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The K469E genetic variant in the *ICAM1* gene is associated with type 2 diabetes but not with its vascular complications: a meta-analysis

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by diminished insulin secretion and hyperglycemia leading to damage of multiple organs. The present study is aimed to test the association between type 2 diabetes vascular complications and K469E variant (rs5498) of the intercellular adhesion molecule-1 (*ICAM1*) gene.
Methods: Online databases were searched to retrieve all publications relating to the ICAM1 rs5498 variant in human diabetic vascular complications. In the present meta-analysis, we included all eligible studies and calculated the pooled results using MetaGenyo web tool.
Results: Studies concerning *ICAM1* gene K469E variant association with either type 2 diabetes or diabetes related vascular complications were included in this meta-analysis. Fifteen articles were included in this analysis (n=10 for T2DM; n=5 for diabetes nephropathy; n=8 for diabetes retinopathy). *ICAM1* K469E variant significantly increased the risk of T2DM in the allelic (OR = 1.10, 95% CI: 1.01-1.20, $P = 0.032$) and recessive models (OR = 1.27, 95% CI: 1.08-1.49, $P = 0.004$). However, the *ICAM1* gene K469E variant is not associated with diabetic nephropathy or diabetic retinopathy. No noticeable evidence of publication bias was detected.
Conclusion: In summary, our study indicated that *ICAM1* K469E variant was significantly associated with the increased risk of diabetes but not with the diabetic vascular complications.

Implication for health policy/practice/research/medical education:
Diabetes mellitus is a chronic metabolic disease characterised by diminished insulin secretion and hyperglycemia leading to damage of multiple organs. Intracellular adhesion molecule 1 (ICAM1) is a cell surface glycoprotein that expressed in endothelial cells as well as leucocytes. Several studies have examined the relationship between ICAM1 K469E genetic variant and diabetic vascular complications; however, the results are inconclusive. We performed a meta-analysis of ICAM1 K469E studies. Our study indicated that the ICAM1 K469E variant was significantly associated with the increased risk of diabetes, but not with the diabetic vascular complications.
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Introduction

Diabetes mellitus is a chronic metabolic disease characterized by diminished insulin secretion and hyperglycemia leading to damage of multiple organs (1). Long-term diabetes is associated with the damage of macro and microvasculature of various organs and increases the risk for cardiovascular diseases (2). The diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic neuropathy are the main microvascular complications. Coronary artery disease, peripheral vascular disease, and stroke are major macrovascular complications. Although the exact mechanisms underlying diabetic vascular complications are not fully understood, a common pathological hallmark is the presence of endothelial dysfunction and followed by inflammation (3,4). Lowering blood glucose and controlling blood pressure is the main therapeutic approach to manage the vascular complications of diabetes. Diabetic nephropathy occurs in 30%-40% of diabetic patients and DR affects up to 80% of long standing diabetes patients. Recent studies have shown that the DR itself is a predictive factor for DN (5,6).

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Diabetes, DN and DR are multifactorial and polygenic diseases that are influenced by both environmental and genetic factors. It has been shown that some genetic variants predispose individuals to diabetes and diabetic vascular complications (7). Intercellular adhesion molecule 1 (ICAM1) is a distinct cell surface glycoprotein that expressed in endothelial cells as well as leukocytes. Several lines of evidence demonstrated that the ICAM1 play a major role in the pathogenesis of diabetes, DN and DR (8,9). The gene coding for ICAM1 has been mapped to chromosome 19p13.2. Two genetic variants of the *ICAM1* gene (K469E and G241R) have been identified and studied for their association with vascular complications in various diseases (10-13). The K469E variant (rs5498) is located in exon 6 and encodes Ig-like domain 5-Lys or Glu (14). This substitution was known to affect the topology of ICAM1. Several studies have examined the relationship between ICAM1 K469E genetic variant and diabetic vascular complications; however, the results are inconclusive (12,15-18). Hence we conducted this meta-analysis to investigate the relationship between ICAM1 K469E variant and type 2 diabetes and related vascular complications.

