META-ANALYSIS OF MCP-1 GENE POLYMORPHISM AND INCIDENCE OF DIABETIC NEPHROPATHY IN THE ASIAN POPULATION

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ABSTRACT

Background: *Diabetes poses a serious threat to global public health, and it has a severe impact on people's health. In the development of diabetic nephropathy, monocyte chemoattractant protein-1 is considered as a pathogenic agent, as well as it is a robust stimulating factor for macrophage recruitment.*

Methods: *At present, in the MCP-1 gene, we have found polymorphic genes, and the A-2518 G polymorphism in the MCP-1 promoter region is considered to be an essential factor for regulating gene expression and affecting plasma MCP-1 concentration. Some studies have shown that the occurrence of kidney disease is associated with the MCP-1 A-2518 G gene.*

Results: *So, we speculate that MCP-1-2518, A / G gene polymorphism can affect diabetes and kidney disease. In this meta-analysis, we have total of nine studies including four Chinese people related, four Indian people related, two Korean people related and one Turkish people described.*

Conclusion: *The analysis showed that it was not obvious to address the correlation between diabetic nephropathy and GG genotype in China, Korea, and Turkey. However, in Indian people, the GG genotype is related to a reduced risk of diabetic nephropathy ($p<0.05$). From the study of diabetic nephropathy, it was hard to find out significant correlations between G alleles and AA genotypes among people in China, Korea, Turkey, and India. Therefore, among people in China, Korea, and Turkey, we preliminarily concluded that there is no apparent interaction between the MCP-1 A-2518G gene polymorphism and the risk of diabetic nephropathy. However, among Indians, GA genotype has an essential impact on the occurrence of diabetic nephropathy ($p<0.05$).*

Keywords: *Diabetes, MCP-1, polymorphic gene, meta-analysis.*

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Introduction

In diabetic nephropathy, the emergence of type 1 diabetes and type 2 diabetes is a significant reason for diseases in both kidney and end-stage renal[(1)]. There are some treatments available to reduce the incidence of diabetic nephropathies, such as controlling blood sugar, blocking renin, blocking angiotensin, blocking the aldosterone system, and changing lifestyles, but we have not yet developed a method to cure diabetic nephropathy altogether[(2)]. Diabetes has been considered a non-immune disease, but more and more studies now reveal the role of inflammatory factors in type 1 and type 2 diabetes. Among them, MCP-1 was first discovered and is the most widely studied chemokine associated with diabetic nephropathy[(3)].

MCP-1 can mediate the release of monocytes from the bone marrow, directing monocytes to the site of inflammation, thereby it can reduce the mi-

gration of blood leukocytes to inflammatory tissues. Besides, MCP-1 has a direct signaling role in monocytes, and it gives enormous effects on leukocyte migration, proliferation, and differentiation. By the kidney disease model, the disease was improved after blocking MCP-1, indicating that MCP-1 is significant in renal inflammatory diseases[4].

In the MCP-1 gene, the A-2518 G polymorphism of the distal regulatory region of MCP-1 is thought to regulate gene expression and can affect plasma concentrations. Genetic polymorphism is considered to be one of the reasons for the onset of diabetic nephropathy.

At present, more and more scholars are systematically studying diabetic nephropathy, hoping to find a way to treat diabetic nephropathy. There are more and more studies on the interaction between MCP-1 A-2518 G gene polymorphism and diabetic nephropathy risk, and the results of the study are controversial[5].

In this study, the data in the electronic database was collected, the articles were screened in strict accordance with the requirements, and the relationship between the polymorphism of A-2518 G gene in the MCP-1 promoter region and diabetic nephropathy was analyzed.

Materials and methods

Document retrieval

In PubMed, CNKI, Embase database, monocyte chemoattractant protein-1 (MCP-1), monocyte chemoattractant protein-1 (MCP-1) A-2518 G gene polymorphism, diabetic nephropathy Data related to MCP-1 A-2518 G gene polymorphism and diabetic nephropathy.

Then, by manually reading the abstract, further screening is performed.

