Original article

Lack of association between Kidd blood group system and chronic kidney disease

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ABSTRACT

Background: The Kidd blood group system has three antigens, \( \text{Jk}^a \), \( \text{Jk}^b \) and \( \text{Jk}^3 \), found on red blood cells and on endothelial cells of the inner lining of blood vessels in the renal medulla. These are known as urea transporter B (UT-B). Researchers have found that individuals carrying the \( \text{Jk}(a \rightarrow b\rightarrow) \) or \( \text{Jk}\)-null (UT-B null) phenotypes have a lower urine-concentrating capability and risk of severe renal impairment. This study evaluated the distribution of the Kidd phenotypes in patients with chronic kidney disease and a possible association of Kidd antigens with the development of renal disease.

Methods: \( \text{Jk}^a \) and \( \text{Jk}^b \) antigens were phenotyped using the gel column agglutination test (ID-cards Bio-RAD) in 197 patients with chronic kidney disease and 444 blood donors, as the control group. The phenotype and antigen frequencies between patients and controls were evaluated using the Chi-square method with Yates correction and logistic regression after adjustments for gender and age.

Results: No differences were observed between the Kidd phenotypes frequency distribution between patients with chronic kidney disease and blood donors \( \text{Jk}(a \rightarrow b\rightarrow) = 22.3\% \text{ and } 27.2\%; \text{Jk}(a + b\rightarrow) = 30.5\% \text{ and } 24.3\%; \text{Jk}(a + b+) = 47.25\% \text{ and } 48.4\% \), respectively.

Conclusion: The distribution of Kidd phenotypes found in the studied population is expected for Caucasians; \( \text{Jk}^a \) and \( \text{Jk}^b \) antigens were not found and phenotypes were not related to susceptibility for chronic kidney disease.

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Introduction

The red blood cell (RBC) membrane contains many anchored surface proteins and proteins that cross the lipid bilayer carrying different blood group antigens. Currently, 36 systems\(^1\) of RBC groups have been described according to the International Society of Blood Transfusion (ISBT) (http://www.isbtweb.org). Among them, the Kidd blood group system (\( \text{JK} \); ISBT 009) has been recognized as clinically important since its identification in 1951.\(^2\)

Antigens of the Kidd blood group system are expressed on type 3 glycoproteins, also known as the urea transporter B...
Urea transport is an important function of the kidney, and the ability to maintain proper blood urea levels is crucial for kidney health. The Kidd blood group system, which includes the Kidd proteins and their isoforms, plays a role in this process.

### Methods

The ethical and methodological aspects of this study were approved by the Research Ethics Committee on Human Beings from the Maringa State University (COEPF-UEM # 1.141.385/2014, CAAE 43117115.0.0000.0104, according to the Resolution of the Brazilian Council on Health-CNS 466/12).

### Subjects

This retrospective case-control study enrolled 197 unrelated patients with chronic kidney disease (CKD group) and 444 unrelated blood donors as a control group, living in the same geographical area as the patients. The individuals were attended and immunophenotyped between 2013 and 2015 at the Regional Blood Bank of Pato Branco, southwest region of Parana (located in the southern region of Brazil at 26°13′46″–09°S and 52°40′16″–09°W).

### Serologic tests

Red blood cell phenotyping for Kidd blood group systems was performed on a gel card (ID-Perfil II – k-Kp<sup>+</sup>-Kp<sup>–</sup>-jk<sup>–</sup>-jk<sup>+</sup>-ctl) using monoclonal antibodies according to the manufacturer's instructions (Diaimed ID-Cards, DiaMed<sup>®</sup> AG, Switzerland). RBCs were suspended in Bromelin solution (BioRad ID-Diluent 1) at a final concentration of 1:21 or 5%.

### Statistical analysis

The antigen and phenotype frequencies were estimated and the data was tested for their fit to the Hardy-Weinberg equilibrium<sup>22</sup> by calculating the expected frequencies of the genotypes and comparing them with the observed values. The Student's t-test was used to compare differences between groups. Statistical comparisons between these groups were performed and the estimated risk of developing CKD in individuals who have genetic polymorphisms was calculated by determining the Odds Ratio (OD) with a 95% of confidence interval (CI) adjusted for gender and age. Association tests were carried out to identify the predominant, dominant, recessive, overdominant and log-additive genetic inheritance models. p-Values < 0.05 by the Chi-square test with Yates correction and logistic regression were considered statistically significant. All statistical analyses were performed using the software OpenEpi program Version 2.3.1 (<http://www.openepi.com>) and SNPStats<sup>23</sup> (<http://bioinfo.iconcologia.net/index.php>).

