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What do donor-specific antibody changes mean in kidney transplant patients?

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ABSTRACT

Background The role of immunological evaluation is significant in selecting a suitable donor to reduce post-transplant complications in kidney transplantation (KTx). It is unknown how often donor-specific antibody (DSA) positivity causes rejection or how often rejection will develop in patients who do not develop DSA positivity. We aimed to evaluate the relationship between the DSA changes and the KTx patients' biochemical parameters.

Material and Methods The study was a cross-sectional study evaluating 45 KTx patients. Demographic and clinical characteristics of the patients, pre-transplant DSA values, post-transplant DSA values, and biochemical parameters were retrospectively scanned from the hospital system. The patients' data were divided into three groups according to DSA changes.

Results DSA was negative in 21 (46%) patients and positive in 24 (54%) before transplantation. In the post-transplant follow-up, it was observed that the DSA value became positive in 7 patients and turned negative in 9 patients. Rejection developed in 22% of 9 patients whose DSA was positive before transplantation and turned negative after transplantation, and in 28% of 7 patients turned positive from negative. Estimated glomerular filtration rate (e-GFR) and creatinine levels in the post-transplant period were associated with the change in DSA. Also, e-GFR and neutrophil values were independently associated with rejection.

Conclusions Although DSA change affects kidney functions, we found that DSA positivity alone cannot predict rejection, and rejection may occur in the DSA-negative group. Neutrophil count and e-GFR changes were closely related to rejection. Therefore, DSA levels should be monitored regularly, but DSA change alone is insufficient for rejection evaluation.

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INTRODUCTION

Kidney transplantation (KTx) is the most effective treatment option for end-stage kidney disease. A successful kidney transplant improves the quality of life and significantly reduces mortality risk compared to dialysis treatment.[1,2] The role of immunological evaluation is significant in selecting a suitable donor before transplantation to reduce post-transplant complications.[3] As in all organ transplants, immunological problems in KTx have not been fully resolved yet. One of the most critical follow-up goals after KTx is to reduce the risk of antibody-mediated rejection. Sensitisation is the most vital immunological mechanism for rejection before and after transplantation.[4] The most critical risk factors for immunological sensitisation are incompatibility in human leukocyte antigen (HLA) and antibodies against these antigens. While reasons such as previous transplantation history, pregnancy, and blood transfusions are responsible for pre-transplant immunological sensitisation, the most critical risk factors for post-transplant immunological sensitisation are acute rejections, insufficient immunosuppression, and incompatibility observed in tissue antigens.[5,6]

Donor-specific antibodies (DSA) are anti-human leukocyte antigen antibodies formed against mismatched antigens in the donor. Many investigators have demonstrated the effects of DSAs on graft survival, including graft rejection and worse graft function. It has been shown that de-novo anti-HLA antibodies can develop even if the graft function is normal in KTx patients, which can predict graft dysfunction in long-term follow-up.[7,8] In addition, more metabolic side effects occur due to increased immunosuppressive therapy in patients with DSA positivity.[9-11]

It is unknown how often DSA positivity, which is an essential part of immunological follow-up in KTx, causes rejection or how often it will develop in patients who do not develop DSA positivity. We aimed to evaluate the relationship between the changes in DSA values measured before and after KTx and the clinical and biochemical parameters of the patients.

MATERIAL AND METHODS

The study was cross-sectional, and ethics committee approval was obtained from Konya Necmettin Erbakan University (Ethics Committee Number: 2019-2223). The data of 45 kTx patients (all transplants were from living donors and up to 4th-degree relatives) were scanned retrospectively, and medical records (including age, gender, transplantation dates, laboratory results, pre-transplantation induction therapy, and immunosuppressive treatment regimens in the follow-up periods) were recorded from our hospital system.

The patients ' DSA levels and biochemical tests DSA levels and biochemical tests of the patients when the kidney function tests stabilised after transplantation were recorded as pre-transplant values. Biochemical tests and DSA levels requested during the last control of the patients who completed at least three months of follow-up after kTx were recorded as post-transplant values. Patients were divided into three groups according to the changes in DSA status: Group 1: Patients with positive DSA levels; Group 2: Patients with negative DSA levels; and Group 3: Patients with stable DSA levels.

All biochemical analyses were undertaken in the Central Biochemistry Laboratory of our hospital. Serum creatinine was measured with the Jaffe Method. An automated clinical chemistry analyser measured serum C-reactive protein (CRP) levels with an immunoturbidimetric assay (Diasis Diagnostic System). Serum levels of calcium, phosphate, and intact parathyroid hormone (iPTH) were measured. iPTH was measured using the Elecsys PTH assay. For the 24-hour urinary proteinuria levels, total protein concentration levels were measured by a turbidometric assay using benzethonium chloride. The results were expressed as mg/L.