Materials and Methods

Literature search

Studies assessing the association between diabetic vascular complications and *ICAM1* K469E variant were identified through searching the PubMed, Web of Science and Embase databases. The retrieval strategy was covering the search terms "*ICAM1*, 1462A>G, K469E; rs5498, type 2 diabetes, diabetic complications, diabetic nephropathy, diabetic retinopathy, intercellular adhesion molecule-1, gene polymorphism, genetic variant". The last search update was conducted on July 31, 2019. No language restrictions were imposed. From all suitable studies, name of the first author, year of publication, country of publication, ethnicity, genotyping method, genotypes from both cases and controls were collected.

Statistical analysis

The association between diabetic vascular complications and *ICAM1* K469E variant was assessed by odds ratio (OR) with a 95% confidence interval (CI). Allelic and dominant genetic models were adopted to estimate the pooled OR and 95% CI. To evaluate the between-study heterogeneity, we used Q and I^2 statistics. Egger's test and Begg's funnel plot was used to determine the publication bias. All statistical analysis were done using a web tool MetaGenyo (19).

Results

The literature selection process is depicted in Figure 1. There are 15 articles that deal with the ICAM1 gene K469E variant association with either type 2 diabetes or diabetes-related vascular complications. Of the fifteen articles selected, genotype data for pooled analysis of type 2 diabetes mellitus (T2DM), DN and DR comparisons were found respectively in 10, 5 and 8 articles. General characters and genotype data of the studies selected for this meta-analysis were presented in Table 1.

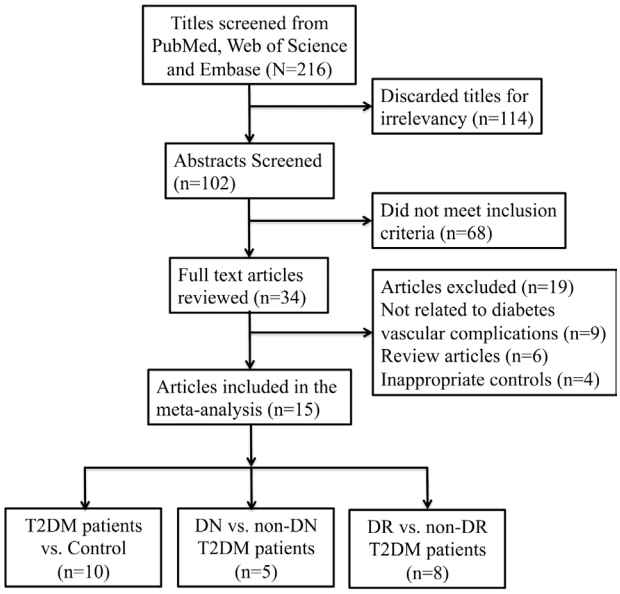

Figure 1. Flow diagram depicting the detailed process of systematic literature review.

Meta-analysis of T2DM and ICAM1 gene K469E variant

Ten studies with a total of 2685 T2DM and 2193 controls were finally included in meta-analysis (12,17,18,20-26). The pooled effect estimates under meta-analysis revealed that the ICAM1 K469E variant is significantly associated with T2DM in the allelic model (G vs. A; OR = 1.10, 95% CI: 1.01-1.20, P = 0.032) and recessive model (GG vs. AG+AA; OR = 1.27, 95% CI: 1.08-1.49, P = 0.004) (Figure 2A). The pooled effect estimates in dominant model is not statistically significant (AG+GG vs. AA; OR = 1.08, 95% CI: 0.82-1.41, P = 0.594) (Table 2). The present meta-analysis allelic and recessive models did not reveal significant heterogeneity among studies (I^2 ranged from 0 to 0.13). There is no apparent asymmetry in the funnel plot shape (Figure 3A). In support of this, Egger's test also did not reveal the signs for publication bias (Table 2). Further subgroup analyses based on ethnicity revealed statistically significant association between T2DM and ICAM1 K469E variant in Asians but not in Caucasians (GG versus AG+AA; Asians OR = 1.27, 95% CI: 1.051.52, P = 0.011; Caucasian OR = 1.27, 95% CI: 0.90-1.78, P = 0.173).

