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Genetic association of ACE gene I/D polymorphism with the risk of diabetic kidney disease; a meta-analysis

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ABSTRACT

Introduction: Diabetic nephropathy (DN) is a progressive renal disease characterized by persistent albuminuria that leads to end-stage renal disease in both type 1 diabetes (T1DM) and type 2 diabetes (T2DM) patients. The renin-angiotensin-aldosterone system (RAAS) plays a major role in the onset and progression of DN.

Objectives: The present meta-analysis is intended to synthesize evidence on the association between ACE gene insertion and deletion (ACE I/D) polymorphism and the risk of DN.

Methods: PubMed, Scopus, Google Scholar and Embase were searched to retrieve relevant publications. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the association between ACE I/D polymorphism and DN risk. The Cochrane Q test and I^2 statistic were used to detect heterogeneity. To assess between-study heterogeneity, subgroup analysis and sensitivity analysis were performed. Funnel plots and Egger's test were used to estimate publication bias.

Results: Around 45 articles (47 studies) with 6124 patients of DN and 2492 T2DM patients (controls) were ultimately considered for meta-analysis. Overall, the ACE I/D polymorphism was associated with DN under three different genetic models (allelic model: OR = 1.34; 95% CI: 1.20-1.49; $P<0.001$; dominant model: OR= 1.54; 95% CI: 1.31- 1.81; $P<0.001$; and recessive model: OR= 1.39; 95% CI: 1.19- 1.63; $P<0.001$). Significant heterogeneity ($I^2 > 50\%$) was present in the analysis for all ethnic groups. Further, there is no evidence for publication bias in this meta-analysis.

Conclusion: The current meta-analysis provided confirmation that the ACE I/D polymorphism is correlated with an increased risk of DN in patients with T2DM and the D allele of ACE I/D was a susceptible factor.

Implication for health policy/practice/research/medical education:
Diabetic nephropathy (DN) is one of the most common causes of renal impairment in patients with diabetes. Renin-angiotensin-aldosterone system (RAAS) that controls body's blood pressure is an independent risk factor of DN. Several studies have investigated ACE I/D as a risk factor in DN; however, the results are inconclusive. Our meta-analysis of ACE I/D studies indicated that this variant increases the risk of developing DN.

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Review

Introduction

Diabetic nephropathy (DN) is one of the causes of renal impairment in type 1 diabetic (T1DM) or type 2 diabetic (T2DM) patients that leads to dialysis or kidney transplantation (1). About 40% of people with diabetes develop DN. DN is characterized by reduced glomerulus function, increased albumin excretion through urine and gradual loss of renal function (2). Chronic hyperglycemia linked with variations in blood pressure (BP) may adversely affect renal function. Hence maintaining blood sugar and controlling BP may delay the progression of DN (3). Clustering of DN in T2DM families indicates a strong

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genetic susceptibility for its development and progression (4). Therefore several genetic factors have been studied to unveil the predisposition to the development of DN in T2DM patients. Due to technical advances in DNA sequencing methods, several candidate susceptibility genes of DN have so far been identified and studied extensively (5).

Several lines of evidence indicated that the renin-angiotensin-aldosterone system (RAAS) regulating body's blood pressure is an independent risk factor of chronic kidney disease (CKD) (6). Further, the use of angiotensin-converting enzyme (ACE) inhibitors prevents progression to CKD (7). Therefore the genes involved in this RAAS pathway were studied for their association with the development of DN. ACE transforms angiotensin I to angiotensin II and consequently regulates the activity of angiotensin (8). The expression of ACE was found in proximal tubule brush borders and glomerular endothelial cells of the kidney (9).

The gene coding for ACE is located at chromosome region 17q23.3. Intron 16 of ACE gene has an insertion (I allele) and deletion (D allele) (ACE I/D) functional polymorphism. The D allele has been shown to result in higher levels of circulating ACE (10). In recent years, the relationship between ACE I/D polymorphism and DN has been reported in many studies (11). However, the correlation between ACE I/D and DN remains controversial. In the present study, we performed a meta-analysis to investigate whether ACE I/D polymorphism is associated with DN risk or not.

