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Interleukin-10 gene promoter variants and susceptibility to diabetic nephropathy; a meta-analysis

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ABSTRACT

Introduction: Diabetic nephropathy (DN) is a leading cause of chronic kidney disease (CKD) in diabetes patients. There is ample evidence that the inflammatory pathways are central to both diabetes and DN. Several studies that examined the link between the interleukin-10 (IL10) polymorphisms and DN risk yielded conflicting results.

Objectives: The purpose of this meta-analysis is to evaluate the associations between IL10 promoter polymorphisms and DN risk.

Methods: A bibliographic search was carried out on PubMed, Google scholar and Web of Science from the beginning until July 30, 2020. Association between IL10 promoter variants (-1082 A>G, -819 C>T and -592 C>A) and DN risk were assessed by considering diabetes without nephropathy (DWN) as well as healthy controls. Data were retrieved and the pooled odds ratio (OR) with 95% confidence interval (CI) was calculated.

Results: For the IL10 -1082 A> G analysis, a total of 4 studies with DWN controls (682 cases and 529 controls) and 5 studies with healthy controls (1025 cases and 1625 controls) were considered. For the IL10 -819 C> T analysis, a total of three studies with DWN controls (9619 cases and 445 controls) and 5 studies with healthy controls (1005 cases and 1537 controls) were considered. For the IL10 -592 C> T analysis, a total of 5 studies with DWN controls (819 cases and 645 controls) and 5 studies with healthy controls (1005 cases and 1537 controls) were considered. In addition, there was no evidence of publication bias for IL10 promoter variants. No substantial association was observed between IL10 promoter variants and DN risk.

Conclusion: Our study signifies that polymorphisms of IL10 -1082 A>G, -819 C>T and -592 C>A are not linked with DN risk.

Implication for health policy/practice/research/medical education:
In the present study, we investigated the association between diabetic nephropathy and IL10 promoter variants using meta-analysis. This study demonstrated that the IL10 gene promoter variants (-1082 A>G, -819 C>T and -592 C>A) are not associated with the development of diabetic nephropathy.

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Meta-analysis

Introduction

Diabetic nephropathy (DN) causes serious health problems and is a leading cause of morbidity and mortality. The occurrence of DN is relatively high among type 2 diabetes mellitus (T2DM) patients representing huge health and economic burden (1). DN is the leading cause of chronic kidney disease (CKD), which leads to end-stage renal disease (ESRD). DN is characterised by micro albuminuria, loss of glomerular filtration rate to progressive CKD in patients with long standing diabetes (2). Several lines of research revealed that the DN is a complex disorder involving both genetic and environmental components (3). Diabetic kidney disease (diabetic nephropathy) is induced by inadequate glycaemic control in diabetic

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patients (4). Insulin resistance caused by hyperinsulaemia in diabetic patients leading to inflammation (5). Increasing evidences demonstrated that the inflammatory pathways are central to both diabetes and DN (6). The association of inflammatory mediator's such as interleukins, tumor necrosis factor-α, and macrophage chemotactic protein-1 has been documented in the literature (7).

Interleukin-10 (IL-10) is one of the important regulators of inflammation during diverse pathological conditions. Interleukin-10 is mainly produced by macrophages, B-cells, dendritic cells, monocytes, mast cells, neutrophils and eosinophils (8). IL-10 is an anti-inflammatory cytokine, which involved in progression of T2DM (9). Interleukin-10 levels are significantly corelated with the development of T2DM as well as DN. IL-10 is encoded by the IL10 gene, which is located on chromosome 1 and has several polymorphic variants that determine its expression. Three IL10 gene variants (-1082 A>G, -819 C>T and -592 C>A) have been studied for their association with DN (10). However, there is no consensus regarding the association of these polymorphism with DN in different populations, due to ethnic differences and less sample sizes used in the studies. In order to assess the exact role of these variants we conducted a meta-analysis by pooling the data from previous association studies.

Methods

Literature search

Articles assessing the association between IL10 gene variants and DN were retrieved from PubMed, Google Scholar, and Web of Science. The keywords used for retrieving the literature include diabetic nephropathy, interleukin-10 or IL10, -1082 A>G, -819 C>T and -592 C>A, polymorphism or variants. Specific inclusion and exclusion criteria were adapted to select the papers for data extraction. The inclusion criteria include 1) case control studies analysing IL10 variants and DN, 2) Comparison group having either healthy controls or diabetes without nephropathy (DWN), 3) Studies having genotype data in both DN and comparison groups for estimating odds ratio and 95% confidence interval. Studies that do not follow the above criteria were excluded from the study. From each article genotypic data of both cases and control (healthy controls and/or DWN) were extracted and tabulated.

