) risk and IgAN progression.

CI: confidence interval; OR: odds ratio.



Figure 2. Association of aldosterone synthase *CYP1 IB2-344C/T* gene polymorphism with IgA nephropathy (IgAN) progression in overall populations. (a) C vs T; (b) CC vs CT + TT; (c) TT vs CT + CC.

Sensitivity analysis for the relationship between *CYP11B2*-344C/T gene polymorphism and IgAN risk was also performed according to sample size of case (<100 vs \geq 100). We found that the results were also similar to the non-sensitivity analysis, but the *CYP11B2*-344C/T gene polymorphism was not associated with IgAN risk in the sensitivity analysis according to sample size of less than 100 (data not shown).

Discussion

Gene polymorphism, one of the most important factors, takes part in the etiology of IgAN disease. There were some interesting studies performed to assess the association of the polymorphism of some genes with IgAN risk or IgAN progression. Zhou et al.² performed a meta-analysis to evaluate the association between angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism and end-stage renal disease (ESRD) susceptibility in IgAN patients, and reported that the DD homozygote was a significant genetic molecular marker for the onset of ESRD in IgAN patients. Qin et al.³ performed a meta-analysis to evaluate the association of ACE gene polymorphism with IgAN in different ethnic groups, and showed that the D allele or DD genotype was associated with IgAN risk in the Asian population, but not in the Caucasian population; there was no significant association between the D allele or DD gene and IgAN progression for Asians and Caucasians. In this meta-analysis, we also performed a meta-analysis to assess the association of CYP11B2-344C/T gene polymorphism and IgAN risk or IgAN progression.

In this study, the average distribution frequency of *CYP11B2*-344C/T C allele in the IgAN group was 0.84-fold increased when compared with that in control group. The average distribution frequency data indicated that the *CYP11B2*-344C/T C allele in IgAN group was lower when compared with that in control group. However, there were only three studies for this calculation, and this result might be less robust.

There was no meta-analysis performed to investigate the association of *CYP11B2*-344C/T gene polymorphism and the risk of IgAN in the past. This study was conducted firstly to assess the relationship between *CYP11B2*-344C/T gene polymorphism and the risk of IgAN and the progression of IgAN.

Four studies were included in this meta-analysis. We found that most of them reported that *CYP11B2*-344C/T gene polymorphism was not associated with the risk of IgAN. Kim et al.¹⁵ included a total of 238 IgAN and 300

healthy cohorts in their study, and showed that the genotype distributions of the polymorphisms were similar between patients and controls, and the individual genotypes taken alone were not associated with the progression of renal dysfunction. Huang et al.¹⁶ included 130 Chinese patients with IgAN and 120 healthy Chinese subjects, and reported that the CYP11B2-344C/T genotype distributions were similar in patients with IgAN and in controls, and the CYP11B2-344C/T gene polymorphism was not associated with ESRD progression in IgAN-ESRD patients. Bantis et al.¹⁷ conducted a study in 143 patients with biopsyproven IgAN and 100 healthy controls, and indicated that aldosterone synthase gene C-344T polymorphism was a risk factor for accelerated progression in Caucasian patients with IgAN. Pawlik et al.¹⁸ included 31 IgAN patients and 187 controls, and reported that the CYP11B2-344C/T gene polymorphism might be an independent risk factor for IgAN. These two studies from the Caucasian population might get a more positive result than in the Asian population.

Our meta-analysis indicated that the *CYP11B2*-344C/T gene polymorphism was not associated with IgAN risk for overall populations and Asians in this meta-analysis. Interestingly, the C allele and CC genotype were associated with the risk of IgAN in Caucasians, but the TT genotype not. The outcome might be robust to some extent. However, those findings should be regarded cautiously because many other ingredients, such as small sample size of the included report, limited statistical power, heterogeneity of enrolled cases, variable study designs and different interventions, were closely related to affect the results. Since the number of included studies is rather small, more studies should be performed to evaluate the relationship in the future.

In conclusion, the results in our study support that *CYP11B2*-344C/T gene polymorphism was not associated with IgAN risk for overall populations and Asians in this meta-analysis. Interestingly, C allele and CC genotype were associated with the risk of IgAN in Caucasians, but not the TT genotype. However, more association investigations are required to further clarify the role of the *CYP11B2*-344C/T gene polymorphism in predicting the risk of IgAN and the progression of IgAN.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

 Hastings MC, Moldoveanu Z, Suzuki H, et al. Biomarkers in IgA nephropathy: Relationship to pathogenetic hits. *Expert Opin Med Diagn* 2013; 7: 615–627.

