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Degree of human leukocyte antigen mismatch and its effect on live donor kidney transplant recipients

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ABSTRACT

Background: There is a strong evidence of importance of HLA matching in kidney transplantation and associations between HLA-DR mismatches and rejection, transplant glomerulopathy, graft failure, and death with functioning graft following kidney transplantation.

Objective: to evaluate the effect of degree of HLA mismatch on live donor kidney transplant recepients.

Patients and Method: The current study is a retrospective cohort study which was performed in Urology and Nephrology Center, Mansoura University, Egypt. The study included 2200 kidney transplant recipients who underwent renal transplantation between March 1976 and August 2019. The patients were divided into 3 main groups according to the degree of HLA mismatch: Group I: 0, 1, 2 HLA mismatch (568 patients). Group II: 3 , 4 HLA mismatch (1462 patients). Group III: 5 HLA mismatch (170 patients)

Results: Demographic and medical characteristics were comparable among the 3 groups. Transplantation from unrelated donors was more frequent among group III (p value: 0.001). Ischemia time was comparable and over 90% of the patients had immediate diuresis. Incidence of post-transplant Hypertension and Diabetes mellitus was higher in group III (p value: 0.004, 0.016 respectively).

Conclusions: Higher HLA mismatch was associated with higher incidence of diabetes and hypertension and has no effect on other medical and surgical complications.

Key words: HLA mismatch; Transplantation; graft survival.

Introduction

Several databases, representing thousands of kidney transplant patients from a large number of collaborating centers, showed strong evidence for the importance of HLA matching in kidney transplantation [1]. Other studies have shown associations between HLA-DR mismatches and rejection, transplant glomerulopathy, graft failure, and death with functioning graft following kidney transplantation [2]. Furthermore, it was found that HLA-DR mismatch is an independent risk factor for the development of de novo DSA and T-cell mediated rejection in elderly kidney transplant recipients [3]. However, some studies suggested that HLA mismatch did not influence graft survival. In a cohort of 2600 deceased donor kidney transplants in Spain, Morales et al. found no effect of HLA mismatch on graft survival [4]. Many of the current practices in kidney transplantation revolve around controlling the immune system, including immunosuppression strategies, rejection treatment, and understanding tolerance. In this work, we will highlight the impact of the different degrees of HLA mismatch on live donor kidney transplant recipients.

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Subjects and methods.
A retrospective cohort study was conducted at the urology and nephrology center, Mansoura University.

Ethical consideration: Our study is a retrospective study. The data was retrieved from our patient information system at the urology and nephrology center after an agreement from the head of the department and director of the center. We confirm that we do not use patients' names, initials, or hospital numbers. The medical research and ethics committee of Zagazig University approved the study. The work was carried out under The Code of Ethics of the World Medical Association. Written informed consent was obtained from all participants. The ethical research committee approved the study of the Faculty of Medicine, Zagazig University.

Subjects: The data of kidney transplant recipients who underwent renal transplantation in the Urology & Nephrology Center, Mansoura University, Egypt, from March 1976 to August 2019, were retrospectively analyzed. After excluding recipients aged less than 18 years and patients with no baseline data about HLA, 2200 kidney transplant recipients were included in the study.

Immunosuppression Protocols: Patients received different regimens of induction therapy:
•Antithymocyte globulin (ATG) (1.5 mg/kg/day administered by IV infusion for 7 to 14 days).
•Basiliximab (Simulect) (20 mg infused over 20-30 minutes by central or peripheral intravenous administration. The first 20 mg dose should be given within 2 hours prior to transplantation surgery. The recommended second 20 mg dose should be given 4 days after transplantation).the role in our center is preserving ATG for recipients with high immunological risk like high PRA or low HLA match and also for some patients with high risk of recurrence of original kidney disease. all patients received calcineurin inhibitors (CNI)-based immunosuppressive therapy, consisting mainly of cyclosporine (CsA) or tacrolimus. Cyclosporine was introduced either in dual therapy with prednisolone by a dose of 12 mg/kg/day or triple therapy protocol with prednisolone and azathioprine or MMF by 10 mg/kg/day. We targeted cyclosporine (CsA) trough levels between 200 and 400 ng/ml in the first two months. Then we aimed the level between 125 and 175 ng/ml after that. Tacrolimus therapy was introduced to the patients by a dose of 0.15 mg/kg in two divided doses. Tacrolimus was used as rescue therapy in some patients or as a substitution of CsA in case of inevitable side effects. A trough level between 5 and 10 ng/ml was targeted for tacrolimus. All acute rejections were biopsy-proven and managed by pulses of methylprednisolone 500 mg/day for five days. Antithymocyte globulin (ATG) or orthoclone (OKT3) were used in cases of steroid-resistant rejections.

