

# Seroprevalence of Herpes Simplex Virus-2 in Kidney Transplant Recipients

## A Single-Center Experience

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**Keywords.** herpes simplex virus, kidney transplantation, serologic tests

**Introduction.** Viral infections are a real threat in kidney transplant recipients because of their immunocompromised condition. This study aimed to evaluate herpes simplex virus-2 (HSV-2) seropositivity among kidney transplant recipients.

**Materials and Methods.** Serum samples of 91 kidney transplant recipients from Urmia, Iran, were examined serologically for antibodies against HSV-2 using an enzyme-linked immunosorbent assay.

**Results.** The mean time from transplantation at HSV-2 testing was  $5.04 \pm 4.45$  years. The anti-HSV-2 immunoglobulin G antibody was positive in 5.4% of the kidney transplant recipients. Seropositive patients did not present any clinical manifestations of genital herpes infection. There was no association between HSV-2 seropositivity and age, gender, history of hemodialysis and transplantation, blood transfusion, or immunosuppressive regimen.

**Conclusions.** Seroprevalence of HSV-2 is not high among our kidney transplant recipients. However, it remains a source of concern, considering the compromised immune system in this specific population.

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### INTRODUCTION

Herpes simplex virus-2 (HSV-2) is a virus from the herpes virus family that has the ability to establish latency and become reactivated in a later time.<sup>1</sup> Its seroprevalence varies substantially by region; it was 22% among general population in the north-west of Europe<sup>2,3</sup>; however, the prevalence is mentioned to be mostly higher in developing regions than developed countries.<sup>4</sup> The HSV-2 seroprevalence is assumed to be higher among immunodeficient people.

The most common manifestation of HSV-2 in organ transplant recipients is mucocutaneous lesions of the genital region.<sup>1</sup> Considering immune deficiency, which is already present in patients with kidney failure,<sup>5,6</sup> and also drug-induced

immunosuppression in kidney transplant recipients, viral infections become a greater threat to this particular population. The use of new and very potent immunosuppressants has made it possible to reduce rejection incidence and improve kidney allograft survival, although the infections have significantly increased.<sup>7</sup>

Reactivation of HSV-2 in organ transplant recipients is more frequent and may be more invasive or taking longer time to heal. The HSV-2 infection has a greater potential for dissemination to the visceral organs than it does in the immunocompetent hosts.<sup>8</sup> The aim of this study was to evaluate the seroprevalence of HSV-2 among kidney transplant recipients.

**MATERIALS AND METHODS**

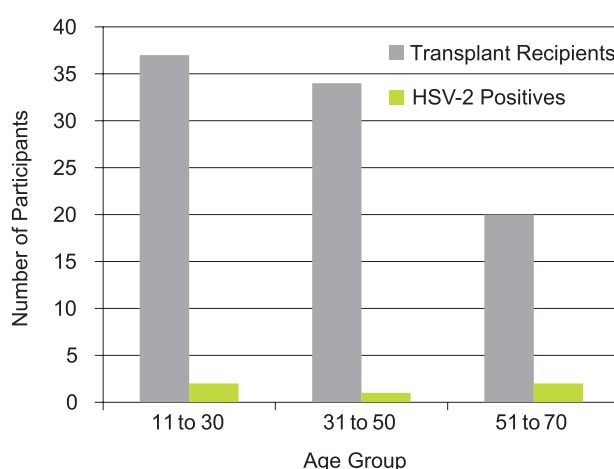
We randomly selected 91 kidney transplant recipients who were transplanted in Imam-Khomeini Hospital of Urmia and followed up regularly at the Clinic of Transplant for our cross-sectional study. All of the participants provided informed consent.

The participants were received an antiviral prophylactic treatment with acyclovir during the 3-month posttransplant period. Data were collected regarding these variables: age, gender, education, history and duration of hemodialysis, duration of posttransplant period, etiology of kidney failure, immunosuppressant regimen, and previous blood transfusion. In all of the patients, diagnostic serology was performed for HSV-2 using HSV-2-specific glycoprotein immunoglobulin G 2 tested by an enzyme-linked immunosorbent assay.

**RESULTS**

The mean age of the study population was 37.26 ± 14.22 years old, and 57 (62.6%) were men. Seventy patients (76.9%) were married. The participants had been on hemodialysis for 6.39 ± 4.31 years before transplantation. The mean posttransplant period was 5.04 ± 4.45 years. Four of the kidney recipients were transplanted for the 2nd time and had a history of graft rejection. Sixty-one patients (67.0%) had a blood transfusion history. Primary causes of kidney failure among the study population are demonstrated in the Table. The maintenance immunosuppressive regimen consisted of cyclosporine, azathioprine, and prednisolone in 31 (34.1%) and cyclosporine, mycophenolate mofetil, and azathioprine in 60 (65.9%).

Overall, 5 kidney transplant recipients (5.4%) were seropositive for anti-HSV-2 immunoglobulin



Kidney transplant recipients and herpes simplex virus-2 (HSV-2)-seropositive ones based on different age groups.

G antibody (3 men and 2 women). As demonstrated in the Figure, there were 2 seropositive subjects in the age range of 11 to 30 years old, 1 in the range of 31 to 50 years, and 2 in the range of 51 to 70 years old. Four of the patients were married. Two of the HSV-2-positive patients had end-stage renal disease for less than 5 years, while, the remaining 3 had kidney failure for 5 to 10 years. Four of the patients had received a kidney transplant during the past 5 years, and only 1 was a recipient for more than 5 years. A positive history of blood transfusion was reported in 3 of the patients.