Statistical analysis

The strength of the association between the IL10 promoter variants (-1082 A>G, -819 C>T and -592 C>A) and DN was assessed for all studies. The crude odds ratios (ORs) and their corresponding 95% confidence interval (CI) limits were calculated. The presence of heterogeneity was evaluated with the Cochran's Q test and inconsistency I^2 statistics. Based on the extent of heterogeneity, fixed effects model or random effects model were adopted for pooled analysis. The association between IL-10 polymorphisms and DN was analysed in dominant, recessive, and allelic genetic models. To assess the robustness of the study, sensitivity analysis was performed by excluding each study once and estimating the OR for the rest of the studies. Publication bias was measured by drawing a funnel plot and Egger's linear regression method.

Results

Characteristics of the included studies

The bibliographic search strategy and the selection process of the articles for this meta-analysis are presented in Figure 1. A total of 10 articles that analysed DWN controls or healthy controls or both were included in the pooled analysis (11-20). Out of these only 5 articles studied all theree IL10 promoter variants (-1082 A>G, -819 C>T and -592 C>A). For *IL10* -1082 A>G pooled analysis, four studies including 682 cases and 529 DWN controls and 5 studies including 1025 cases and 1625 healthy controls were included. For *IL10* -819 C>T pooled analysis, three studies including 619 cases and 445 DWN controls and 5 studies including 1005 cases and 1537 healthy controls were included. For *IL10* -592 C>A pooled analysis, five studies including 819 cases and 645 DWN controls and 5 studies including 1005 cases and 1537 healthy controls were included. The genotype distribution in both cases and controls for each study was included in Table 1.

Heterogeneity

The association between IL10 promoter variants and DN risk did not exhibit considerable heterogeneity between studies in all three genetic models (Table 2). Nevertheless, for the association between -1082 A>G, -592 C>A

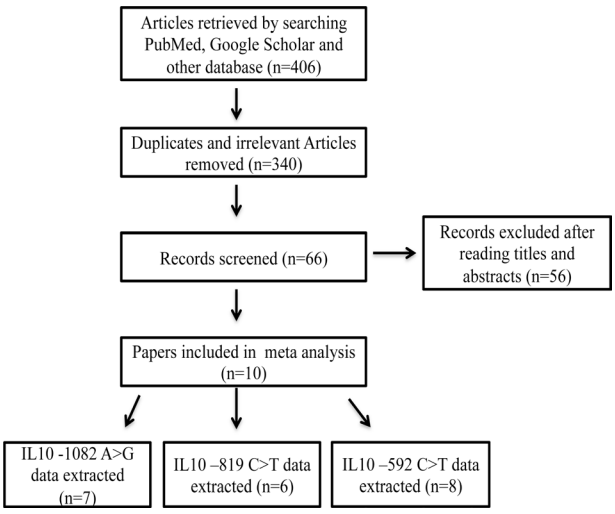

Figure 1. Study selection process for the meta-analysis.