DSA measurements

DSA values before and after transplantation were studied using the Luminex method. For longitudinal analysis of DSA levels, bead assays were performed retrospectively (centralised analysis) to avoid influences of day-by-day variations in test results (test batches including samples from four to six patients each). Donor specificity was defined according to serological and/or low- or high-resolution donor/recipient HLA typing (HLA-A, -B, -Cw, -DR, -DQ, -DP on availability) provided by the local HLA lab. Test results were documented as mean fluorescence intensity (MFI) of the immunodominant DSA. An MFI threshold > 1,000 was considered positive.

Statistical analysis

Analytical and graphical methods were used to

evaluate the data regarding normal distribution, kurtosis values of analytical methods, Shapiro-Wilk test, and coefficient of variance. The histogram and detrended Q-Q plot graphs were assessed among the visual methods, and the normal distribution was decided. The Mann-Whitney U test was used as a non-parametric test to compare the non-normally distributed numerical variables between the two groups. The Kruskal Wallis Test was used to reach more than two groups. Fisher's exact test or Chi-square test was used to compare categorical variables. Binomial Logistic Regression, a Back-Step method, was used to independently assess the factors associated with rejection in those who showed rejection. If the p-value is less than 0.05, it is considered statistically significant. SPSS version 14.0 was used for statistical calculations.

RESULTS

Forty-five patients, 17 women (37.8%) and 28 men (62.2%), who had kidney transplants from living donors, were included in this study. The mean follow-up period of the patients was 27 ± 18 months, and the mean age was 43.36 ± 13.92 years. DSA was positive in 24 (53%) patients before transplantation and negative in 21 (47%) patients. In the post-transplant evaluation, DSA was positive in 22 patients and negative in 23 patients. In the follow-up of 7 patients whose DSA was negative before transplantation, their DSA became positive. In 9 patients whose previous DSA test was positive, DSA tests became negative in the follow-up. The patients were divided into three groups: decreased, stable and increased DSA levels. The data on the biochemical properties of the groups according to the DSA changes were presented in Table 1.

In this study, acute rejection developed in 7 of 45 patients (15.6%) during the follow-up period. All rejections were biopsy-proven, and the mean development time was 25 ± 19 months. While the group without rejection had higher estimated glomerular filtration rate (e-GFR) and calcium values, the serum urea, creatinine, phosphorus, white blood cell count, and neutrophil count were statistically higher in the group with rejection ($p < 0.05$) (Table 2). In this study, rejection developed in 22% of the patients whose DSA level was positive before transplantation and became negative after transplantation. The rejection rate was

