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BK virus seroprevalence in renal transplant donors and recipients.

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Abstract

Introduction: BK virus (BKV) is highly prevalent in the general population; in renal transplant (RT) patients, it is the main cause of infectious tubulointerstitial nephritis, leading to graft dysfunction or loss. The seroprevalence in the Mexican population is unknown. The present study seeks to establish the seroprevalence of BKV in renal donors and recipients in the Mexican adult population.

Methods: This cross-sectional study was conducted at the National Institute of Sciences Medical and Nutrition Salvador Zubirán in Mexico City from June 2017 to April 2018. Seroprevalence before renal transplantation was evaluated in donors and recipients of RT through qualitative BK-IgG ELISA (MyBioSource Inc, San Diego, CA).

Results: The ELISA method was used to qualitatively measure IgG for BK virus in 80 donors and 88 renal recipients. The seroprevalence in donors was 56.3% (95% CI, 45%-67%), while in recipients, it was 45.5% (95% CI, 35%-56%). None of the variables analyzed showed an association with an increased risk of seropositivity for BKV in either recipients or donors.

Conclusion: The seroprevalence of BKV in our center was lower than expected for a developing country, having a sufficient sample size to extrapolate it to the Mexican population.

Keywords:

BK Virus; Kidney Transplantation; Histocompatibility Antigens; Graft Rejection; Seroprevalence.

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The BK virus (BKV) is highly prevalent in the general population, ranging from 60 to 90% [1] depending on the population studied; it is typically acquired during childhood and is asymptomatic in the vast majority of cases; however, in patients with kidney transplants, it is the leading cause of infectious tubulointerstitial nephritis (1 to 10%) [2 - 5] and is invariably associated with the intensity of immunosuppression. Late diagnosis leads to irreversible renal function decline, poor response to treatment, and graft loss in approximately 50% of patients [6–8]. The incidence is highest between 3 and 6 months posttransplant, with positivity found in blood in 5 to 15% and urine in 20 to 40%. After the first year, the risk of BKV reactivation decreases (approximately 3% for viremia and 9% for viruria) [9].

To date, only posttransplant monitoring is performed with viruria, viremia, or decoy cells to detect active infection; however, it is not a clinical practice to measure pretransplant serology to establish risk, even before starting immunosuppression.

Immunosuppression should be reduced in patients with significant viruria and viremia, as well as BKV nephropathy, established in renal biopsy. After reduction, blood BKV levels decrease between 7 and 13 weeks, a widely accepted marker of the onset or resolution of BKV nephropathy [10].

In Mexico, the seroprevalence of BKV is unknown, and whether risks can be stratified from the pretransplant stage based on the combination of the donor and recipient's serological status. This procedure would help individualize the type of induction and maintenance therapy that each recipient requires for a kidney transplant.

Materials and methods

Study design

This cross-sectional study established prekidney transplant seroprevalence for BKV in kidney donors and recipients.

Scenery

The study was conducted in the Nephrology and Mineral Metabolism Department of the Salvador Zubirán National Institute of Medical Sciences and Nutrition in Mexico City. The ethics committee approved the protocol on June 12, 2017, when patient recruitment began on April 1, 2018. The recruited patients were followed up for one year posttransplant or until the study's closure on May 31, 2018, whichever occurred first.

Participants

The ELISA method was used to qualitatively measure IgG for the BK virus in 80 kidney donors and 88 recipients of 168 subjects. Patients who refused to participate in the study or did not sign the informed consent form were excluded.

Variables

The variables were age, sex, socioeconomic level, previous kidney transplant, type of donor, haplotypes, etiology of CKD, type and duration of replacement therapy, % of Reactive Panel of antibodies, presence of donor-specific antibodies, serology for CMV, risk for BKV according to serological status (High (D+/R-), Medium (D±/R+), Low (D-/R-)), and % of latent tuberculosis (PPD > 5 mm).

Data sources/measurements

Patients who were already ready and scheduled for transplant or at the time of hospitalization for a kidney transplant were recruited from the kidney transplant clinic.

The recipients of deceased donors were invited to participate once the intention to transplant them from a specific donor was defined, and the sample was taken when they were channeled. His donor's sample was recovered from the leftover serum used for infectology studies. The serum samples used were from couples who had recently been transplanted (before the start of the study) and whose serum was left over and intended to be eliminated.