Meta-analysis of DN and ICAM1 gene K469E variant

Five studies with a total of 1031 T2DM patients with nephropathy and 996 T2DM patients without nephropathy

Table 1. Characteristics of the studies assessing the association between ICAM1 K469E variant and risk of type 2 diabetes and vascular complications

No.	Reference	Ethnicity	Country	Genotyping	AA	AG	GG	AA	AG	GG	HWE *P* values
T2DM vs. Control						T2DM			Control		
1	(20)	Asian	Japan	PCR-RFLP	152	158	50	61	73	18	0.587
2	(21)	Asian	China	PCR-HA SSCP	97	20	55	28	42	10	0.343
3	(22)	Asian	China	PCR-RFLP	22	48	30	19	46	33	0.680
4	(23)	Asian	China	PCR-RFLP	39	96	54	30	54	27	0.782
5	(24)	Asian	China	PCR-RFLP	30	14	2	21	8	1	0.827
6	(25)	Asian	China	PCR-RFLP	54	45	21	75	51	24	0.005
7	(17)	Asian	China	TaqMan genotyping	192	152	41	330	292	50	0.181
8	(26)	Asian	Malaysia	TaqMan genotyping	23	451	106	59	412	91	<0.001
9	(18)	Caucasian	Turkey	PCR-RFLP	39	66	33	41	75	22	0.205
10	(12)	Caucasian	Slovakia	TagMan genotyping	172	306	117	59	105	36	0.365
DN versus non-DN T2DM patients						DN			Non-DN T2DM		
11	(22)	Asian	China	PCR-RFLP	24	54	16	22	48	30	0.735
12	(23)	Asian	China	PCR-RFLP	13	49	32	26	47	22	0.932
13	(26)	Asian	Malaysia	TaqMan genotyping	8	261	34	15	190	72	<0.001
14	(17)	Asian	China	TaqMan genotyping	207	169	26	193	152	41	0.182
15	(18)	Caucasian	Turkey	PCR-RFLP	39	66	33	41	75	22	0.205
DR versus non-DR T2DM patients						DR			Non-DR T2DM		
16	(27)	Asian	Japan	PCR-RFLP	34	35	12	10	30	40	0.255
17	(21)	Asian	China	PCR-HA SSCP	81	40	11	16	15	9	0.152
18	(28)	Caucasian	Slovenia	PCR-RFLP	47	96	52	44	77	22	0.218
19	(29)	Asian	India	Snapshot	103	162	80	99	174	86	0.578
20	(24)	Asian	China	Allele specific PCR	10	24	6	24	14	2	0.982
21	(25)	Asian	China	PCR-RFLP	37	44	21	54	45	21	0.039
22	(16)	Asian	India	DNA sequencing	60	92	47	29	84	44	0.317
23	(15)	Asian	China	PCR-LDR	221	193	34	166	154	24	0.142

were finally included in meta-analysis (17,18,22,23,26). The pooled effect estimates did not reveal any significant relationship between the ICAM1 K469E variant and nephropathy in T2DM patients in the allelic model (G vs. A; OR = 0.97, 95% CI: 0.76-1.25, P = 0.830), recessive model (GG vs. AG+AA; OR = 0.77, 95% CI: 0.40-1.46, P = 0.416) (Figure 2B) and dominant model (AG+GG vs. AA; OR = 1.20, 95% CI: 0.84- 1.71, P = 0.324) (Table 2). Significant heterogeneity among studies was found in all genetic models (I^2 ranged from 0.50–0.84). There is no obvious asymmetry in the funnel plot shape (Figure 3B). In support of this, Egger's test also did not reveal the signs for publication bias (Table 2). As all studies concerning the DN and ICAM1 K469E variant are only of Asian origin, subgroup analyses based on ethnicity was not possible (Table 2).