### Results

The Kidd phenotype frequency distribution in the studied populations was in Hardy–Weinberg equilibrium (p-value = 0.48: CKD and p-value = 0.51: controls).

The characteristics of patient and control subjects are described in Table 1. The CKD patients were between 45 and 90 years old (62.8 ± 13.9) and from both genders (male: 55.8%; female: 44.2%). Regarding ethnicity, all patients declared themselves Caucasians. The control group was formed by 444 individuals between 18 and 64 years old (30.6 ± 11.1; p-value < 0.0001) from both genders (1:1) with 98.4% declaring themselves Caucasians. Because CKD was observed only in individuals > 45 years old, the control group was subdivided...
(n=94) for analyses, considering the minimum age reported by patients. In this group, the mean age was 52.54±5.36 years (p-value<0.0001), and 58.9% were males and 41.1% females with all of them being self-declared Caucasians.

The distributions of antigen and phenotype frequencies for the Kidd blood group systems in CKD patients and controls (total group and group >45 years old) are shown in Table 2. The phenotype frequencies for the Kidd blood group system in CKD patients were 22.3% for Jk(a−b+), 30.5% for Jk(a+b−), and 47.2% for Jk(a+b+). For controls (total and >45 years old, respectively) the phenotype frequencies were 27.2% and 30.8% for Jk(a−b+), 24.3% and 24.5% for Jk(a+b−), and 48.4% and 44.7% for Jk(a+b+). The null phenotype was not observed in any of the groups.

Differences in distributions of the Jk\textsuperscript{a} and Jk\textsuperscript{b} antigen and phenotype frequencies were not observed when case and control groups were compared according to inheritance models or after logistic regression stratified by age.

**Discussion**

In this association study, patients with CKD on hemodialysis were analyzed in order to investigate the distribution of JK phenotypes in patients with CKD and a possible influence of Jk\textsuperscript{a} and Jk\textsuperscript{b} antigens and phenotypes in the development of renal disease. However, differences between Jk\textsuperscript{a} or Jk\textsuperscript{b} antigen and phenotype frequencies were not observed between patients and controls.

The patients’ ages ranged from 45 to 95 years old (55.8 ± 13.9) and the predominant gender and ethnic group were male (62%) and Caucasian (100%). When the age range of CKD patients was compared with that of the control group, significant differences were found. This was because the control group was formed of blood donors from the Pato Branco Blood Bank with ages ranging between 18 and 64 years (BRASIL, ordinance 2712 of November 12, 2013). Therefore, the great majority of control individuals (78.8%) were between the ages of 18 and 44, and none of the CKD patients was under 45 years of age. On the other hand, 44.7% of the patients were between the ages of 65 and 90, but none of the control group were this old. In order to circumvent these differences in age distribution, a control subgroup was defined with only individuals over 45 years of age. However, differences between Jk\textsuperscript{a} or Jk\textsuperscript{b} antigen and phenotype frequencies were not observed between the two control groups (total of individuals and >45 years old).

Non-matching between patients and controls with respect to age may be a weakness of this study. This bias may occur because in complex diseases many genetic and environment factors contribute to the outcome; individuals from the
control group with an age of under 45 are possible candidates for developing renal dysfunction in the future. On the other hand, in case-control studies, ideally there should be at least one control per case, and the control group of individuals older than 45 years had fewer patients than the CKD Group. However, the Jk\textsuperscript{a} or Jk\textsuperscript{b} antigen and phenotype frequencies in both control groups of this study were similar to those frequencies found in another Brazilian population, thereby validating the results in this study.

The urea transporter in the kidney enables its medulla to maintain a high concentration of both urea and urine, as well as conserve water. Individuals with the Jk(a – b –) phenotype had lower urine-concentrating ability. In animal models, long-term UTB deficiency was associated with severe renal dysfunction and structural damage. On the other hand, genetic variations of the SLC14A1 gene were associated with bladder cancer and, some genotypes were associated with higher morbidity, and rejection after renal transplant. However, we did not find any null alleles in CKD patients or controls that could be identified as a risk factor for the disease.

In this study, more than 50% of the CKD patients were homozygous carrying either Jk(a+b−) or Jk(a−b+) phenotypes, in agreement with the results reported in the literature for Caucasians. Furthermore, no differences were observed between patients and controls regarding the distribution of Jk\textsuperscript{a} or Jk\textsuperscript{b} antigen and phenotype frequencies. Thus, Kidd phenotype was not associated to CKD.

## Conclusion

The distribution of Kidd phenotypes found in the studied population was as expected for Caucasians and therefore, Jk\textsuperscript{a} and Jk\textsuperscript{b} antigens and phenotypes were not found to be associated to the development of CKD.

## Conflicts of interest

The authors declare no conflicts of interest.

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## References