Table 1. Comparison of laboratory change according to DSA change status

Changing Parameter	Total (n = 45) medium (min):(max)	Patients with decreased DSA (n = 12) medium (min):(max)	Patients with stable DSA (n = 15) medium (min):(max)	Patients with increased DSA (n = 18) medium (min):(max)	*p* value
eGFR (ml/min)	-9 (-96):(75)	5,5 (-57):(75)	-6 (-42):(27)	-20 (-96):(12)	**0.018**
Urea (mg/dl)	-13 (-56):(61)	-24 (-56):(7)	-14 (-53):(6)	-4,5 (-43):(61)	0.056
Creatinine (mg/dl)	0,1 (-0,4):(3)	-0,1 (-0,4):(1,5)	0,1 (-0,4):(0,9)	0,4 (-0,2):(3)	**0.009**
Sodium (mmol/L)	2 (-6):(8)	4,5 (-3):(8)	1 (-6):(5)	0 (-5):(4)	**0.008**
Potassium (mmol/L)	-0,5 (-1,4):(1,6)	-0,6 (-1,4):(-0,1)	-0,5 (-1,4):(-0,6)	-0,2 (-1,1):(1,6)	0.103
Calcium (mg/dl)	0,2 (-1,1):(1,9)	0,17(-0,2):(0,8)	0,2 (-0,4):(1,4)	0,2 (-1,1-1,9)	0.737
Phosphorus(mg/dl)	0,5 (-1,9):(1,7)	0,5 (-0,7):(1,7)	0,2 (-1,9):(1,4)	0,6 (-1,3):(1,6)	0.324
Albumine (mg/dl)	4 (-9):(15)	4 (-2):(12)	3 (-3):(15)	4 (-9):(11)	0.986
SGPT (u/L)	-5 (-58):(59)	-5 (-17):(29)	-5 (-17):(29)	-7,5 (-58):(59)	0.999
CRP (mg/L)	0,1 (-51,4):(33)	2,25(-10):(14,3)	0 (-51,4):(33)	-0,3 (-3):(29)	0.403
WBC (10^3 /uL)	-1,2 (-12,5):(4,5)	-3,6 (-2,1):(9,1)	-0,2 (-8,1):(4,5)	-1,5 (-12,5):(2,7)	0.139
Neutrophil (10^3/uL)	-1,8 (-11):(3,1)	-5 (-8,7):(1)	-1,2(-8,8):(2,8)	-2,9 (-11):(3,1)	0.228
Lympohcyte (10^3/L)	0,5 (-6,7):(4,3)	0,5 (-0,6):(2)	0,8 (-0,4):(3)	0,5 (-6,7):(3)	0.246
Hemoglobin (g/dL)	1,8 (-1,6):(5,7)	1,8 (-1,2):(5,3)	1,8 (-0,4):(4,8)	2 (-1,6):(5,7)	0.979
Platelet (10^3 /L)	1 (-202):(380)	-11 (-53):(139)	60 (-42):(380)	-14(-202):(128)	**0.027**
Proteinuria (gr/day)	-0,1 (-1):(3,6)	0,03 (-0,6):(1)	0,24 (-1):(0,1)	-0,1 (-0,5):(3,6)	**0.018**
Parathormone (ng/L)	0 (-831):(278)	-15 (-460):(67)	0 (-203):(128)	-0,5 (-831):(278)	0.819

eGFR: Estimated Glomeruler filtration rate, SGPT: serum glutamate pyruvate transaminase, CRP: C-reactive protein, WBC:White blood cell, Bold parameters indicate statistically significance

Table 2. Comparison of biochemical parameters according to rejection status

Parameter		Total Median (IQR) or n (%)	Patient Without Rejection (n = 38) Median (IQR) or n (%)	Patient with Rejection (n = 7) Median (IQR) or n (%)	*p* value
Age		46(19-68)	46(19-68)	46(20-56)	0.549
Gender	Female	17(%37,8)	14(%36,8)	3(%42,9)	1.000
	Male	28(%62,2)	24(%63,2)	4(%57,1)	
Pre-Transplant DSA	Negative	21(%46,7)	18(%47,4)	3(%42,9)	1.000
	Pozitive	24(%53,3)	20(%52,6)	4(%57,1)	
DSA Change	Stable or Decreased	27(%60)	24(%63,2)	3(%42,9)	0.412
	Increased	18(%40)	14(%36,8)	4(%57,1)	
Tacrolimus At First	On Target	17(%37,8)	14(%36,8)	3(%42,9)	1.000
	Off Target	28(%62,2)	24(%63,2)	4(%57,1)	
Tacrolimus at Follow-up	On Target	29(%64,4)	24(%63,2)	5(%71,4)	1.000
	Off Target	16(%35,6)	14(%36,8)	2(%28,6)	
eGFR (ml/min)		63(13-205)	64(13-205)	36(27-62)	**0.001**
Urea (mg/dl)		41(20-111)	36(20-111)	59(36-92)	**0.016**
Creatinine (mg/dl)		1,2(0,5-4)	1,2(0,5-4)	1,8(1,3-2,6)	**0.002**
Calcium (mg/dl)		9,5(8,4-10,7)	9,5(8,4-10,7)	8,9(8,4-9,7)	**0.007**
Phosphorus (mg/dl)		3,2(1,3-4,4)	3,2(1,3-4,4)	3,8(2,9-4,1)	**0.037**
Albumıne (mg/dl)		44(29-51)	44(29-51)	45(42-47)	0.975
SGPT (u/L)		14(5-75)	15,5(5-63)	8(6,8-75)	0.316
CRP (mg/L)		2(0,3-35)	2(0,3-35)	4,5(0,4-31)	0.825
WBC (10^3 /uL)		7,1(3,1-16)	6,9(3,1-16)	10(6,6-10)	**0.042**
Neutrophil (10^3 /uL)		4,5(1,6-9,3)	4,2(1,6-9,3)	7(5-8,4)	**0.003**
Lympohcyte (10^3 /L)		1,7(0,4-6,3)	1,7(0,4-6,3)	1,5(0,6-3,4)	0.293
Hemoglobin (g/dL)		13,4(9,9-16,8)	13,6(9,9-16,8)	12,3(10,3-15,1)	0.259
Platelet (10^3 /L)		232(124-658)	235,5(124-658)	224(128-323)	0.398
Proteinuria (gr/day)		0,2(0,1-4,9)	0,2(0,1-4,9)	0,3(0,1-3,7)	0.307

eGFR: Estimated Glomeruler filtration rate, SGPT: serum glutamate pyruvate transaminase, CRP: C-reactive protein, WBC: White blood cell, Bold parameters indicate statistically significance

28% in the patient group whose DSA value was negative before and became positive after transplantation.