Meta-analysis of DR and ICAM1 gene K469E variant

A total of 1542 T2DM patients with retinopathy and 1283 T2DM patients without retinopathy from eight articles were finally included in meta-analysis (15,16,21,24,25,27-29). The pooled effect estimate in the allelic model revealed that there are no significant associations between the ICAM1 K469E variant and retinopathy in T2DM patients (G versus A; OR = 0.88, 95% CI: 0.62-1.24, P = 0.470), recessive model (GG versus AG+AA; OR = 0.85, 95% CI: 0.52-1.38, P = 0.503) (Figure 2C) and dominant model (AG+GG versus AA; OR = 0.87, 95% CI: 0.57-1.32, P = 0.495) (Table 2). Significant heterogeneity among studies was found in all genetic models (I^2 ranged from 0.77–0.88). There is no obvious asymmetry in the funnel plot shape (Figure 3C). In support of this, Egger's test also did not reveal the signs for publication bias (Table 2). Further subgroup analyses are not informative due to the lack of sufficient eligible studies in different ethnic groups (Table 2).

Discussion

T2DM is an inflammatory disease in which increased pro-inflammatory cytokines and chemokines were reported consistently. T2DM is characterized by glucose and lipid metabolism disorders, oxidative stress, glomerular hemodynamic changes, and corneal neovascularization, which lead to the DN and DR complications. ICAM1 is an acute-phase marker of inflammation. Multiple studies indicated that higher soluble ICAM1 levels were significantly correlated with micro-angiopathic complications in diabetic patients (30,31). Animal studies

Table 2. Meta-analysis of the association of ICAM1 K469E variant on type 2 diabetes and vascular complications

Model		**Allele contrast (G vs. A)**			**Recessive model (GG vs. AG+AA)**			**Dominant model (AG+GG vs. AA)**		
Ethnicity		**Overall**	**Asian**	**Caucasian**	**Overall**	**Asian**	**Caucasian**	**Overall**	**Asian**	**Caucasian**
T2DM versus Control										
Number of studies		10	8	2	10	8	2	10	8	2
Test of association	Model	Fixed	Fixed	Fixed	Fixed	Fixed	Fixed	Random	Random	Fixed
	OR (95% CI)	1.10 (1.01-1.20)	1.10 (0.99- 1.21)	1.10 (0.911.32)	1.27 (1.08-1.49)	1.27 (1.051.52)	1.27 (0.90-1.78)	1.08 (0.82-1.41)	1.08 (0.76-1.54)	1.04 (0.78-1.40)
	P value	0.032	0.054	0.342	0.004	0.011	0.173	0.594	0.652	0.778
Test of heterogeneity	I^2	0	0	0	0.134	0.244	0.118	0.692	0.760	0
	P value	0.894	0.806	0.485	0.320	0.235	0.287	<0.001	<0.001	0.896
Egger's test *P* value		0.565	0.454	NA	0.434	0.595	NA	0.762	0.800	NA
DN versus non-DN T2DM patients										
Number of studies		5			5			5		
Test of association	Model	Random			Random			Random		
	OR (95% CI)	0.97 (0.76-1.25)			0.77 (0.40-1.46)			1.20 (0.84- 1.71)		
	P value	0.830			0.416			0.324		
Test of heterogeneity	I^2	0.711			0.844			0.504		
	P value	0.008			<0.001			0.089		
Egger's test *P* value		0.338			0.253			0.190		
DR versus non-DR T2DM patients										
Number of studies		8	7	1	8	7	1	8	7	1
Test of association	Model	Random	Random	Fixed	Random	Random	Fixed	Random	Random	Fixed
	OR (95% CI)	0.88 (0.62-1.24)	0.82 (0.56-1.19)	1.44 (1.06-1.95)	0.85(0.52-1.38)	0.73 (0.44-1.21)	2 (1.15-3.48)	0.87 (0.57-1.32)	0.80 (0.50-1.28)	1.40 (0.86-2.27)
	P value	0.470	0.288	0.021	0.503	0.228	0.014	0.495	0.354	0.173
Test of heterogeneity	I^2	0.884	0.883	NA	0.799	0.770	NA	0.824	0.834	NA
	P value	<0.001	<0.001	NA	<0.001	<0.001	NA	<0.001	<0.001	NA
Egger's test *P* value		0.725	0.689	NA	0.707	0.649	NA	0.800	0.744	NA

