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The aquaporin 5 promoter polymorphism and cytomegalovirus infection in kidney transplant recipients

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ABSTRACT

Introduction: Cytomegalovirus (CMV) infection is a significant complication in kidney transplant recipients, impacting graft function and overall patient outcomes. Aquaporin 5 (AQP5) is a transmembrane channel that regulates renal function and impacts important mechanisms of immune cell migration and inflammation.

Objectives: This research aimed to evaluate the impact of *AQP5* polymorphism (-1364A/C) on the risk of CMV infection in kidney transplant recipients.

Patients and Methods: One-hundred kidney transplant recipients were included in this study, divided into two groups; CMV^+-positive (n=50) and CMV^--negative (n=50) patients. Additionally, a control group of 50 healthy individuals was included. The frequency of the *AQP5* (-1364A/C) gene polymorphism was determined using the ARMS-PCR technique.

Results: About 26% and 16% of patients in the CMV^+ and CMV^- groups experienced acute rejection after renal transplantation, respectively ($P=0.220$). The CC genotype of *AQP5* (-1364A/C) polymorphism was present in 8% (n=4) of CMV^+ and 4% (n=2) of CMV^- recipients (4%); however, it was not observed in the control group ($P=0.354$).

Conclusion: The results revealed that carrying at least one C-allele of the AQP5 1364A/C polymorphism (AC or CC genotypes) does not have a significant association with the incidence or presence of CMV infection in kidney transplant patients.

Implication for health policy/practice/research/medical education:
The results of the present study indicated that gene polymorphism at the promotor region of aquaporin 5 (1364A/C) as the regulatory transmembrane protein coding gene, does not have a significant association with the incidence or presence of cytomegalovirus infection in kidney transplant patients.

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Introduction

Renal allograft transplantation is the most effective alternative therapy for patients with end-stage renal disease, significantly enhancing both life expectancy and quality of life. Despite advancements in surgical techniques and immunosuppressive therapies, various infections following kidney transplantation remain one of the primary complications (1). Infectious complications typically occur during one of the three time periods following transplantation: early-onset, through peak immunosuppression, and late-onset infections (2). Multiple factors influence the timing of these infections, including donor-transmitted viruses, preexisting infections or immunodeficiencies, the overall state of immunosuppression, and the use of antibiotic prophylaxis (3).

Cytomegalovirus (CMV) infection can occur among allograft recipients and may present as primary, secondary, or reactivated infections (4). The prevalence of CMV infection in kidney recipients is related to reduced graft

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and patient survival, increased cardiovascular events, the development of opportunistic infections, reduced GFR, and acute or chronic graft rejection (5). To prevent CMV infections, strategies such as preventative therapy, universal prophylaxis, and a combined post-preventive care approach can be beneficial techniques (6). Identifying risk factors is crucial for enhancing the efficacy of post-transplantation treatments. Additionally, genetic factors may enhance the likelihood of CMV infection in renal transplant patients (7).

Aquaporins (AQPs), transmembrane proteins, play a critical role in regulating immunity and kidney function (8). Studies indicate that AQPs significantly influence the proliferation and migration of immune cells (9,10). Therefore, high AQP gene expression increases immune system activity and transplant rejection, while low AQP gene expression may lead to CMV infection by lowering immunological activity (11). Recent research on immune responses has focused on the impact of AQPs on transplant rejection and CMV infection (11,12).

Considering the high risk of CMV infection and its detrimental complications in kidney transplant recipients, it is vital to identify related predictors and prescribe appropriate therapy for susceptible transplant candidates.

Objectives

This study aimed to assess the frequency of -1364 A/C single nucleotide polymorphism (SNP) in the promoter region of the *AQP5* gene and study its effect on the incidence of CMV infections among renal allograft recipients. To our knowledge, there is currently no evidence to evaluate the frequency of this SNP among the Iranian population following kidney transplantation.