Binomial logistic regression analysis evaluated the factors associated with rejection ($p < 0.05$). The logistic regression model was statistically significant, $\chi^2(2) = 18.698$, $p < 0.001$. The model explained 58.7% (Nagelkerke R2) of the variation in rejection and correctly classified 91.1% of cases. e-GFR and neutrophil values at follow-up were independently associated with rejection. In follow-up, each unit increase in neutrophil value was associated with rejection by 2.13 fold; each unit decrease in follow-up e-GFR was associated with a 1.11-fold increased probability of rejection (Table 3).

DISCUSSION

In this study, we evaluated the DSA levels of the patients in the pre-transplant and post-transplant follow-up periods and the relationship between DSA, biochemical parameters, and rejection status. First, we showed that, as expected, post-transplant DSA change can affect kidney function. The second significant result was that DSA positivity alone was insufficient to predict rejection, and rejection was possible in the DSA-negative group. Finally, we found that the two most valuable criteria for predicting rejection were neutrophil count and e-GFR change.

The most important risk factors for immunological sensitisation are the incompatibility of HLA antigens

Table 3. Parameters Associated with Rejection

	Univariate Analysis			Multivariate Analysis		
	OR	%95 CI	*p-value*	OR	%95 CI	*p-value*
Calcium (mg/dl)	0,085	0,012-0,627	0,016			
Neuthrophil (10^3 /uL)	1,773	1,113-2,825	**0,016**	2,131	1,092-4,156	**0,026**
Creatinine (mg/dl)	4,333	1,015-18,49	0,048			
Urea (mg/dl)	1,044	1,002-1,088	0,041			
e-GFR (ml/min)	0,912	0,851-0,977	**0,009**	0,908	0,847-0,974	**0,007**
e-GFR Change (ml/min)	0,955	0,921-0,99	0,012			
Creatinine Change(mg/dl)	3,887	1,01-14,959	0,048			

Among the parameters that were found to be significant related to rejection in the univariate analysis, those with $p < 0.05$ were included in the multivariate analysis. Backward Stepwise method was used in logistic regression analysis ($\chi^2(2) = 18.698$, $p < 0.001$ Nagelkerke R Square = 0.587 and the final model (step 7) is shown in the table Abbreviations: OR = odds ratio CI = confidence interval, eGFR: Estimated glomeruler filtration rate, Bold parameters indicate statistically significance.

and antibodies against these antigens.[3] De novo anti-HLA antibodies can develop even if the graft function is normal in kTx patients, which can predict graft dysfunction in long-term follow-up.[5,6] It has long been known that anti-HLA antibodies are a risk factor for worse allograft outcomes before transplantation.[12,13] With the reporting of the relationship between de novo anti-HLA antibody formation and rejections after transplantation, the effects of newly developed anti-HLA antibodies on graft outcomes are now more clearly known.[7,14,15] Many studies found significant correlations between anti-HLA antibodies and acute rejection, several rejection attacks, chronic rejection, and decreased graft survival.[8,15,16] At the same time, donor-specific antibodies produced after transplantation were correlated with immunological complications and graft failure.[17,18] In addition, some studies draw attention to the strong relationship between non-donor-specific antibodies and rejection.[19,20] In this study, we didn't find a significant association between DSA positivity before transplantation or an increase in DSA titer in the post-transplantation period and the development of rejection. One of the most important reasons this association could not be demonstrated may be the inability to detect non-donor-specific antibody-induced rejections.

Contrary to the literature, our study had no significant relationship between DSA change and rejection. One reason may be the inability to differentiate C1q (+)/(–) DSA. In recent years, it has been shown that C1q (+) DSAs cause a higher risk of organ rejection and graft loss compared to C1q (–) DSA. In studies, C1q (+) DSAs have been shown to have significantly higher MFIs than C1q (–) DSAs, independent of rejection.[21,22] it was also revealed that more intense C4d accumulation and more frequent graft loss were observed in kidney biopsies in patients with C1q (+) DSA.