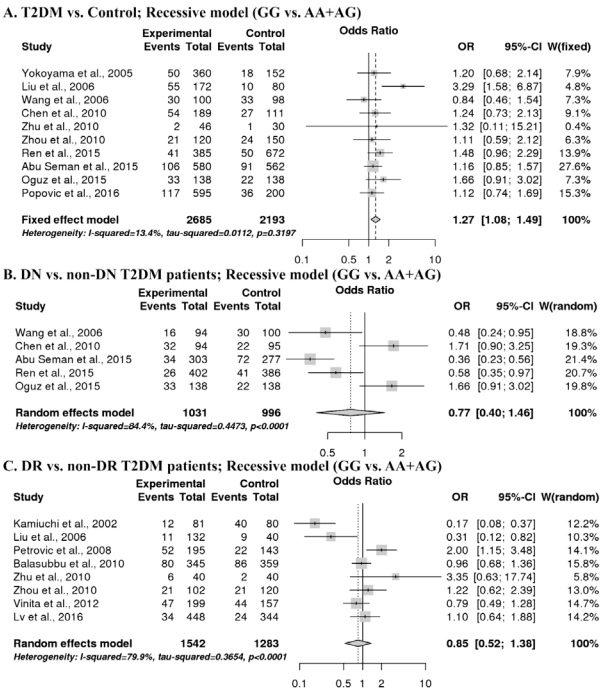

Figure 2. Forest plot displaying meta-analysis of the effect of ICAM1 K469E on type 2 diabetes and vascular complications. A. T2DM vs. Control; B. DN vs. non-DN T2DM patients; C. DR versus non-DR T2DM patients.