Measurement of antibodies against the BK virus

All the serum samples were frozen at −70°C until analysis. The previous night, the samples were thawed in a cold room (2–8°C). According to the supplier's instructions, igG against the BK virus was determined using the qualitative IgG-BK ELISA test (MyBioSource, Inc., San Diego, CA). Each ELISA set had 96 wells containing two positive and two negative controls. Ten microliters of serum were added to each well along with 40 µL of the diluent solution, after which 100 µL of conjugated reagent was added to all the wells, and the plates were incubated for 1 hour at 37°C. Subsequently, four washes of 30 µl each were performed with washing buffer, and chromogens A and B were added. The mixture was incubated in the dark for 20 min at 37°C. Then, 50 µl of stopping solution was added to each well. The samples were immediately analyzed with an ELISA microplate reader (EPOCH/2, BioTek Instruments, Inc., USA). The measurement scale was qualitative, and a sample with measurements > 0.15 was considered positive, as indicated on the kit.

Study size

A consecutive convenience sample of patients who underwent transplantation was included from April 1, 2017, to March 31, 2018. An approximate calculation of the size required for the study was made using a formula for calculating the sample size of a population-based proportion, with an expected proportion of 70%, a confidence level of 95%, and an absolute precision of 10%. This resulted in a sample size of 81 subjects. If we expected a proportion of 80%, the sample size would drop to 62 (the reported incidence ranges from 60 to 90%, higher in underdeveloped countries such as ours).

Statistical analysis

Descriptive statistics were used according to the level of measurement of the variables. Categorical variables are shown as frequencies and percentages. In contrast, continuous numerical variables are presented as the mean +/- standard deviation for those with a normal distribution and the median with quartiles 25 and 75 for those with an abnormal distribution. The chi-square test was used to compare categorical variables between risk groups for BKV infection. In

contrast, Student's t test or the Mann–Whitney U test was used for continuous numerical variables, as applicable. $P < 0.05$ was considered to indicate statistical significance. The prevalence is shown with its 95% confidence interval. The statistical package used was SPSS 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.).

Results

Study participants

Qualitative measurement of IgG against the BK virus was performed via ELISA in 80 kidney donors and 88 recipients. The proportion of male patients was 40 (50%) for donors and 52 (59%) for recipients. The age of the recipients was 38.5 years, and that of the donors was 45 years. A total of 25/80 patients (31.25%) were deceased. The causes of death were cardiovascular disease in 14 patients (56%), head trauma in 8 patients (32%), and other causes in 3 patients (12%).

A total of 62.5% of recipients did not share haplotypes with their donor. Most recipients were receiving hemodialysis at the time of transplant, and most had panel reactive antibodies (PRA) between 1 and 30%. One-third had donor-specific antibodies. The remaining general characteristics are shown in Table 1.

The seroprevalence in donors was 56.3% (95% CI, 45%-67%), while in recipients, it was 45.5% (95% CI, 35%-56%) (Table 2).

Main results

The recipients (n=88) were divided into seropositive and seronegative groups to compare their baseline characteristics and identify risk factors associated with positive serology. As presented in Table 3, no variable was related to serological status. Like the recipients, the donors were classified into two groups: seropositive and seronegative.

As shown in Table 4, no baseline characteristics were associated with seropositive status in the donors.

Discussion

BKV infection is the leading cause of tubulointerstitial nephritis (1-10%) in the posttransplant period, especially during the first year, and is invariably associated with the intensity of immunosuppression. Between 2 and 5 years, the incidence of NAFLD decreases to less than 5% and decreases further [11]. A seropositivity of 60 to 90% has been reported, which varies depending on the age group and the population studied [12-17]. This highlights the need for each country to determine its local epidemiology.

The present study established the seroprevalence for BKV in the Mexican adult population, obtaining a seropositivity of 56.3% (95% CI, 45%-67%) in donors and 45.5% (95% CI, 35%-56%) in kidney recipients. This percentage is well below what is expected for a developing country since greater dissemination is generally scheduled in states of poverty, overcrowding, and deficient essential services.