Materials and Methods

Literature search and selection

To synthesize evidence on the association between ACE gene I/D polymorphism and the risk of DN, a meta-analysis was conducted. For this purpose, PubMed, Scopus, Embase and Google Scholar were searched, to retrieve association studies published as of August 20, 2019. The keywords used were "angiotensin converting enzyme", "ACE", "ACE I/D", "diabetic nephropathy", "T2DN", "diabetic kidney disease" and "insertion-deletion polymorphism". The search of articles is restricted to the English language. Inclusion criteria were as follows: (1) article should study the association between type 2 diabetic nephropathy (T2DN) and ACE I/D polymorphism; (2); the study should provide ACE genotype distribution; (3) case-control study design; and (4) a comparison between a T2DN group and a T2DM control group. Exclusion criteria were as follows: (1) the study did not meet the inclusion criteria; (2) studies with ACE I/D polymorphism and T1DM and (3) articles not written in English. From all eligible studies, lead author's name, publication year, country of origin, ethnicity, and genotypes from T2DN and T2DM groups were collected.

Statistical analysis

The association between ACE gene I/D polymorphism and DN in T2DM were estimated for each study and pooled odds ratios (ORs) with a 95% confidence interval (CI) were calculated in allelic, dominant and recessive genetic models. The presence of heterogeneity between studies was assessed with the Q test and I^2 statistics. Random-effects model (REM) or fixed-effects model (FEM) was used based on the presence or absence of heterogeneity. To test for robustness of the meta-analysis, we conducted a sensitivity analysis by excluding one study each time and estimating the pooled OR for the rest of the studies. The publication bias for comparisons was assessed by funnel plot and Egger's test. An ethnicity-based subgroup analysis was performed to assess the geographic-specific effects on the meta-analysis. Data for the meta-analysis were analyzed using a web tool MetaGenyo (12).

Results

Study characteristics

The search strategy adopted in the meta-analysis is depicted in Figure 1. Our systematic search identified 45 papers (47 studies) that analyzing the association between ACE gene I/D polymorphism nephropathy in T2DM patients. The study by Jayapalan et al included Malaysian, Chinese and Indian patients and hence it was considered as three independent studies (13). The basic characteristics of each study along with their genotype frequencies of ACE gene I/D polymorphism were documented in Table 1. The years of publication spanned from 1994 and 2018. The ACE I/D polymorphism deviated from Hardy–Weinberg

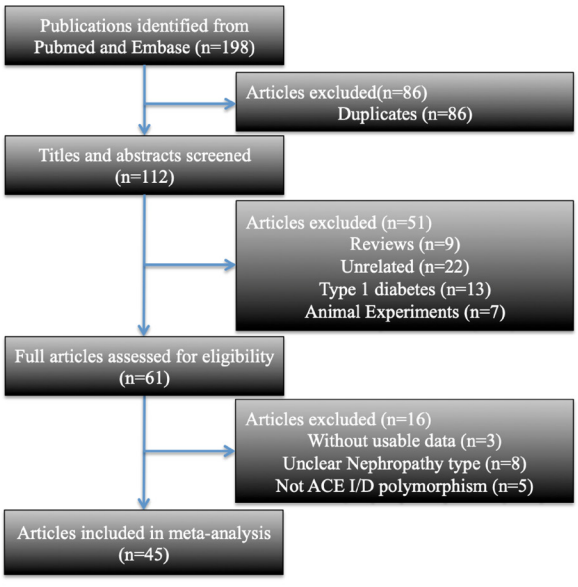

Figure 1. Study selection flow chart of meta-analysis.