Follow-Up Data: The patients were divided into three main groups according to the degree of HLA mismatch: the first group includes 0, 1, and 2 HLA mismatch (568 patients) while the second group involves 3 and 4 HLA mismatch (1462 patients), and the last group has those with 5 HLA mismatch (170 patients). The demographic data of the recipients and donors, pre-transplant co-morbidities, original kidney disease (OKD), immunosuppression regimens, post-transplant hypertension, diabetes mellitus, infections, hepatic problems, the occurrence of malignancies.

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Statistical analysis

The findings were recorded, tabulated, and analyzed using SPSS statistics version 21 for Windows (SPSS Inc. Chicago). T-test was used to compare the continuous normally distributed data between the three groups. Kruskal-Wallis test was used to compare abnormally distributed continuous data. Categorical data were compared using the chi-square test. The graft and patient survival were computed using the Kaplan-Meier technique. P-value < 0.05 was considered statistically significant.

Results

Table (1): demographic data of studied groups:

	Group I (568 KTRs) No. (%)	**Group II (1462 KTRs) No. (%)**	**Group III (170 KTRs) No. (%)**	**p value**
Recipient age Mean ± SD	31.1 ± 8.3	31.5 ± 9.4	32.1 ± 9.2	0.48
Recipient Sex: Male	417 (73.4%)	1096 (75%)	138 (81.2%)	0.121
Donor age Mean ± SD	35.1 ± 10.3	33.4 ± 10.7	32.4 ± 7.8	0.1
Donor Sex: Male	295 (51.9%)	682 (46.6%)	82 (48.2%)	0.101
Consanguinity: Related	541 (95.2%)	1193 (81.6%)	107 (62.9%)	**0.001**

Table (2): Original Kidney Disease:

	Group I (568 KTRs) No. (%)	**Group II (1462 KTRs) No. (%)**	**Group III (170 KTRs) No. (%)**	**p value**
Glomerulonephritis	129(22.7%)	287(19.6%)	33(19.4%)	0.233
Nephrosclerosis	161(28.3%)	405(27.7%)	50(29.4%)	
Polycystic kidney disease	10(1.8%)	34(2.3%)	9(5.3%)	
Obstructive uropathy	21(3.7%)	52(3.6%)	4(2.4%)	
Hereditary	10(1.8%)	37(2.5%)	6(3.5%)	
Unknown	237(41.7%)	647(44.3%)	68(40%)	

Table (3): Pre-transplant medical conditions:

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	Group I (568 KTRs) No. (%)	Group II (1462 KTRs) No. (%)	Group III (170 KTRs) No. (%)	p value
Hypertension	315(55.5%)	867(59.3%)	97(57.1%)	0.27
Diabetes	2 (0.35%)	5 (0.35%)	3 (1.76%)	0.06
Hepatitis C	47(8.3%)	91(6.2%)	7(4.1%)	**0.034**
Hepatitis B	3(0.5%)	6(0.4%)	0(0%)	0.19
Hemodialysis:	541(95.2%)	1411(96.5%)	165(97.1%)	0.34
Hemodialysis Duration (median, range)	1.3 (0.3, 9.3)	1.2 (0.04, 13.1)	1.1 (0.04, 8.1)	0.78

Table (4): pre-transplant blood transfusion and blood group matching:

	Group I (568 KTRs) No. (%)	Group II (1462 KTRs) No. (%)	Group III (170 KTRs) No. (%)	p value
Prior blood transfusion:	237(41.7%)	674(46.1%)	66(38.8%)	0.064
Blood group matching	483(85%)	1194(78.6%)	124(72.9%)	**0.001**

Table (5): Post-transplant medical complications:

	Group I (568 KTRs) No. (%)	Group II (1462 KTRs) No. (%)	Group III (170 KTRs) No. (%)	p value
Hypertension	283(49.8%)	825(56.4%)	106(62.4%)	**0.004**

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Diabetes	33(5.8%)	107(7.3%)	21(12.4%)	**0.016**
Hepatic impairment	63(11.1%)	179(12.2%)	16(9.4%)	0.477
Gastrointestinal troubles	15(2.6%)	68(4.7%)	7(4.1%)	0.112
Bacterial infection	76(13.4%)	171(11.7%)	23(13.5%)	0.510
Viral infection	43(7.6%)	137(9.4%)	11(6.5%)	0.246
Malignancy	25 (4.4%)	79 (5.4%)	10 (5.8%)	0.6