Table 1. Distribution of IL-10 promoter polymorphisms in the eligible studies

Author	Year	Country	Ethnicity	Genotype method	DN			DM control			Non DM control			HWE *P* value	
IL10 -1082 A>G (rs1800896)					**AA**	**AG**	**GG**	**AA**	**AG**	**GG**	**AA**	**AG**	**GG**	**DWN control**	**Healthy Control**
Babel et al (11)	2006	Germany	Caucasian	PCR-RFLP	12	8	24	11	12	36	30	42	42	<0.001	0.032
Ezzidi et al (12)	2009	Tunisia	Caucasian	PCR	59	239	217	62	187	153	106	326	316	0.697	0.354
Erdogan et al (13)	2012	Turkey	Caucasian	PCR-RFLP	12	31	0	10	38	0	-	-	-	<0.001	-
Rodrigues et al (14)	2015	Brazil	Caucasians	PCR- SSP	33	40	7	10	5	5	-	-	-	0.049	-
Yin et al (15)	2015	China	Asian	PCR-RFLP	26	80	66	-	-	-	27	153	163	-	0.437
Ma et al (16)	2016	China	Asian	PCR-RFLP	29	94	71	-	-	-	25	141	154	-	0.437
Chavarria-Buenrostro et al (17)	2019	Mexico	Caucasians	PCR-RFLP	47	46	7	-	-	-	48	41	11	-	0.618
IL10 -819 C>T (rs1800871)					**CC**	**CT**	**TT**	**CC**	**CT**	**TT**	**CC**	**CT**	**TT**		
Ezzidi et al (12)	2009	Tunisia	Caucasian	PCR-ASA	299	184	32	199	173	30	488	228	32	0.543	0.464
Kung et al (18)	2010	Taiwan	Asian	PCR-RFLP	0	24	0	0	23	0	1	24	0	<0.001	<0.001
Yin et al (15)	2015	China	Asian	PCR-RFLP	38	77	57	-	-	-	67	150	127		0.156
Rodrigues et al (14)	2015	Brazil	Caucasians	PCR- SSP	38	31	11	10	8	2	-	-	-	0.831	
Ma et al (16)	2016	China	Asian	PCR-RFLP	39	90	65	-	-	-	57	142	121		0.295
Chavarria-Buenrostro et al (17)	2019	Mexico	Caucasians	PCR-RFLP	31	46	23	-	-	-	36	45	19		0.464
IL10 -592 C>A (rs1800872)					**CC**	**CA**	**AA**	**CC**	**CA**	**AA**	**CC**	**CA**	**AA**		
Ezzidi et al (12)	2009	Tunisia	Caucasian	PCR-ASA	247	214	54	178	181	43	403	298	47	0.831	0.512
Kung et al (18)	2010	Taiwan	Asian	PCR-RFLP	4	13	7	0	23	0	1	24	0	<0.001	<0.001
Kazemi Arababadi et al (20)	2012	Iran	Caucasian	PCR-RFLP	47	47	6	60	36	4	-	-	-	0.831	
Yin et al (15)	2015	China	Asian	PCR-RFLP	26	79	67	-	-	-	57	155	132		0.512
Rodrigues et al (14)	2015	Brazil	Caucasians	PCR- SSP	38	30	12	10	8	2	-	-	-	0.831	
Mahmoud et al (19)	2016	Egypt	Caucasians	PCR-RFLP	10	38	52	12	40	48	-	-	-	0.831	
Ma et al (16)	2016	China	Asian	PCR-RFLP	39	90	65	-	-	-	57	142	121		0.442
Chavarria-Buenrostro et al (17)	2019	Mexico	Caucasians	PCR-RFLP	18	49	33	-	-	-	16	47	37		0.868

Table 2. Associations of interleukin 10 gene promoter polymorphisms with the risk of diabetic nephropathy

Pooled Analysis	DWN control			Healthy control		
IL10 -1082 A>G	Allele G vs. A	Dominant GG+AG vs. AA	Recessive GG vs. AG+AA	Allele G vs. A	Dominant GG+AG vs. AA	Recessive GG vs. AG+AA
I^2 (Pheterogeneity)	23.3% (0.271)	27.5% (0.242)	62.4% (0.070)	74.2% (0.003)	70.5% (0.008)	67.6 % (0.015)
OR (95% CI)	1.09 (0.92-1.29)	1.19 (0.87-1.63)	1.08 (0.84-1.38)	0.90 (0.80-1.01)	0.89 (0.71-1.11)	0.86 (0.73-1.02)
Model	FEM	FEM	FEM	REM	REM	REM
Eggers *P* value	0.059	0.264	0.299	0.887	0.282	0.985
IL10 -819 C>T	T vs. C	CT+TT vs. CC	TT vs. CT+CC	T vs. C	CT+TT vs. CC	TT vs. CT+CC
I^2 (Pheterogeneity)	0 % (0.531)	0 % (0.389)	0 % (0.514)	56.4 % (0.057)	28.6% (0.231)	28.6% (0.231)
OR (95% CI)	0.81 (0.67-0.98)	0.73 (0.56-0.94)	0.87 (0.53-1.41)	1.07 (0.95-1.21)	1.17 (0.98-1.40)	0.98 (0.78-1.23)
Model	FEM	FEM	FEM	FEM	FEM	FEM
Eggers *P* value	0.180	0.454	0.534	0.753	0.698	0.552
IL10 -592 C>A	A vs. C	AC+AA vs. CC	AA vs. AC+CC	A vs. C	AC+AA vs. CC	AA vs. AC+CC
I^2 (Pheterogeneity)	12.8% (0.332)	44.3% (0.127)	12.4% (0.334)	48% (0.104)	20% (0.287)	67% (0.016)
OR (95% CI)	1.03 (0.88-1.21)	0.98 (0.79-1.23)	1.13 (0.82-1.55)	1.10 (0.97-0.12)	1.13 (0.95-1.36)	1.13 (0.75-1.69)
Model	FEM	FEM	FEM	FEM	FEM	REM
Eggers *P* value	0.116	0.946	0.046	0.596	0.033	0.381

