*Tropical Journal of Nephrology Vol.13 No 1, June, 2018* 17 - 20

# HLA Matching and Kidney Allograft Function, Experience From a South African Transplant Centre

***Aminu M Sakajiki[1, 2] and Saraladevi Naicker[1]***

*[1]Division of Nephrology, University of Witwatersrand, Johannesburg, South Africa*
*[2]Department of Medicine, Usmanu Danfodiyo University, Sokoto*

**ABSTRACT**

There have been controversies regarding the role of HLA matching in kidney allograft survival. While recent studies have reported diminishing importance of HLA matching, others have suggested the continuing importance of these loci. We examined the role of HLA matching in kidney allograft function in a South African transplant centre.

*Methods:* One hundred kidney transplant recipients were grouped into seven, based on their HLA matching. Comparison was made between groups in terms of their graft function, proteinuria, number and type of biopsy proven rejection.

*Results:* Graft function measured using estimated glomerular filtration rate is higher in kidney transplant recipients with higher HLA match ($p=0.033$). However, there was no difference in proteinuria ($p=0.786$) or biopsy proven rejection ($p=0.773$)

*Conclusion:* HLA matching has significant relationship with kidney allograft function; the impact of this matching on proteinuria and incidence of graft rejection is not marked. Improving on the HLA matching before kidney transplantation is recommended for better allograft function.

**Keywords:** *HLA match, graft function, proteinuria, rejection*

## INTRODUCTION

HLA matching between donors and recipients improves the outcome of kidney transplantation, and the best outcomes are observed with complete matches between donor and the recipient at any of the 6 loci of the HLA-A, ŠB, and DR antigens[1,2].

The relative risk of graft failure is weakly related to the number of HLA-A or -B antigen mismatch, but more strongly associated with increases in the number of antigen mismatches at HLA-DR[3].

However, there have been controversies regarding the role of HLA matching in kidney allograft survival with recent studies reporting diminishing importance of HLA matching[4]; others have suggested the continuing importance of these loci[5-7]. We examined the role of HLA matching in kidney allograft function in a South African transplant centre.

## METHODS

Patients who received kidney transplant over five-year period (January 2005 to December 2009) at the Charlotte Maxeke Johannesburg Academic Hospital, South Africa were enrolled in this cross-sectional study. Information on age, gender, number of HLA matches, biopsy proven rejection, type of immunosuppressive medications and laboratory results of each follow up visits were collected from the case files. Graft dysfunction was defined as

estimated GFR of less than 60 ml/min/1.73m$^2$ based on the modification of diet in renal disease (MDRD) formula. Proteinuria was quantified using spot urine specimen. All recipients were T-cell and B-cell cross match negative. Acute rejection was biopsy proven. Patients were grouped into seven, based on the number of HLA matching (0-6). Comparison was made between groups in terms of their graft function, proteinuria and presence of biopsy proven rejection.

## STATISTICAL ANALYSIS

All data obtained was analyzed using the statistical package for social science (SPSS) for windows software version 22. Differences in means for continuous variables were compared using Student's t-test, while categorical variables were compared using Chi-square or Fisher's exact tests as appropriate. P value of dŠ 0.05 was considered significant.

## ETHICAL APPROVAL

Ethical approval was obtained from the institutional ethical committee.

## RESULTS

There were 63 males and 37 females, with a M: F ratio of 1.7:1. Their mean age was 42.2 ± 12.42 years with a range of 19 to 70 years. Six (6%) recipients had complete HLA match while 18 patients (18%) had complete HLA mismatch. Proteinuria was present in 51 patients (51%) and graft dysfunction was seen in 52 (52%). Standard immunosuppression protocols were calcineurin inhibitor (tacrolimus or cyclosporine), mycophenolate mofetil and prednisolone. Twenty six patients (26%) had acute cellular rejection (ACR), 6 (6%) had antibody mediated rejection (AMR). There was at least 3 years duration of transplant for each of the study participant with others having the graft for up to 8 years.