The prevalence of BKV has been found to be as low as 5% only in Aboriginal populations without contact with the modern world, as justified by the absence of exposure to the virus. However, suppose the isolated population is exposed to the virus. In that case, the seroprevalence increases until it is equal to that reported worldwide, as evidenced by the indigenous people of Putumayo in Colombia and Suguirisua [18]. Therefore, a lower seroprevalence is also expected in infants, with subsequent development of antibodies at 6 to 10 years of life comparable to that in the adult population. Despite this, in 1978, serostatus was reported in the Mexican pediatric population, with seropositivity similar to that found in our study in children between 1 and 4 years old [19]. However, the method used for seroprevalence analysis needs to be specified. Strikingly, the adult population has a lower prevalence than we analyzed.

The phenomenon of seroconversion reported in adults > 50 years of age [20] is another variable that explains the low seroprevalence found. The age of the patients in this study was analyzed, with a median of 45 years (from 34 to 50 years) for the recipients and 38.5 years (from 28 to 52 years); age was not biased, and the data can be extrapolated to the adult Mexican population in general.

Notably, immunodeficiency associated with chronic kidney disease did not impact the percentage of adults receiving IgG for BKV, as evidenced by the similarity of incidence between donors and recipients. This could be explained by exposure to this virus and the development of specific immunity beginning in childhood.

Table 1. General characteristics of the recipients.

Variable	Receivers N=88 (%)
# HLA shared (recipient - donor)	
0	55 (62.5%)
1	27 (30.7%)
2	6 (6.8%)
CMV serology (D/R)	
-High Risk (D+/R-)	10 (11.4%)
-Intermediate/Low Risk (D+/R± or D-/R-)	78 (88.6%)
Latent tuberculosis	26 (29.5%)

CMV: Cytomegalovirus. D:Donor. HLA: Antigen leukocyte human. R: receiver.

Table 2. Seroprevalence in donors and recipients.

IgG BK virus	Donors n =80 (%, 95% CI)	Receivers n =88 (%, 95% CI)
Seronegative	35 (43.7%, 33-55%)	48 (54.5%, 44-65%)
Seropositive	45 (56.3%, 45-67%)	40 (45.5%, 35-56%)

CI: confidence interval.

Table 3. Analysis of factors associated with positive serological status in kidney transplant recipients (n=88).

Variable	Total n=88	Receiver Sero-positive n=40 (%)	Receiver Sero-negative n=48 (%)	*P*
Male (n, %)	52 (59.1%)	26 (65.0%)	26 (54.2%)	0.417
Age group (n, %)				
< 35 years	38 (35.0%)	14 (35.0%)	24 (50.0%)	0.258
35 - 50 years	24 (27.5%)	11 (27.5%)	13 (27.1%)	
>50 years	26 (37.5%)	15 (37.5%)	11 (22.9%)	
Etiology of CKD (n, %)				
-Unknown	36 (40.9%)	17 (42.5%)	19 (39.6%)	0.529
-Type 2 Mellitus diabetes	17 (19.3%)	9 (22.5%)	8 (16.7%)	
-Lupus	12 (13.6%)	3 (7.5%)	9 (18.8%)	
-Glomerulonephritis	8 (9.1%)	4 (10.0%)	4 (8.3%)	
-Others	15 (17.0%)	7 (17.5%)	8 (16.7%)	
Socioeconomic level				
1 and 2	47 (53.4%)	20 (50.0%)	27 (56.2%)	0.711
3 – 7	41 (46.6%)	20 (50.0%)	21 (43.8%)	
Transplant Previous (n, %)	12 (13.6%)	5 (12.5%)	7 (14.6%)	1,000
TRR type (n,%)				
- Hemodialysis	37 (42.0%)	14 (35%)	23 (47.9%)	0.270
- Peritoneal dialysis	22 (25.0%)	11 (27.5%)	11 (22.9%)	
-HD/DP	21 (23.9%)	9 (22.5%)	12 (25.0%)	
- Anticipated transplant	8 (9.1%)	6 (15.0%)	2 (4.2%)	
Months TSR (median, IQR)	25.5 (14.0-50.5)	26.5 (15.3 – 61.3)	24.0 (12.0 – 43.8)	0.421
% PRA Class I pre KT (n, %)				
0	25 (28.4%)	14 (35.0%)	11 (22.9%)	0.071
1-30	58 (65.9%)	26 (65.0%)	32 (66.7%)	
>30	5 (5.7%)	0 (0.0%)	5 (10.4%)	
% PRA Class II pre-KT (n, %)				
0	25 (28.4%)	11 (27.5%)	14 (29.2%)	0.947
1-30	58 (65.9%)	27 (67.5%)	31 (64.5%)	
>30	5 (5.7%)	2 (5.0%)	3 (6.3%)	
Pretransplant donor-specific antibodies (n,%)	25 (28.4%)	11 (27.5%)	14 (29.2%)	1,000