Not all individuals exposed to foreign HLA alloantigens are equally likely to be sensitised. Similarly, rejection does not develop in all patients with positive DSA levels or increased titers during follow-up. In our study, rejection developed in 4 (22%) of 18 patients whose DSA values increased during follow-up. In 14 (88%) patients, there was no significant change related to rejection. Only some individuals are equally susceptible, possibly due to the immunogenic difference of the antigens encountered and the differences in the immune response genes that are prone to form antibodies against foreign HLA antigens.[23] The absence of rejection in every sensitive individual can be explained by accommodation.[24]

One of the significant results of our study is the frequency of rejection in the DSA-negative patient group. Rejections due to HLA incompatibility in kTx are not only due to donor-specific class I and II antibodies. Rejections may also result from unclassifiable and non-donor-specific antibody responses.[18,25] The damaging effects of these antibodies, called non-DSA, on graft survival are equivalent to those of DSAs.20 In studies of patients who developed acute rejection, most had HLA antibodies.[26] However, it has been reported that 8-20% of patients did not develop HLA antibodies during acute rejection attacks.[27] Only DSA levels were considered in our study, and non-donor-specific antibodies were not considered. However, considering that non-donor-specific antibodies have the same effect on graft survival, the cumulative effect will be proportional to the level of DSA.[28] In our study, 42.9% of the patients who developed acute

rejection had negative DSA levels, and 57.1% were positive. The high rate of rejection was remarkable in the group with negative DSA. Our study's data also supports that antibodies other than DSA may be the reason for rejection.

When we examined the relationship between rejection and changes in biochemical parameters, we observed that changes in e-GFR and creatinine predict rejection. Since rejection is expected and biopsy is planned according to the change in e-GFR and creatinine, the most critical indicators that alert the clinician to rejection are still the changes in eGFR and creatinine values. Because creatinine levels will provide late information about developing kidney injury in clinical follow-up, many centres have recently been researching to predict both immunological damage and immune sensitisation with an earlier and better predictor. Monitoring anti-HLA antibodies after transplantation will be a suitable method for detecting chronic immune damage and early detection of rejection development in the long term. Decreased e-GFR value in the follow-ups in transplant outpatient clinics warns the clinician of rejection. This study found that a one-unit decrease in e-GFR during the follow-up period was associated with 1.11-fold increased rejection. As a result of our logistic regression analysis, each unit increase in neutrophil values during the follow-up period was found to be 2.13-fold associated with rejection. Microvascular inflammation accompanied by endothelial damage and inflammatory events dominated by neutrophils, especially in antibody-mediated rejections, are present in acute rejections.29-31 Considering the increase in neutrophils as a precursor of inflammation, the increased risk of rejection with an increase in neutrophils was already an expected finding.

Our study has three main limitations. First, the sample size was relatively small. Second, non-DSA antibodies were not investigated, and C1q (–) and (+) differentiation could not be made in patients with DSA positivity. Third, all of the patients enrolled in the study were Turkish. One should consider that our results cannot, therefore, be applied to all patients because of the differences between nationalities.

Despite all the studies, whether immunological monitoring can be performed on developing HLA antibodies in KTx patients is still unclear. Although the development of HLA antibodies is a risk for rejection, some patients may experience rejection without the development of antibodies, or the graft function may be normal despite the development of antibodies. For this reason, the titer, type, positivity time of the antibodies, and their relationship with the treatments should be investigated in more detail.

CONCLUSIONS

In conclusion, this study found that DSA change can affect kidney functions, and neutrophil count and e-GFR change are closely related to rejection. Therefore, DSA levels should be monitored regularly, but DSA change alone is insufficient for rejection evaluation. Further research on more valuable markers is also needed to predict the risk of rejection.

Highlights

•Post-transplant DSA change may affect kidney function.

•DSA positivity alone was insufficient to predict rejection.

•Rejection was possible in the DSA-negative group.

•The two most valuable criteria for predicting rejection were neutrophil count and e-GFR change.

Conflict of Interest

All authors declare that there is no conflict of interest in this study.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Necmettin Erbakan University, Meram School of Medicine, Konya, Turkey. (Decision number: 100, date: 27.12.2019).

Authors' Contribution

Study Conception: TA, KT,; Study Design: KT, TA, HÖ,; Literature Review: HÖ, TA,; Critical Review: KT,; Data Collection and/or Processing: HÖ, TA, İB,; Analysis and/or Data Interpretation: FS; Manuscript preparing: İB, TA.

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