Table (6): Post-transplantation surgical complications:

	Group I (568 KTRs) No. (%)	**Group II (1462 KTRs) No. (%)**	**Group III (170 KTRs) No. (%)**	**p value**
Bleeding	9(1.6%)	27(1.8%)	3(1.8%)	0.922
Hematomas	6(1.1%)	32(2.2%)	1(0.6%)	0.106
Wound dehiscence	15(2.6%)	45(3.1%)	8(4.7%)	0.394
Wound infection	4(0.7%)	10(0.7%)	0(0%)	0.554

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Renal artery thrombosis	9(1.6%)	8(0.5%)	1(0.6%)	0.063
Renal artery stenosis	2(0.4%)	6(0.4%)	0(0%)	0.701

Table (1) showed that There was no statistical significant difference among the studied group regarding donor and recipient age and sex. transplantation from unrelated donors was more frequent in group III than the other 2 groups.

Table (2) the majority of patients had unknown original kidney disease and the difference between the 3 groups is insignificant statistically.

Table (3) There was no statistical significant difference among the 3 groups regarding the prevalence of pre-transplant hypertension, diabetes, hepatitis B . While, hepatitis C infection occurred more frequently among group 1 with statistical significant difference The majority of population was maintained on hemodialysis for comparable duration.

Table (4) there is no statistical significant difference regarding history of blood transfusion.The difference was significant among the studied groups as same compatible transplantation was performed more frequently among group I.

Table (5) Incidence of post-transplant Hypertension and DM was higher in group III with statistical significant difference between the three groups**.**

Table (6) there was no statistical difference between studied groups regarding other medical and surgical complications.

Discussion

Renal transplantation is the standard gold therapy for end-stage renal disease patients [5]

The immunological aspects of transplantation include testing for ABO compatibility, human leukocyte antigens (HLA) typing, testing for anti-HLA antibodies in the recipient serum against common antigens in the population (panel reactive antibody [PRA]), and testing for antibodies in recipient serum against the specific donor, i.e., donor-specific antibodies (DSAs) [6]

The importance of HLA matching has been established in renal transplantation, and the extent of HLA mismatches at the A, B, and DR loci form an essential part of the assessment of the immunological risk of potential transplant candidates [7] the percentage of unrelated couples was higher in group 3 (37.1%) than group1 and 2 (4.8% and 18.4%, respectively). This agrees with other investigators as the number of live related transplants with better HLA match are significantly higher than in the live unrelated transplants [8, 9]. Regarding original kidney disease, there was no statistical difference between the three

groups. This is primarily due to late presentation at the time of diagnosis of end-stage renal disease. The majority of patients had unknown original kidney disease.

Couples with the same blood group received kidney transplantation were more frequent in group1 and showed better graft survival. Some investigators found that blood group matching has no significant impact on graft survival [10]. The longer duration of follow-up could explain this difference, and a more considerable number of patients followed up at our study. Our research found that hepatitis C infection occurred more frequently among group 1 which includes kidney transplant recipients with better HLA match and, consequently, better graft survival. Other authors disagreed with our finding and found a significant decrease in graft survival in recipients transplanted with positive hepatitis C virus antibodies (HCV Abs) recipients [11]. There was no statistically significant difference between the three groups regarding the operation details (ischemia time, time to diuresis, and primary urinary continuity).

Post-transplant hypertension and DM were higher in group 3, with a statistically significant difference between the three groups **(p-value: 0.004, 0.016 respectively).** This can be explained by more dependence on steroid and calcineurin inhibitor-based regimens of immunosuppression known to cause the development of hypertension and DM. Regarding hypertension, some authors agreed with our finding [12, 13]. Tacrolimus was used more with group 1 (p-value: 0.002), while cyclosporine was used more with group 3 (p-value: 0.001). Interestingly, some studies reported that patients receiving tacrolimus had a higher frequency of post-transplant DM than those taking cyclosporine [14, 15]. This could be due to impaired insulin release or increased insulin resistance, islet cell damage in the form of cytoplasmic swelling, and vacuolization due to CNI therapy.

there was no statistical difference between studied groups regarding other medical and surgical complications.

Conclusion and Recommendation

We can conclude that a better HLA match between donor and recipient plays a crucial role in successful renal transplantation and also improve long term outcome of post transplant hypertension and diabetes

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