CMV: Cytomegalovirus. D: Donor. PD: Peritoneal dialysis. HD: hemodialysis . HLA: Antigen leukocyte human. PRA: antibody reagent panel. KT: kidney transplant. TRR: therapy renal replacement.

Table 4. Analysis of factors associated with positive serological status in kidney donors (n=80).

Variable	Donor Sero-positive N=45	Donor Sero-negative N=35	*P*
Age group (n, %)			
<35 years	10 (22.2)	10 (28.6)	0.665
35-50 years	24 (53.3)	19 (54.3)	
>50 years	11 (24.4)	6 (17.1)	
Male (n, %)	22 (48.9)	18 (51.4)	1,000
Any component of Metabolic Syndrome (SAH, DM2, obesity) (n, %)	5 (11.1)	2 (5.7)	0.459

SAH: Systemic arterial hypertension. DM2: Diabetes Mellitus type 2.

In pediatric studies, Ali et al. [21] reported that the combination of high titers of IgG-BKV in the donor and low titers in the recipient is associated with a greater risk for the early presentation of viremia. Ginevri et al. [22] initially reported that seronegative recipients, as determined by a hemagglutination inhibition assay, have a greater risk of viral reactivation (58.3%) than seropositive recipients (21.4%). However, these authors could not confirm these data when switching to ELISA, which is the serostatus determination method. Smith et al. [23] reported that 83.3% of pediatric patients with BKV nephropathy were seronegative for BKV-IgG. This evidence established it as a high-risk group (D+R-) and intermediate- and low-risk group (D-R+, D+R+, and DR-).

Conclusion

The Mexican population has a seroprevalence for BK virus of 58%, lower than expected in the adult population of a developing country. In theory, this would put at greater risk of developing BKV nephritis in the posttransplant period when a recipient is seronegative, and it may be helpful to establish the serological status for BKV in the post-transplant stage and thus identify the groups at highest risk.

Abbreviations

PRA: antibody reagent panel, PD: peritoneal dialysis. ER-PAD: autosomal dominant polycystic kidney disease. HD: hemodialysis. HLA: Human leukocyte antigen. GMN: glomerulonephritis. Tb: Tuberculosis. RRT: renal replacement therapy. TR: kidney transplant.

Supplementary information
The supplementary materials have not been provided.

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Does not apply.

Author contributions
Andrea Portilla Jiménez: Data curation, Formal analysis, Funding acquisition, Research, Methodology, Project administration, Resources, Software, Writing – original draft.
Idalia Parra Avila: Conceptualization, research, methodology.
Rodrigo Rosado Canto: research, methodology, project administration.
Roberto Marino Sánchez: methodology, project administration, resources, writing-original draft.
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Josefina Alberú: Conceptualization, project administration, resources, writing-original draft.
Luis Eduardo Morales Buenrostro: Conceptualization, Supervision, Validation, Visualization, Writing: review and editing.
All the authors read and approved the final version of the manuscript.

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The procedures are part of the institution's regular transplant protocol and were not an additional cost to patients. The authors provided the administrative expenses for the preparation of this research.

Availability of data or materials
The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality; however, they may be shared upon reasonable academic request.

Statements

Ethics committee approval and consent to participate
The study was authorized by the INCMNSZ Research Ethics Committee on June 12, 2017, with approval number 2017-2227. The participants signed informed consent for participation in the study.

Consent for publication
Patient photographs, tomography scans, and X-ray studies were not needed.

Conflicts of interest
The authors declare that they have no conflicts of interest.

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