Patients and Methods

Study design

This cross-sectional study was undertaken in the Kidney Transplantation ward at Imam Reza General Hospital in Tabriz, Iran. Due to the restricted number of kidney transplant patients, no strict inclusion criteria were considered for this investigation. However, being a candidate for kidney transplantation during the past 10 years, having a CMV infection, and completing file information were required for study participants.

One hundred kidney transplant recipients—with (n= 50) and without (n= 50) CMV infection—were enrolled to this study (2014-2019). In addition, 50 healthy individuals without any diseases were enrolled as a control group. Body mass index (BMI), height, age, weight, and gender of all individuals were recorded. Moreover, some other clinical data such as the cause of end-stage renal disease and comorbidities in the recipient, type of dialysis, type of donor (live or deceased), history of acute rejection and urinary tract infection, antibiotic, and immunosuppressive drug usage were recorded. The results of the panel reactive antibody test were also documented. The diagnosis of acute graft rejection was established based on key clinical instances, and clinical indicators, with acute rejection episodes characterized by a rapid increase in serum creatinine after ruling out alternative causes. Furthermore, early graft failure was defined as the loss of the graft within the first year following transplantation. Graft failure was defined as the necessity for dialysis or the patient's death due to renal complications. DNA extraction from blood samples was conducted by magnetic nanoparticles from the ZiAViZ commercial kit (https://ziaviz.com/). A genetic study was performed according to Rahmel et al (11).

Statistical analysis

The data were analyzed by SPSS version 18. The independent T-test and one-way ANOVA followed by Tukey post-hoc tests were applied to compare numerical variables, while Fisher's exact and chi-square tests were applied to examine categorical variables. A statistically significant relationship was established with a *P* value of less than 0.05.

Results

Based on our findings, 34 patients (68%) in the CMV^+ group, 26 patients (52%) in the CMV^- group, and 31 individuals (62%) in the control group were male (*P*=0.25). There were no statistically significant differences in age, weight, height, and BMI between the studied groups ($P > 0.05$; Table 1).

Table 1. Comparison of demographic information of participants

Variables		Groups			*P* value
		Kidney transplant recipients		Healthy controls (n= 50)	
		CMV^+ (n= 50)	CMV^- (n= 50)		
Gender	Male	34 (68%)	26 (52%)	31 (62%)	0.25[a]
	Female	16 (32%)	24 (48%)	19 (38%)	
Age (years)		45.32 ± 13.12	40.82 ± 9.9	44.72 ± 9.44	0.086[b]
Weight (kg)		67.86 ± 13.24	68.66 ± 13.43	68.78 ± 10.24	0.92[b]
Height (cm)		164.7 ± 9.64	168.3 ± 8.17	164.7 ± 9.63	0.08[b]
BMI (kg/m^2)		25.05 ± 4.61	27.58 ± 4.17	25.61 ± 4.92	0.24[b]

CMV: Cytomegalovirus, BMI: Body mass index.

[a] Qualitative values were compared via the chi-square test and reported as numbers (percentages).

[b] Quantitative values were reported as mean± standard deviation.

P value < 0.05 was considered a significant result.

It was revealed that 38 patients (76%) in the CMV$^+$ group and 43 patients (86%) in the CMV$^-$ group received a renal graft from living donors. Moreover, 13 recipients in the CMV$^+$ group (26%) and 8 patients in the CMV$^-$ group (16%) had a history of acute allograft rejection. In evaluating the medication consumption rate of patients, it was found that 30 patients in the CMV$^+$ group (60%) and eight patients in the CMV$^-$ group (16%) received anti-thymocyte globulin (ATG). Moreover, 64% of patients in the CMV$^+$ group (n=32) and 66% of patients in the CMV$^-$ group (n=33) were prescribed Valganciclovir. Before kidney transplantation, hemodialysis was the most prevalent kind of dialysis for patients in both groups, with rates of 84% in the CMV$^+$ group compared to 76% in the CMV$^-$ group. Diabetes mellitus was identified as the leading cause of kidney failure among these patients, with a confirmed family history of the disease present in 13 CMV$^+$ patients (26%) and 7 CMV$^-$ patients (14%). Before transplantation, urinary tract infections were reported in 5 patients in the CMV$^+$ group (10%) and 7 patients in the CMV$^-$ group (14%) (Table 2).