The screening conditions are as follows:

• The data after 2000 is selected for inclusion in our study;

• The case-control group data is chosen as the study subject;

• The data related to diabetic nephropathy are determined, and only those related to diabetes are not met. Requirements;

• The data should include the diabetic nephropathy case group and the diabetes control group;

• The study population is the Asian population.

After screening the required data in the database according to the above conditions, we finally selected nine studies on the diabetic nephropathy group-diabetic control group. Data were extracted from these nine studies for meta-analysis in this study.

Data extraction

In the study, information was extracted including author data, publication time, where the subject was located, case group genotype, and control genotype. After retrieving the corresponding genotype distributions of each group, the G allele frequencies of each group were calculated.

Statistical analysis

Statistical analysis was performed on each of the extracted study data using Stata software (version 12.0). According to the Q test ($p<0.05$ significance level) results, heterogeneity, and consistency were evaluated for the selected nine studies.

If there is a different selection random-effects model to calculate the odds ratio (OR) and 95% confidence interval (95% CI), otherwise choose a fixed effect model.

The OR was calculated using the following four methods:

• Comparison between alleles (G allele and A allele);

• Comparison between GG genotype and the other two genotypes (GG and AA) +GA);

• Comparison between AA genotype and the different two genotypes (AA and GG+GA);

• Comparison between GA genotype and the different two genotypes (GA and AA+GG).

Enter the Hardy-Weinberg formula in the Excel table, enter the distribution according to the control genotype, calculate it in the table, and check whether the genotype distribution of the control group in each research is consistent with Hardy-Weinberg equilibrium (HWE) (Hardy-Weinberg: $p<0.05$ significance level). With Stata, we can assess whether there is bias, and a p-value<0.05 would be thought to be statistically essential[6].

Results

Research characteristics

According to the data searched in the electronic database, 240 studies on diabetic nephropathy were initially examined, and studies that did not meet the requirements were screened out, including review studies, non-case-control studies, and data incomplete studies. In the end, we included a total of 9 studies, and the studies targeted the Asian people,

including four studies for people in China[7-10], and two studies for people in India[11, 12] and two studies for people in Korea[13, 14] and one study for people in Turkey[15]. The study involved 1010 cases and 1016 controls. According to statistics, the distribution of G alleles is as follows: The gene frequency of G allele in Chinese people is 52.3% and 51.4% in the case group and control group, respectively.

The gene frequency of the G allele in Indian people was 34.0% in the case group and 29.2% in the control group.

In Korean people, the gene frequency of the G allele in the case group was 60.5%, and that in the control group was 65.1%. The gene frequency of the G allele in Turkish people was 22.1% in the case group and 19.8% in the control group.

After calculation, the ratio of the average frequency of the G allele in the case group and the control group was the highest in India, 1.16, the lowest in Korea was 0.93, the Chinese were 1.02, and the Turk was 1.12 (Figure 1).

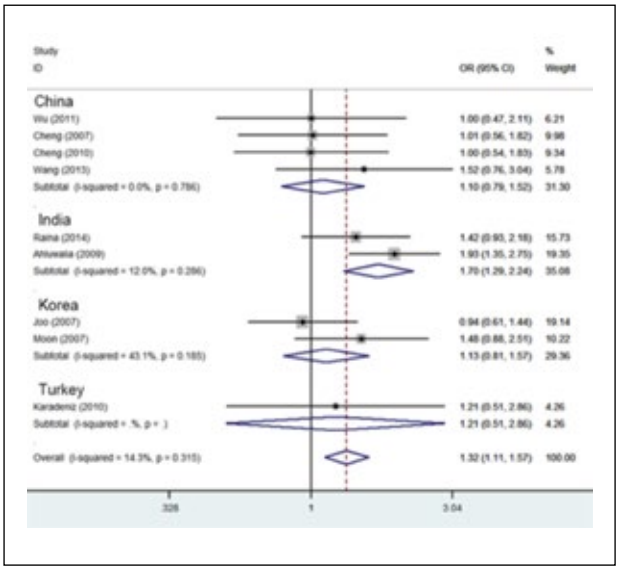

Figure 1: Relationship between MCP-1 A-2518 G gene polymorphism and the risk of diabetic nephropathy.