Table 1. The distribution of ACE I/D polymorphism genotypes in T2DM patients with or without diabetic nephropathy

Author, year	Ethnicity	Country	DN+ ACE genotypes			DN-ACE genotypes			DN criteria	HW *P* value	Ref.
			II	ID	DD	II	ID	DD			
Powrie et al	Caucasian	Australia	4	8	7	24	37	24	ACR >3 mg/mmol	0.233	(14)
Doria et al	Caucasian	USA	15	35	24	20	41	16	UAE >30 µg/min	0.552	(15)
Fujisawa et al	Asian	Japan	24	23	7	17	12	6	Proteinuria/hemodialysis	0.157	(16)
Mizuiri et al	Asian	Japan	11	50	19	11	11	9	UAE >20 µg/min	0.110	(17)
Panagiotopoulos et al	Caucasian	Australia	10	25	15	29	44	42	UAE >20 µg/min	0.016	(18)
Schmidt et al	Caucasian	Germany	41	105	101	34	91	83	UAE >20 µg/min	0.289	(19)
Yoshida et al	Asian	Japan	43	46	7	25	28	19	SCr >2 mg/dL	0.066	(20)
Ringel et al	Caucasian	Germany	33	84	44	36	69	35	UAE >30 mg/d	0.866	(21)
Schmidt et al	Caucasian	Germany	61	129	121	62	154	131	UAE >30 mg/d	0.158	(22)
Grzeszczak et al	Caucasian	Poland	103	230	129	63	118	73	ACR (men >1.9 mg/mol & women >2.8 mg/mol)	0.269	(23)
Hanyu et al	Asian	Japan	7	13	4	14	5	2	UAE >20 µg/min	0.180	(24)
Wong et al	Asian	China	20	17	4	49	46	13	UAE >30 mg/d	0.665	(25)
Tomino et al	Asian	Japan	310	337	98	163	189	55	UAE >20 µg/min	0.986	(26)
Taniwaki et al	Asian	Japan	32	40	14	31	26	12	UAE >30 mg/d	0.125	(11)
Gohda et al	Asian	Japan	47	55	25	271	259	91	UAE >30 mg/d	0.026	(27)
Viswanathan et al	Asian	India	17	45	24	10	8	5	Proteinuria >500 mg/dL	0.196	(28)
Ha et al	Asian	Korea	35	62	43	33	57	9	Creatinine >2 mg/dL	0.026	(29)
Arzu Ergen et al	Caucasian	Turkey	5	11	9	5	21	24	UAE >300 mg/d	0.897	(30)
Prasad et al	Asian	India	67	74	55	76	97	52	UAE rate > 200 mg/L	0.055	(31)
Nikzamir et al	Caucasian	Iran	12	47	26	16	52	17	UAE >30 mg/d	0.039	(32)
Uddin et al	Asian	Bangladesh	13	22	24	24	28	14	UAE >500 mg/d	0.285	(33)
Arfa et al	Caucasian	Tunisia	9	41	40	6	24	21	UAE >30 mg/d	0.829	(34)
Ezzidi et al	Caucasian	Tunisia	88	260	167	156	192	54	ACR >30 mg/d	0.674	(35)
Ahluwalia et al	Asian	India	44	64	132	49	117	89	UAE >200 µg/min and ACR >300 mg/g	0.345	(36)
Palomo-Pinon et al	Caucasian	Mexico	87	105	43	85	91	24	ACR >30 mg/g	0.962	(37)
Naresh et al	Asian	India	4	15	11	12	7	11	UAE >500 mg/d	0.004	(38)
Jayapalan et al	Asian	Malaysia	35	26	8	22	18	3	ACR >30 mg/g	0.792	(13)
Jayapalan et al	Asian	China	7	16	1	14	12	7	ACR >30 mg/g	0.171	(13)
Jayapalan et al	Asian	India	11	15	8	19	21	13	ACR >30 mg/g	0.151	(13)
Al-Harbi et al	Caucasian	Bahrain	12	39	59	79	75	96	Not mentioned	<0.001	(39)
Felehgari et al	Caucasian	Iran	6	30	32	14	32	26	ACR >300 mg/g	0.467	(40)
Patel et al	Asian	India	10	24	27	58	66	42	UAE >20 mg/d	0.011	(41)
Paz-Pacheco et al	Asian	Philippines	6	11	4	13	5	3	UAE >20 mg/L	0.078	(42)
El-Baz et al	Caucasian	Saudi Arabia	4	58	40	5	72	23	ACR >30 mg/g	<0.001	(43)
Shaikh et al	Asian	Pakistan	18	98	52	123	148	25	UAE >300 mg/d	0.034	(44)
Rahimi et al	Caucasian	Iran	19	66	55	14	32	26	ACR >30 mg/g	0.467	(45)
Bhaskar et al	Asian	India	14	29	11	24	30	13	UAE >300 mg/d	0.514	(46)
Shaker et al	Caucasian	Egypt	7	13	25	10	20	10	ACR > 30 mg/g	1.000	(47)
Shaikh et al	Asian	Pakistan	27	45	38	33	41	41	GFR (mL/min)	0.002	(48)
Hussein et al	Asian	Iraq	16	56	25	20	18	13	UAE >300 mg,day	0.045	(49)
Seruga et al	Caucasian	Solvenia	43	143	90	91	169	115	GFR (mL/min)	0.066	(50)
Wang et al	Asian	China	8	26	20	26	33	15	ACR > 30 mg/g	0.449	(51)
Fawwaz et al	Caucasian	Lebanon	6	20	24	14	29	21	Not mentioned	0.508	(52)
Alharbi	Caucasian	Saudi Arabia	5	21	35	10	27	24	UAE >300 mg/d	0.609	(53)
Mansouri et al	Caucasian	Morocco	12	42	76	6	32	47	ACR >30 mg/g	0.863	(54)
Wyawahare et al	Asian	India	52	56	21	18	26	6	ACR >30 mg/g	0.464	(55)
Abuaisha et al	Caucasian	Palestine	1	28	14	0	28	13	Not mentioned	0.001	(56)