**Table 1:** HLA-match (0-6) and measured outcomes

| *Variable* | *0* | *1* | *2* | *3* | *4* | *5* | *6* | *P* |
|---|---|---|---|---|---|---|---|---|
| Age | 42.4±11.8 | 44.95±13.0 | 43.36±12.1 | 41.33±12.0 | 37.11±15.2 | 50.0±0.0 | 35.14±10.5 | *0.489* |
| Gender M | 15 | 15 | 19 | 6 | 3 | 1 | 4 | |
| F | 3 | 5 | 14 | 6 | 6 | - | 3 | |
| Creatinine | 158.8 | 151.65 | 114.4 | 158.7 | 116.2 | 113.0 | 130.7 | *0.024* |
| (µmol/L)eGFR | ±15.8 | ±9.4 | ±5.5 | ±7.5 | ±26.9 | ±0.0 | ±4.5 | |
| (ml/min/ 1.73m$^2$) | 56.6±30.1 | 59.7±3.1 | 79.7±2.8 | 51.0±3.3 | 72.2±29.5 | 98.0±0.0 | 63.1±3.2 | *0.033* |
| Proteinuria | 11 | 7 | 15 | 4 | 3 | - | 4 | *0.786* |
| Rejection | | | | | | | | |
| ACR | 4 | 5 | 11 | 4 | 2 | - | - | |
| AMR | - | 1 | 2 | - | 1 | - | - | |
| ACR+AMR | - | 1 | - | - | - | - | - | *0.773* |
| Total =100 | 18 | 20 | 33 | 12 | 9 | 1 | 7 | |

*HLA=human leukocyte antigen, ACR=acute cellular rejection, AMR=antibody mediated rejection, eGFR=estimated glomerular filtration rate, M=male, F=female.*

**Table 3:** Regression analysis showing the impact of some variables on graft function

| *Variable* | *B* | *Df* | *OR* | *95% CI* | *P-value* |
|---|---|---|---|---|---|
| Age | 0.026 | 1 | 1.03 | 0.927-1.137 | *0.49* |
| Gender –M | -1.76 | 1 | 0.17 | 0.005-6.00 | *0.33* |
| Donor type-Deceased | 18.24 | 1 | 0.006 | 0.875-1.412 | *0.99* |
| Rejection | 2.73 | 1 | 15.29 | 0.124-1.88 | *0.27* |
| Proteinuria | 0.88 | 1 | 2.41 | 0.09-65.0 | *0.60* |
| Smoking | -1.36 | 2 | 0.04 | 0.008-8.66 | *0.45* |
| Obesity | -4.91 | 1 | 0.007 | 0.097-5.33 | *0.28* |

*B=correlation, df= degree of freedom, OR=odds ratio, CI=confidence interval*

Different HLA match group and corresponding graft function are tabulated.

## DISCUSSION

Recent studies have shown a consistent linear relationship between kidney allograft survival and degree of HLA match[8-11] and these survival advantages were independent of the HLA locus.[12] This study demonstrated that HLA matching had a significant relationship with graft function measured using both serum creatinine and estimated glomerular filtration rate. Takemoto *et al*[13] have reported that HLA mismatching affect transplant immunity in several ways which include stimulating B cells to produce alloantibodies, which are involved with humoral mechanisms of transplant rejection. Few patients were observed to have developed AMR in this study; reason for this could be due to the small size of the study population and relatively good HLA matching observed as HLA matching between donors and recipients improves the outcome of kidney allograft function.[14]

Although several other factors affect kidney allograft function and survival such as access to health care and compliance, donor type (living/deceased), smoking, obesity, proteinuria and rejection, our study did not obtain significance with deceased donor type, smoking, obesity, proteinuria and rejection. The study was conducted in a public health facility where access to care is guaranteed and compliance to medications is assured as recipients are listed only when they have been certified by allocation committee to be compliant and therefore fit for transplantation.

Biopsy proven rejection of the cellular type was higher than that by antibody mediation in this study; it still had no effect on graft function as was observed by Shatat *et al*[15] in United States.

Children and young adults with transplanted kidneys have higher risk of graft failure than other age groups, mainly due to issues with compliance, [16], however, age did not affect graft function or HLA mismatch in this study. Compliance must be guaranteed for listing in this transplant centre and therefore noncompliance as a factor in graft outcome is eliminated.

Graft function has been shown to be superior in living donor than a deceased donor[17], however, in this study, graft function was comparable between the two donor types. Reason for this could not be explained.

A significant linear relationship was found between HLA mismatch and poor allograft survival in deceased donor transplant in a study by Williams *et al.*[14] Amatya *et al*[18] have reported that HLA matched deceased donor kidney transplants had a better graft survival than the mismatched deceased donor transplants. These findings are consistent with the findings in this study as well as more recent studies that showed continuous importance of HLA matching in the present era of kidney transplantation. Even with a small sample size, graft function is better with higher HLA match as this study as demonstrated.