Publication bias assessment

The publication bias in the study has a great influence on the authenticity and reliability of the meta-analysis results.

Therefore, we first use the Stata software for publication bias evaluation. In the funnel plot results, there is no significant asymmetry, so the bias is within an acceptable range. (G and A: Begg p=0.917, Egger p=0.816; GG and GA+AA: Begg p=0.266, Egger p=0.394; AA and GA+GG: Begg p=0.466, Egger p=0.151; GA and GG +AA: Begg p=0.602, Egger p=0.215) (Figure 2).

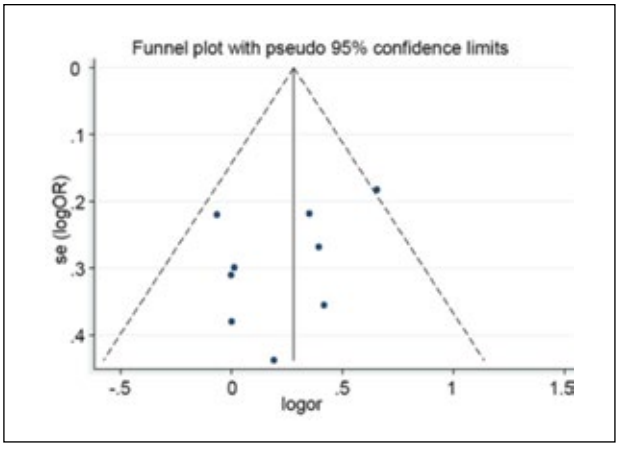

Figure 2: Published bias analysis of the relationship between MCP-1 A-2518 G gene polymorphism and Asian diabetic nephropathy risk. If OR >1, MCP-1 A-2518 G gene is a risk gene for diabetic nephropathy, and if OR <1, MCP-1 A-2518 G gene is a protective gene for diabetic nephropathy.

A relationship between MCP-1 -2518G/A gene polymorphism and risk of diabetic nephropathy

The data indicate that the G allele, GG genotype, and AA genotype do not affect diabetic nephropathy (Table 1).

Among Chinese, Koreans and Turks, no significant relationship was found between AA genotype and risk of diabetic nephropathy, but in Indians, AA genotype was found to be related to a reduced risk of diabetic nephropathy (p=0.001; Table 2).

The GA genotype was related to susceptibility in diabetic nephropathy, particularly in Indians (p=0.000, Table 2). Among Chinese, Koreans and Turks, there was a significant correlation between the MCP-1 A-2518 G gene polymorphism and the risk of diabetic nephropathy.

			Diabetic nephropathy				Diabetes				G allele (%)		HWE
First author	Year	Region	GG	AA	GA	Total	GG	AA	GA	Total	Cases	Control	p
Wu	2011	China	18	13	25	56	26	5	25	56	54.5	68.8	0.771
Cheng	2007	China	26	24	44	94	22	24	40	86	51.1	48.8	0.521
Cheng	2010	China	24	28	42	94	19	23	34	76	47.9	47.4	0.370
Wang	2013	China	21	10	31	62	17	24	27	68	58.9	44.9	0.104
Raina	2014	India	14	59	72	145	8	113	84	205	34.5	24.4	0.112
Ahluwalia	2009	India	16	94	130	240	36	122	97	255	33.8	33.1	0.024
Joo	2007	Korea	65	26	73	164	68	23	78	169	61.9	63.3	0.933
Moon	2007	Korea	35	16	61	112	51	11	50	112	58.5	67.9	0.804
Karadeniz	2010	Turkey	0	24	19	43	0	26	17	43	22.1	19.8	0.106

Table 1: Characteristics of MCP-1 A-2518 G gene polymorphism on the risk of diabetic nephropathy.
Note: MCP: monocyte chemotactic protein; HWE: Hardy Weinberg test.