DWN: Diabetes without nephropathy; CI: confidence intervals; OR: odds ratio; FEM: Fixed Effect Model; REM: Random Effect Model.

polymorphisms and DN risk, significant heterogeneity was found between the studies when we chose healthy individuals as controls (Table 2).

Association of the IL10 promoter variants and DN risk

The results of this study showed that there was no significant association between IL10 promoter variants and risk of DN in all three genetic comparison models when DWN patients used as controls (Table 2). However, IL10 -819 C>T showed a trend for protective effect towards DN risk when we used DWN as controls, which is not statistically significant. Further, no significant association was observed between IL10 promoter variants and risk of DN when healthy individuals used as controls (Table 2).

Results of sensitivity analysis and publication bias

Sensitivity analysis performed by omitting each study showed that individual studies did not affect the pooled effects estimates for these IL-10 promoter variants, indicating that the results were statistically reliable. The funnel plot shapes were found to be symmetrical for all three IL-10 promoter variants, indicating the absence of publication bias. Egger's linear regression test also showed that there was no evidence of publication bias for all three IL10 promoter variants in all three genetic models (P> 0.050; Table 2). However for IL10 -592 C>T significant publication bias was found in recessive model when used DWN controls and dominant model when used healthy control for comparison (Table 2).

Discussion

The present meta-analysis has shown that there is no significant association between IL-10 gene promoter variants and the risk of diabetic nephropathy. A trend of protective effect for DN was found for -819 C>T polymorphism in a comparison using DWN as controls. No significant heterogeneity between studies was noted for all three promoter polymorphisms. In addition, there was no evidence of publication bias for IL-10 promoter variants were detected. Our meta-analysis is consistent with previous meta-analysis in which a trend for protective effect was documented for -1082 A>G and/or -819 C>T (10,21). Another meta-analysis demonstrated significantly increased risk of DN with -1082 A>G polymorphism (22).

Several *in vivo* and *in vitro* studies have shown that the IL-10 gene expression and IL10-induced signalling pathways are important for the regulation and maintenance of normal kidney function (23). Further abnormal IL-10 expression has been linked to occurrence and progression of various kidney disorders (24). Increased serum levels of IL10 is associated with the severity of nephropathy (25). As an anti-inflammatory cytokine, IL-10 plays a major role in inhibiting a synthesis of pro inflammatory cytokines and modulate the inflammation in the body. Long standing DM and inflammatory conditions are associated with DN (26). Inflammation and subsequent tissue remodeling can increase oxidative stress and initiate kidney damage leading to DN (27, 28). Therefore, selective targeting of IL10 expression and pathways associated with IL-10 may

be one of the therapeutic approaches for treating many of the kidney diseases (24). Abnormal IL10 expressions may contribute to diabetes induced kidney disease. Studies in animal models suggested contradictory results in terms of its association with renal functioning (29, 30).

IL-10 levels are correlated with the polymorphism in promoter of IL-10 gene (31). Subsequent studies demonstrated that the IL-10 secretion is mainly depending on the haplotypes of IL10 locus (32). Further, it is also documented that the ethnicity influences the allele frequency distribution of cytokine polymorphisms (33). Several functional polymorphisms of IL10 gene have been assessed for their association with the risk of DN, however the results are contradictory. Main reasons for the discrepancies are criteria used for characterisation of DN, study design, very low sample sizes and ethnicity. In conclusion, we suggest that IL10 gene promoter variants are not associated with the development of DN.

Authors' contribution

BVKSL conceived the study. GM and SG collected data. GM, SG, TPKR and BVKSL analysed and prepared the manuscript. TPKR and BVKSL critically revised the manuscript. All authors approved the manuscript.

Conflicts of interest

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

Ethical considerations

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

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