## LIMITATIONS

The study was limited by the sample size and its retrospective nature. We did not look at other variables such as socioeconomic status, education and co-morbidities that may serve as confounding factors in graft function.

## CONCLUSION

HLA matching has significant relationship with kidney allograft function; the impact of this matching on proteinuria and incidence of graft rejection is not marked. Improving on the HLA matching before kidney transplantation is recommended for better allograft function.

## REFERENCES


1. Held PJ, Kahan BD, Hunsicker LG, et al. The impact of HLA mismatches on the survival of first cadaveric kidney transplants. *N Engl JMed*. 1994; 331:765–770.
2. Opelz G, Dohler B. HLA matching is a well known predictor of renal allograft survival. A collaborative transplant study report. *Transplantation* 2010;90:292-297
3. Reisaeter AV, Leivestad T, Vartdal F, et al. A strong impact of matching for a limited number of HLA-DR antigens on graft survival and rejection episodes: a single-center study of first cadaveric kidneys to nonsensitized recipients. *Transplantation*. 1998; 66:523–528.
4. Su X, Zenios SA, Chakkera H, et al. Diminishing significance of HLA matching in kidney transplantation. *Am J Transplant*. 2004; 4: 1501–1508.
5. Süsal C, Opelz G. Current role of human leukocyte antigen matching in kidney transplantation. *Curr Opin Organ Transplant*. 2013; 18: 438–444.
6. Lim WH, Chadban SJ, Clayton P, Budgeon CA, Murray K, Campbell SB *et al*. Human leukocyte antigen mismatches associated with increased risk of rejection, graft failure, and death independent of initial immunosuppression in renal transplant recipients. *Clin Transplant*. 2012; 26: E428–E437.
7. Goubella A, Broeders N, Racape J, Hamade A, Massart A, Hougardy JM *et al*. Patient and graft outcome in current era of immunosuppression: A single centre pilot study. *Acta Clin Belg*. 2015; 70: 23–29
8. Smits J, DeMeester J, Persjin GG, Class FHS, van renterghem Y. Long term results of solid organ transplantation. *Eurotranspl Newsletter* 1997; 141:10-23.
9. Mitsuishi Y, Terasaki PI. HLA matching effect on five-year graft survival and half life in the cyclosporine era. *Kidney Int* 1992; 42 (Suppl 38):172-175.
10. Frohn C, Fricke L, Puchta JC, Kirchner H. The effect of HLA-C matching on acute renal transplant rejection. *Nephrol Dial Transplant* 2001; 16:355-360.
11. Zantvoort FA, Joe D'Amoro, Persijin GG, Cohen B, Schreuder G, van Rood JJ *et al*. The impact of HLA-A matching on long term survival of renal allografts. *Transplantation* 1996; 61(5):841-844.
12. Williams RC, Opelz G, McGarvey CJ, Weil EJ, Chakkera HA. The risk of transplant failure with HLA mismatch in first adult kidney allograft from deceased donors. *Transplantation*. 2016 May; 100(5):1094-102. Doi: 10.1097/TP.0000000000001115.
13. Takemoto S, Port FK, Claas FHJ, Duquesnoy RJ. HLA matching for kidney transplantation. *Human Immunology* 2004; 65:1489-1505.
14. Kamoun M, McCullough KP, Maiers M, Vina MAF, Li H, Teal V *et al*. HLA amino acid polymorphism and kidney allograft survival. *Transplantation* 2017; 101(5):c170-177.
15. Shatat IF, Taber DJ, Shrivastava S, Weimert NA, Sas DJ, Charin KO et al. Graft outcomes in Pediatric kidney transplantation: focus on the role of Race. *Saudi J Kidney Dis Transpl* 2012; 23(4):684-692.
16. Foster BJ, Dahhou M, Zhang X, Platt RW, Smith JM, Hanley JA. Impact of HLA mismatch at firs kidney transplant on lifetime with graft function in young recipients. *Am J Transplantation* 2014; 14:876-885.
17. Zhou YC, Cecke JM. Effect of HLA matching on renal transplant survival. *Clin Transpl* 1993, 499-510.
18. Amatya A, Florman S, Paramesh A, McGee J, Kilackney M et al. HLA matched kidney transplantation in the era of modern immunosuppressive therapy. *Nephrol Dialysis Transplantation* 2010; 1-6. DOI:10.1002/dat.20439.