Four of 5 HSV-2-seropositive patients had kidney failure due to a kidney-related cause and 1 due to renal complications of hypertension. The HSV-2 seropositivity was found in 4 kidney recipients with a maintenance immunosuppression regimen of cyclosporine, mycophenolate mofetil, and azathioprine (6.7%), and in 1 of those on cyclosporine, azathioprine, and prednisolone (3.2%).

There was no clinical manifestation of genital herpes among the kidney transplant recipients. We had no data regarding whether the HSV-2 infection was a primo-infection or reactivation. There were no associations between HSV-2 serologic infection and age, gender, history of hemodialysis, transplantation, blood transfusion, and immunosuppressive regimen.

**DISCUSSION**

The frequency of HSV-2 seropositivity was not so high in our kidney transplant recipients in Urmia (5.4%). In a previous study in Iran, Pourmand and

Causes for Kidney Failure in Kidney Transplant Recipients

Cause	Patients (%)
<b>Renal</b>	
Glomerulonephritis	46 (50.6)
Polycystic kidney disease	8 (8.8)
Alport syndrome	1 (1.1)
Lupus nephritis	1 (1.1)
<b>Systemic disease</b>	
Diabetic nephropathy	6 (6.6)
Hypertensive nephropathy	21 (23.1)
<b>Postrenal</b>	
Obstructive uropathy	1 (1.1)
Nephrogenic bladder	1 (1.1)
Nephropathic reflux	6 (6.6)

colleagues<sup>9</sup> demonstrated a serologic frequency of HSV-2 to be 3.3% in the general population. Considering higher level of HSV-2 prevalence in developing countries, both Iranian studies in immunocompetent and immunodeficient populations demonstrated lower prevalence compared with the European studies.<sup>3</sup> In fact, HSV-2 prevalence is in general the lowest in Asia compared with other regions.<sup>10</sup> We also speculate that sexual behavior of the Iranian people, which is usually within the structure of family, may play a significant role in the relatively low prevalence of HSV-2 in this country.

Despite the low prevalence rate, this viral infection remains a source of concern for our kidney transplant recipients. Although rare, HSV-2 disseminated infection in the context of organ transplantation can be life threatening.<sup>11</sup> Also, preventing HSV-2 infection and controlling genital herpes are of utmost importance, because of the accumulating data indicating that HSV-2 infection may increase acquisition and transmission of human immunodeficiency virus.<sup>10,12,13</sup>

Several factors such as age, gender, and clinical history can be associated with HSV-2 infection. It has been mentioned in several studies that HSV-2 infection is more prevalent in women than in men<sup>4,10,14</sup>; however, 3 of our 5 seropositive kidney recipients were men. Moreover, HSV-2 seroprevalence was mentioned to be associated with increasing age,<sup>3</sup> while in our study, there was no significant association between HSV-2 seropositivity and different age groups. According to Naraqi and associates, blood transfusions, hemodialysis, the allograft, and hospital environment are not significant sources of transmission for HSV.<sup>15</sup> This was compatible with our study, in which we found no significant relationship between HSV-2 infection and history of hemodialysis, blood transfusion, and previous transplant.

None of the 5 seropositive cases in our series had clinical manifestations of HSV-2 infection. Pre-existing HSV-1 antibodies can alleviate clinical manifestations of subsequently acquired HSV-2.<sup>16</sup> Although we did not evaluate seroprevalence of HSV-1 in our study population, based on the high prevalence of HSV-1 in general population, this infection might have had a positive role in alleviating clinical symptoms of the HSV-2-seropositive kidney transplant recipients.

In our study there was no significant difference in HSV-2 infection between different immunosuppressive treatment regimens. Immunosuppressive drugs were mentioned in some studies to possibly account for the high incidence of recrudescence infection with HSV in transplant recipients.<sup>15</sup> Some others, such as Merlino,<sup>17</sup> demonstrated no correlation between recurrent HSV infections and the type of immunosuppressive treatment. The influence of immunosuppressants could be various, depending on the associated treatment options. Whereas transplant recipients may develop opportunistic herpes infections, the study of Neyts and Clercq demonstrated that mycophenolate mofetil strongly potentiated the anti-HSV activity of acyclovir.<sup>18</sup> All of our kidney transplant recipients received viral prophylaxis with acyclovir for 3 months posttransplant, which could have a role in the low level of HSV seroprevalence in our study population; however, most of our seropositive patients (4 of 5) were in the group under immunosuppressive treatment with mycophenolate mofetil.

To our best knowledge, there have been no studies addressing the posttransplant incidence of HSV-2 infection or its seroprevalence so far. Our study population was so small. Thus, further studies with larger sample sizes are recommended. Also, we only used enzyme-linked immunosorbent assay for detection of HSV-2-positive patients. No quantitative or qualitative polymerase chain reaction assays were performed in order to detect HSV-2 DNA. The other limitation of our study was that we had no data regarding the serostatus of our patients prior to transplantation. Hence, we cannot have any kind of judgment regarding the time or route of transmission in seropositive cases.

## CONCLUSIONS

The seroprevalence of HSV-2 among a limited number of kidney transplant recipients was not high in Urmia. However, its positivity remains important, considering the compromised immune system in this specific population.

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### CONFLICT OF INTEREST

None declared.

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