equilibrium (HWE) in control group of 11 studies (Table 1). As the comparison group (T2DM) is already having selection, deviation from HWE is not a serious concern in this meta-analysis.

Association of ACE gene I/D polymorphism with susceptibility to DN

The forest plot depicts the relationship of ACE I/D polymorphism with DN in independent studies, as well as an overall pooled estimate in dominant model (Figure 2). As there is a significant between-study heterogeneity, the REM was used to estimate OR. Values related to the association between DN and ACE I/D polymorphism in three genetic models (allele contrast (D versus I), dominant model (DD+ID versus II) and recessive model (DD vs ID+II) were documented in Table 2. Patients with DD/ID genotype were 1.54 times higher to develop DN compared with those who carry the II genotype (OR=1.54, 95% CI 1.31-1.81; I^2: 65%). Similarly, increased risk of DN was found in allelic (OR=1.34; 95% CI: 1.20- 1.49; I^2: 72%) and recessive models (OR=1.39; 95% CI 1.19- 1.63; I^2: 64%). On stratification, both Asian populations and Caucasian populations showed a significant association between ACE I/D polymorphism and DN risk under any genetic models tested (Table 2).

Sensitivity analysis and publication bias

In sensitivity analysis, pooled effect estimates by omitting one study each time were depicted in Figure 3. In the present meta-analysis, there was no substantial deviation in the levels of significance and OR when we omitted one study at a time. There is no evidence of asymmetry in the shape of the funnel's plot (Figure 4). Further, Egger's test (Table 2) also revealed no publication bias (D versus I: Egger's test P = 0.764; DD+ID versus II: Egger's test P = 0.157; DD versus ID+II: Egger's test P = 0.594).