The levels of high-density lipoprotein, low-density lipoprotein, triglycerides, and cholesterol did not differ substantially amongst the three study groups ($P>0.05$). The BK virus gene was detected in the serum and urine samples of 7 CMV$^+$ individuals (14%). The mean BK virus titers in the serum and urine samples of these individuals were 17755 and 2686975, respectively.

Four recipients in the CMV$^+$ group (8%) and 2 patients in the CMV$^-$ group (4%) had the CC genotype, no significant association was observed between the CC genotype of the AQP5-1364 A/C polymorphism and CMV infection following renal transplantation ($P=0.354$) (Table 3). Additionally, 20% of CMV$^+$ patients (n=20) carried at least one C-allele of the AQP5 polymorphism (-1364 A/C), compared to 16% of CMV$^-$ patients (n=16) and 11% of control subjects (n=11).

Discussion

CMV is one of the most prevalent infectious pathogens among kidney transplant recipients that can cause graft rejection, impair the function of the allograft, and even result in the patient's death (13). Based on the outcomes of molecular research and evaluating the genetic polymorphisms of the immune system, diverse genotypes have different immunological responses to infections (14). This study examined the impact of the AQP5-1364 A/C polymorphism on the incidence of CMV infection following renal transplant. Even though a greater proportion of CMV$^+$ patients possessed the C-allele than CMV$^-$ patients and controls, there was no significant association between the C-allele of the AQP5-1364 A/C polymorphism and CMV infection in this population of renal transplant recipients.

Table 2. General variables of kidney transplant recipients

Variables		Groups		*P* value
		CMV$^-$ (n= 50)	CMV$^+$ (n= 50)	
Donor status	Living	43 (86%)	38 (76%)	0.20
	Deceased	7 (14%)	12 (24%)	
History of AR	Positive	8 (16%)	13 (26%)	0.22
	Negative	42 (84%)	37 (74%)	
ATG administration	Yes	8 (16%)	30 (60%)	<0.001
	No	42 (84%)	20 (40%)	
Valganciclovir administration	Yes	33 (66%)	32 (64%)	0.83
	No	17 (34%)	18 (36%)	
Dialysis type	Hemodialysis	38 (76%)	42 (84%)	0.31
	Peritoneal dialysis	12 (24%)	8 (16%)	
Causes of ESRD	Diabetes mellitus	27 (54%)	21 (42%)	0.317
	Polycystic kidney disease	5 (10%)	3 (6%)	0.715
	Urological problems	3 (6%)	6 (12%)	0.487
	Hypertension	12 (24%)	9 (18%)	0.624
	Alport disease	1 (2%)	1 (2%)	1.000
	Chronic glomerulonephritis	1 (2%)	0 (0%)	1.000
	SLE and rheumatologic diseases	2 (4%)	0 (0%)	0.495
	Unknown	3 (6%)	12 (24%)	0.023
Family history of diabetes	Positive	7 (14%)	13 (26%)	0.13
	Negative	43(86%)	37 (74%)	
Urinary tract Infection	Positive	7 (14%)	5 (10%)	0.53
	Negative	43 (86%)	45 (90%)	

AR: Acute rejection, ATG: Antithymocyte globulin, CMV: Cytomegalovirus, ESRD: End-stage renal disease, SLE: Systemic lupus erythematosus. Qualitative values were compared via a chi-square test and reported as number (percentage). *P* value < 0.05 was considered as significant result.