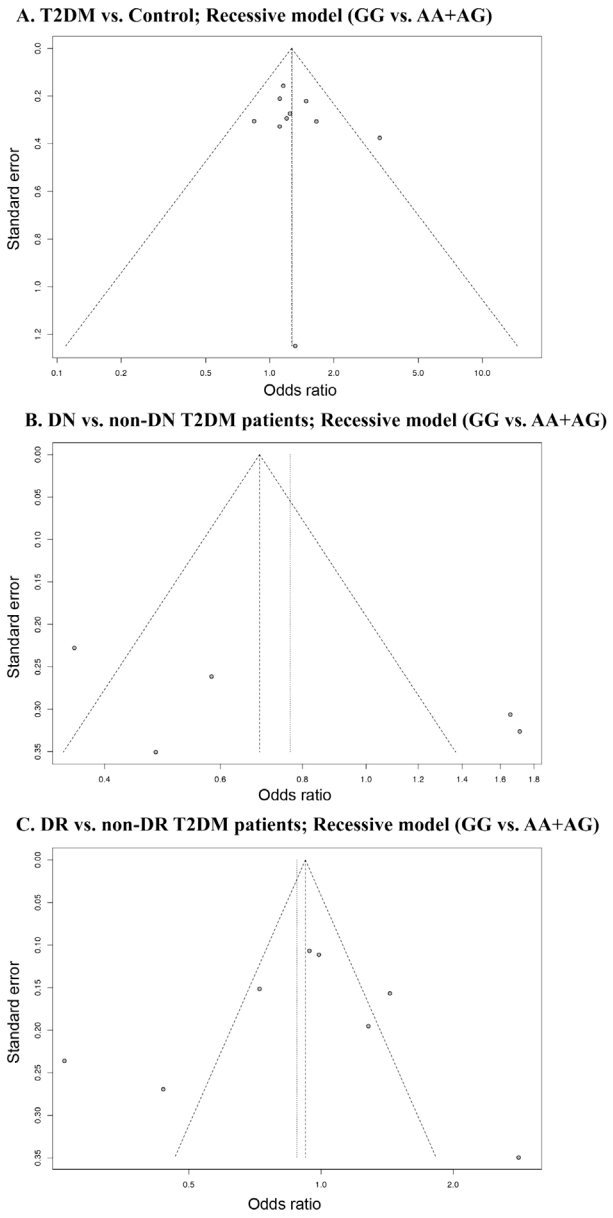

Figure 3. Funnel plot for publication bias in the meta-analysis of ICAM1 K469E variant and the risk of type 2 diabetes and vascular complications

also demonstrated an elevation of serum and urinary ICAM1 levels in streptozotocin-induced rats compared to normal rats (32). In addition to this overexpression of ICAM1 was also noted in the glomeruli diabetic rats (33). The immunohistochemical expression analysis of the conjunctiva of diabetic patients with and without retinopathy revealed upregulation of ICAM1 expression in these tissues (34).

The *ICAM1* gene has seven exons that code for 505 amino acids protein, whose molecular weight varies between 80 and 114 kDa depending upon the cell types or glycosylation levels (35). Several lines of evidence demonstrated that the *ICAM1* gene activity is up-regulated through the binding of NF-kappaB, STAT3 and δCREB transcription factors (36). In contrast to this down-regulated ICAM1 expression was observed on the binding of microRNA, miR-221 (37). Of the *ICAM1* gene polymorphisms, an "A" to "G" transition at three bases upstream of ICAM1 mRNA splicing site which leads to substitution a lysine to glutamic acid at 469 amino acid (K469E; rs5498) is known to influence the RNA splicing patterns (38). Further, ICAM1 K469E variant is strongly correlated with the ICAM1 levels (39).

Our meta-analysis included 15 articles investigating the association between ICAM1 K469E variant and the predisposition of diabetes or diabetic vascular complications. The present meta-analysis across all ethnic populations showed that the ICAM1 K469E variant is associated with diabetes under the allelic and recessive model. But we failed to identify any significant association between the ICAM1 K469E variant and vascular complications in any genetic model. An initial study was conducted by Guja et al, in which more frequent transmission of ICAM1 469E allele observed in Romanian T1DM families (40). Subsequently, several studies showed mixed results of associations of ICAM1 K469E mutant genotypes with diabetes (17,18,21), DN (18,23) and DR (16,24,28) in different populations. Results of our meta-analysis are consistent with one of the most recent meta-analyses, in which ICAM1 K469E was demonstrated as a susceptible factor for T2DM (41). Further, meta-analysis of studies on diabetic microvascular complications

showed that the ICAM1 K469E is associated with DN but not with DR (42,43). Two independent meta-analysis also provided no signs of association for K469E with DR in T2DM patients (44,45).

To the best of our knowledge, this meta-analysis embodies the most comprehensive studies on the association between ICAM1 K469E variant and risk of diabetes and its complications. In summary, ICAM1 K469E variant is associated with the risk of diabetes but there was no evidence for association with DN or DR. As the literature supporting the role of ICAM1 in DN or DR pathophysiology, our results some extent conflict with the biological plausibility that ICAM1 levels modulate diabetes complications, and may warrant additional investigations.

Authors' contribution

BVKSL conceived the study. SL, HKV and BVKSL collected data. BVKSL analyzed data. SL, HKV and BVKSL wrote the manuscript. All authors have read and approved the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

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

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