Genotype	Area	Number of studies	Q test p value	Model	OR(95%CI)	p-value
GvsA	Asial	9	0.004	Random effect	1.035 (0.826-1.296)	0.765
	China	4	0.020	Random effect	1.029 (0.674-1.571)	0.893
	Indian	2	0.032	Random effect	1.281 (0.815-2.013)	0.284
	Korea	2	0.176	Random effect	0.808 (0.578-1.129)	0.211
	Turkey	1	----	Random effect	1.151 (0.552-2.402)	0.708
GGvsGA+AA	Asia	9	0.011	Random effect	0.893 (0.617-1.292)	0.548
	China	4	0.295	Random effect	1.000 (0.671-1.492)	0.999
	Indian	2	0.001	Random effect	1.037 (0.178-6.053)	0.968
	Korea	2	0.102	Random effect	0.745 (0.421-1.319)	0.313
	Turkey	1	----	----	----	----
AAvsGG+GA	Asial	9	0.029	Random effect	0.860 (0.629-1.176)	0.346
	China	4	0.023	Random effect	0.927 (0.457-1.880)	0.834
	Indian	2	0.424	Random effect	0.640 (0.486-0.842)	0.001
	Korea	2	0.635	Random effect	1.360 (0.802-2.126)	0.284
	Turkey	1	----	Random effect	0.826 (0.350-1.948)	0.662
GAvsGG+AA	Asial	9	0.315	Fixed effect	1.322 (1.112-1.572)	0.002
	China	4	0.786	Fixed effect	1.099 (0.795-1.520)	0.569
	Indian	2	0.286	Fixed effect	1.699 (1.291-2.235)	0.000
	Korea	2	0.185	Fixed effect	1.126 (0.808-1.571)	0.483
	Turkey	1	----	Fixed effect	1.211 (0.513-2.855)	0.662

Table 2: The relationship between MCP-1 A-2518 G gene polymorphism and the risk of diabetic nephropathy.

Sensitivity analysis

To make the meta-analysis results more stable and reliable, we did a sensitivity analysis, and the results are shown in Table 3. In the Hardy–Weinberg test, for Indians, we found that the genotype distribution of one of the control groups was not in the HWE and did not meet the requirements.

Therefore, when doing the sensitivity analysis of the Indian population, we only analyze the remaining eight studies. In the study, for Asians, the interaction between G allele, GG genotype, and AA genotype and diabetic nephropathy was consistent in the sensitivity analysis non-sensitivity analysis.

In the Indian population, the AA genotype was related to a reduction in diabetic nephropathy, which was consistent with the results of the non-sensitivity study. Unlike the results of a non-sensitivity analysis, the G allele and GG genotype are associated with susceptibility to diabetic nephropathy in the Indian population. In addition, there was no viousapparent correlation between GA genotype and risk of diabetic nephropathy, and this result was inconsistent with the results of a non-sensitivity analysis. There was no clear correlation between MCP-1 A-2518 G gene polymorphism and diabetic nephropathy among Chinese, Korean, and Turks.

Genotype	Area	Number of studies	Q test p value	Model	OR(95%CI)	p-value
GvsA	Asial	8	0.004	Random effect	1.151 (0.552-2.402)	0.807
	China	4	0.020	Random effect	0.989 (0.689-1.420)	0.893
	Indian	1	----	Random effect	1.000 (0.671-1.492)	0.004
	Korea	2	0.176	Random effect	2.632 (1.074-6.449)	0.211
	Turkey	1	----	Random effect	0.745 (0.421-1.319)	0.708
GGvsGA+AA	Asial	8	0.047	Random effect	----	0.952
	China	4	0.295	Random effect	0.910 (0.620-1.333)	0.999
	Indian	1	---	Random effect	0.927 (0.457-1.880)	0.034
	Korea	2	0.102	Random effect	0.559 (0.363-0.859)	0.313
	Turkey	1	----	----	1.360 (0.802-2.126)	----
AAvsGG+GA	Asial	8	0.021	Random effect	0.826 (0.350-1.948)	0.627
	China	4	0.023	Random effect	1.322 (1.112-1.572)	0.834
	Indian	1	----	Random effect	1.099 (0.795-1.520)	0.008
	Korea	2	0.635	Random effect	1.699 (1.291-2.235)	0.284
	Turkey	1	----	Random effect	1.126 (0.808-1.571)	0.662
GAvsGG+AA	Asial	8	0.802	Fixed effect	1.211 (0.513-2.855)	0.106
	China	4	0.786	Fixed effect	1.099 (0.795-1.520)	0.569
	Indian	1	----	Fixed effect	1.699 (1.291-2.235)	0.108
	Korea	2	0.185	Fixed effect	1.126 (0.808-1.571)	0.483
	Turkey	1	----	Fixed effect	1.211 (0.513-2.855)	0.662

Table 3: Sensitivity analysis of the relationship between MCP-1 A-2518 G gene polymorphism and the risk of diabetic nephropathy.