Table 3. Genotypic and allelic frequencies of AQP5 A/C polymorphism in the studied groups

Variables		Groups			*P* value
		Kidney transplant recipients		Healthy controls (n= 50)	
		CMV$^+$ (n= 50)	CMV$^-$ (n= 50)		
Genotype	AA	34 (68%)	36 (72%)	39 (78%)	0.35
	AC	12 (24%)	12 (24%)	11 (22%)	
	CC	4 (8%)	2 (4%)	0 (0%)	
Allele	A	80 (80%)	84 (84%)	89 (89%)	0.52
	C	20 (20%)	16 (16%)	11 (11%)	

AQP5: Aquaporin 5, CMV: Cytomegalovirus.
Qualitative values were reported as number (percentage) and *P* value < 0.05 was considered as significant result.

AQP5 is a membranous water channel on the apical side of B-type intercalated cells of the renal cortex, adjacent to pendrin (15). Procino et al showed a significant connection between pendrin and AQP5 proteins in the apical membrane and indicated that the functions of these two proteins may be simultaneously regulated (16). Moreover, as an osmosensor, AQP5 can detect luminal fluid hypotonicity of the thick ascending limb and the distal convoluted tubule (16,17).

Regarding CMV infection, innate immunity combats the virus, then neutrophils via their antiviral capabilities block viral replication. The reduction of AQP5 expression inhibits the activity and movement of neutrophil granulocytes across cells (18). Beyond innate immunity, acquired immunity such as CMV-specific T-cells plays a significant role in the ability of transplant patients to combat viral infections (19). It is reported that the promoter polymorphism of the *AQP*3 gene (-1431 A/G) is associated with acute rejection and CMV infection in renal transplants, as it leads to increased expression of AQP3 in T-cells and enhanced migration of immune cells (20). Likewise, AQP5 expression may affect T-cell-driven immune responses (21). According to the findings of recent investigations, the C-allele in the CC and AC genotypes of the *AQP*5 -1364A/C SNP may reduce the AQP5 gene expression and influence the innate and acquired immune responses to CMV infection, making the patient susceptible to CMV (22,23). The present study revealed that a greater proportion of transplant patients with CMV infection carried the C-allele; however, no statistically significant association was found between the presence of the AQP5 SNP in the promoter region (1364A/C) and CMV virus infection. Similar to our findings, Büscher et al found that the AQP5 -1364A/C polymorphism was not linked with renal dysfunction, decreased GFR, and high blood pressure in children. They reported that none of the kidney recipients were C-allele carriers (12). In contrast to our findings, Rahmel et al (11) found that the C-allele (AC/CC genotypes) in the AQP5 -1364A/C polymorphism is significantly related to the incidence of CMV infection (42.3%) in kidney transplant patients (n=259) within 12 months post-transplant, compared to 22.9% for those with the AA genotype. Furthermore, the C-allele was a clinically strong independent risk factor for CMV infection after transplantation, with an estimated hazard ratio of 2.3 (95% CI: 1.40–3.73; p = 0.001) for the AC/CC genotype. Therefore, the presence of the C-allele in the transplant recipients increases the likelihood of CMV infection more than twice compared to those with the AA genotype during the first year post-transplantation.

Conclusion

The findings of the present study indicate that the C-allele in the promoter region of the *AQP*5 gene (the CC and AC genotypes) do not show a significant association with the incidence of CMV infection in renal allograft recipients.

Limitations of the study

Due to the limited number of kidney transplant patients, this study was conducted with a small sample size. Since no correlation was found between the CC/AC genotypes and CMV infection in this research, it is recommended that further studies be undertaken to explore this topic and identify additional risk factors for CMV infection in renal allograft recipients.

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Authors' contribution

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interests

The authors declare no competing interests.

Consent to participate

Participants signed the informed consent form and willingly took part in this study.

Ethical issues

The research was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the ethics board of the Tabriz University of Medical Sciences (Ethics code# IR.TBZMED.REC.1399.255). This study was extracted from the specialty thesis of Samira Matin at this university (Thesis #65075). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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