- 2. Zhou TB, Yin SS and Liang R. A meta-analysis of the association between angiotensin-converting enzyme insertion/deletion gene polymorphism and end-stage renal disease risk in IgA nephropathy patients. *J Renin Angiotensin Aldosterone Syst* 2013; 14: 235–241.
- Qin YH, Zhou TB, Su LN, et al. Association between ACE polymorphism and risk of IgA nephropathy: A meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 215–223.
- Han SR, Kim CJ and Lee BC. Impact of the -675 4G/5G polymorphism of the plasminogen activator inhibitor-1 gene on childhood IgA nephropathy. *Exp Ther Med* 2012; 3: 703–706.
- Suh JS, Cho SH, Chung JH, Moon A, Park YK and Cho BS. A polymorphism of interleukin-22 receptor alpha-1 is associated with the development of childhood IgA nephropathy. *J Interferon Cytokine Res* 2013; 33: 571–577.
- Zhou XJ, Cheng FJ, Qi YY, et al. FCGR2B and FCRLB gene polymorphisms associated with IgA nephropathy. *PLoS One* 2013; 8: e61208.
- Song J, Narita I, Goto S, et al. Gender specific association of aldosterone synthase gene polymorphism with renal survival in patients with IgA nephropathy. *J Med Genet* 2003; 40: 372–376.
- Galmiche G, Pizard A, Gueret A, et al. Smooth muscle cell mineralocorticoid receptors are mandatory for aldosteronesalt to induce vascular stiffness. *Hypertension* 2013. Epub ahead of print 2 December 2013. DOI: 10.1161/HYPERTE NSIONAHA.113.01967.
- Zhou TB, Qin YH, Su LN, et al. The association between angiotensin-converting enzyme insertion/deletion gene variant and risk of focal segmental glomerulosclerosis: A systematic review and meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 624–633.
- 10. Zhou TB, Chen Z, Qin YH, et al. Association of angiotensin-converting enzyme insertion/deletion gene polymorphism with susceptibility of minimal change nephrotic

syndrome in Asians: A meta-analysis. J Renin Angiotensin Aldosterone Syst 2012; 13: 407.

- Zhou TB, Lin N, Liu YG, et al. Association of ACE I/D gene polymorphism with vesicoureteral reflux susceptibility in children: A meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2012; 13: 273–281.
- Zhou TB, Qin YH, Su LN, et al. Insertion/deletion (I/D) polymorphism of angiotensin-converting enzyme gene in steroid-resistant nephrotic syndrome for children: A genetic association study and meta-analysis. *Ren Fail* 2011; 33: 741–748.
- Zhou TB, Yin SS and Qin YH. Association between angiotensin-converting enzyme insertion/deletion gene polymorphism and end-stage renal disease susceptibility. *J Renin Angiotensin Aldosterone Syst* 2012. Epub ahead of print 17 October 2012. DOI: 10.1177/1470320312460898.
- Zhou TB, Qin YH and Xu HL. Association of apoE gene expression and its gene polymorphism with nephrotic syndrome susceptibility: A meta-analysis of experimental and human studies. *Mol Biol Rep* 2012; 39: 9347–9354.
- 15. Kim SM, Chin HJ, Oh YK, et al. Blood pressure-related genes and the progression of IgA nephropathy. *Nephron Clin Pract* 2009; 113: c301–c308.
- Huang HD, Lin FJ, Li XJ, et al. Genetic polymorphisms of the renin-angiotensin-aldosterone system in Chinese patients with end-stage renal disease secondary to IgA nephropathy. *Chin Med J (Engl)* 2010; 123: 3238–3242.
- Bantis C, Heering PJ, Siekierka-Harreis M, et al. Impact of aldosterone synthase gene C-344T polymorphism on IgA nephropathy. *Ren Fail* 2011; 33: 393–397.
- Pawlik M, Mostowska A, Lianeri M, et al. Association of aldosterone synthase (CYP11B2) gene-344T/C polymorphism with the risk of primary chronic glomerulonephritis in the Polish population. *J Renin Angiotensin Aldosterone Syst* 2013. Epub ahead of print 16 May 2013. DOI: 10.1177/1470320313489588.