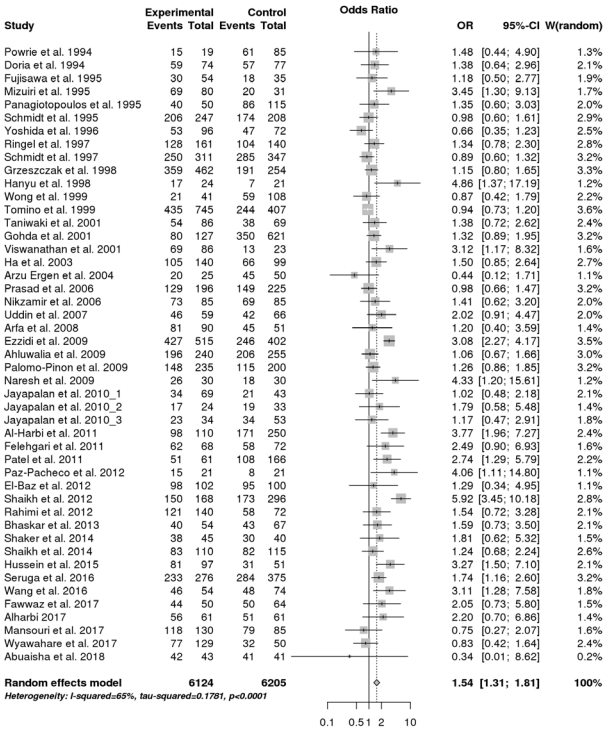

Figure 2. Forest Plot of meta-analysis on ACE I/D polymorphism and diabetic nephropathy.

Discussion

Based on 47 independent case-control studies, including 6124 patients of DN and 2492 T2DM patients (controls), we investigated the association between the ACE I/D polymorphism and DN risk. An significant association between the ACE gene I/D variant and DN risk was found in all genetic models. Sub-group analysis in Asian and Caucasian ethnic backgrounds also revealed a significant association between ACE I/D polymorphism and DN. Meta-analysis of studies on ACE I/D reveals significant heterogeneity between studies. Further, there is no evidence for publication bias on association between ACE gene I/D polymorphism and DN.

DN is one of the most common complications of long-standing T1DM and T2DM. Diabetic kidney disease is

Table 2. Association of ACE I/D polymorphisms and DN in different genetic models

ACE ID	DN vs. DM patients		
	By ethnicity		
	Overall	Asian	Caucasian
No. of studies	47	25	22
Allele contrast (D vs. I)			
I^2 %	72	74	71
Heterogeneity P value	<0.001	<0.001	<0.001
OR	1.34	1.37	1.31
95% CI	(1.20-1.49)	(1.15- 1.62)	(1.13-1.52)
Association P value	<0.001	<0.001	<0.001
Egger's test P value	0.764	0.483	0.711
Dominant model (ID+DD vs. II)			
I^2 %	65	70	58
Heterogeneity P value	<0.001	<0.001	<0.001
OR	1.54	1.63	1.47
95% CI	(1.31-1.81)	(1.28-2.07)	(1.17-1.84)
Association P value	<0.001	<0.001	<0.001
Egger's test P value	0.157	0.005	0.425
Recessive model (DD vs. II+ID)			
I^2 %	64	68	60
Heterogeneity P value	<0.001	<0.001	<0.001
OR	1.39	1.35	1.40
95% CI	(1.19- 1.63)	(1.03- 1.77)	(1.16-1.69)
Association P value	<0.001	0.029	<0.001
Egger's test P value	0.594	0.233	0.598

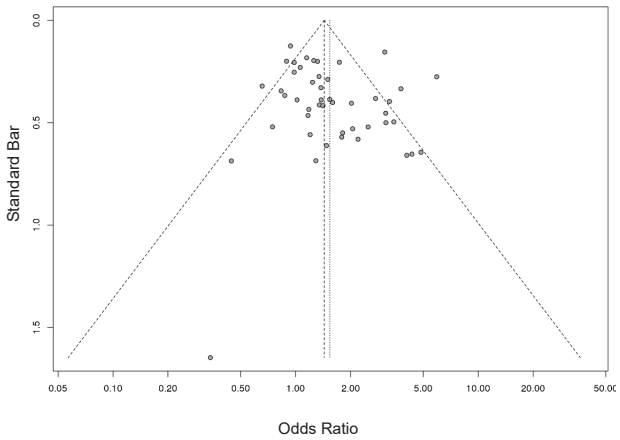

Figure 3. Funnel plot for publication bias in the meta-analysis of ACE I/D polymorphism and diabetic nephropathy risk.

a significant cause of CKD and end-stage renal disease. Almost double the prevalence of hypertension was found in diabetes patients as compared to the general population (57). Although hypertension co-occurs with microalbuminuria or overt nephropathy in T1DM patients, it can be seen prior to kidney disease in T2DM patients (58). Some studies suggested that hypertension is already occurred in newly diagnosed T2DM (59). The development of hypertension in diabetics can partly be explained by the presence of increased inflammation and vascular dysfunction associated with the imbalance between angiotensin II-angiotensin1-7 (60). Hence hypertension is one of the extremely important factors that influence the onset of nephropathy in T1DM or T2DM patients. It is widely recognized that the ACE inhibitor therapy could able to reduce the advancement of DN in patients with T1DM and T2DM (61). Hence ACE is suspected to play a key role as antiproteinuric or renal protective agent. Further, reduced expression of ACE in kidneys of diabetic rats and human diseases suggests its involvement in DN (62).

Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) cohort study on T1DM patients suggested that the ACE II genotype conferred a lower risk for persistent microalbuminuria and severe nephropathy (63). In contrast to this, carriers of ID or DD genotype showed lower incidence of end-stage renal failure in T2DM patients (64). However, the correlation between ACE I/D and DN remains controversial. Our findings from the present meta-analysis are consistent with the findings of the previous meta-analyses, in which significant association between the ACE gene I/D and DN risk was inferred (65-67). In support of this higher ACE activity level was documented in DD and ID+DD carriers (40).

Some limitations should be taken into consideration

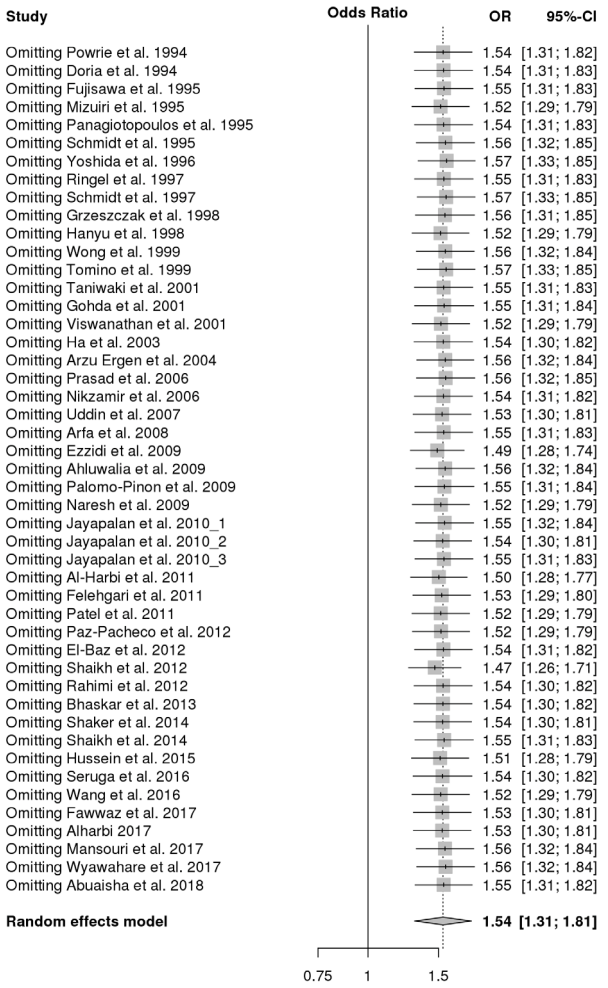

Figure 4. Forest plot in the sensitivity analysis of the ACE I/D polymorphism and diabetic nephropathy risk.

while interpreting our results. Although there is no difference in the ACE I/D genotyping methodology, there were still other existing heterogeneities, such as the diagnostic criteria of DN, selection of controls and race. Further, it should be noted that no access to the diet of subjects (salt and fat consumption) might modulate the effects of ACE I/D polymorphism in DN.

Conclusion

In conclusion, this meta-analysis demonstrated that ACE gene I/D is a risk factor for DN. Further research should be performed to investigate the interactions between hypertension, diabetes duration, RAAS pathway polymorphisms and the risk of DN.

Authors' contribution

BVKSL conceived the study. BVKSL, RLK , HKV and SP performed data collection. BVKSL, RLK, HKV and SP analyzed the data. BVKSL, RLK, HKV and SP wrote

the manuscript. All authors have seen and approved the manuscript.

Conflicts of interest

There is not conflict of interest in this met-analysis.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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