Discussion

In diabetic patients, high blood sugar can damage kidney blood vessels, leading to kidney dysfunction, which makes it easier to get kidney disease. Monocyte chemoattractant protein-1 is a specific chemokine that circulates to the site of inflammation to activate monocytes. Similar to other glomerulonephrites, in diabetic nephropathy, MCP-1 regulates renal interstitial inflammation, tubular atrophy, and interstitial fibrosis by absorbing monocytes/macrophages from the tubulointerstitial[16].

When MCP-1 expression is upregulated, this indicates glomerular injury[17]. Therefore, MCP-1 is a crucial gene, and we further explore the interaction between MCP-1 gene polymorphism and the pathogenesis of diabetic nephropathy. Among Asians, the

MCP-1 GA genotype was substantially related to an increased risk of diabetic nephropathy (DN), especially in India, and we observed a significant correlation ($p<0.05$).

In Indians, the analysis showed that the MCP-1 AA genotype was associated with a reduced risk of DN. The assessment was carried out, and the results showed that the bias was within an acceptable range. Upon HWE testing, we found that one of the Indian studies did not meet the requirement and therefore the study in the sensitivity analysis was removed. Sensitivity analysis showed that there was no clear correlation between MCP-1 A-2518 G gene polymorphism and DN risk. Although the results of the study did not show a deep relationship, a reference for subsequent studies was provided.

With the deepening of the correlation between MCP-1 A-2518 G gene polymorphism and DN, the connection between genotypes and DN can be further analyzed. Before the sensitivity analysis, sensitivity analysis of the Indian population showed that the GG genotype and G allele were significantly related to an increased risk of DN, which was inconsistent with the results. Because one of the studies did not meet the HWE balance, it was removed during the sensitivity analysis, and eventually, the results of the subgroup analysis were inconsistent. Although the published bias of each study was not visible, the publication bias still exists. Moreover, only one group of Indian population data was included in the sensitivity analysis, so we need more data to analyze, which further proves the interaction between MCP-1 A-2518 G gene polymorphism and DN risk. Although they are all Asian people, there may be some varieties in the frequency of the G allele due to regional differences.

For the G-allele mean frequency disease, in the case group and the control group, we found that the Indian ratio is the highest and the Korean rate is the lowest. We did not see a significant correlation between the MCP-1 A-2518 G gene polymorphism and DN among people in China, Korea, and Turkey. The principal reason is that the numbers of researches are not enough to figure out answers. Therefore, more relevant analyses would be needed to get done. At present, more and more scholars have systematically studied diabetic nephropathy.

The interaction between MCP-1 A-2518 G gene polymorphism and the risk of diabetic nephropathy has gradually attracted the broad interest of scholars. This study used meta-analysis to systematically evaluate the correlation between MCP-1 A-2518 G gene polymorphism and the incidence of diabetic nephropathy, to provide a reference for the relationship between the two. Due to the heterogeneity between studies, there will be some impact on the results of the study. Besides, although the publication bias is not apparent, within the scope of acceptance, there are still publication biases that affect the analysis results. The small sample size is also a vital factor to influence the results of our analysis, so more follow-up studies are needed.

Overall, this study demonstrates that among people in Korea, China, and Turkey, the MCP-1 A-2518 G gene polymorphism does not give influence in the risk of diabetic nephropathy, but in Indians, GA genotype may affect diabetes, so the incidence of kidney disease is significantly correlated.

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Availability of data and materials:
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions:
PZ wrote the manuscript. HY, YA, XW and NH designed the study and performed the experiment. YL and YC was responsible for the analysis and discussion of the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate:
The study was approved by the Ethics Committee of Fuwai Hospital Chinese Academy of Medical Science.

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