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RESEARCH ARTICLE

Effect of Human Leukocyte Antigen Compatibility on Renal Transplant Rejection in Kuwaiti patients

Youssef M. Mosaad[1], Merveet Mansour[2], Ibrahim Al-Muzairai[3], Turky Al-Otabi[3], Mohamed Abdul-Moneam[3], Rajaa Al-Attyiah[4], Manal Shahin[5]

1- Clinical Pathology Department, Mansoura Faculty of Medicine, Mansoura University, Egypt.
2-Zoology Department, Faculty of Science, Tanta University, Egypt.
3- Immunology and Organ Transplantation Departments, Hamad Al-Essa Organ Transplantation Center, Kuwait
4-Microbiology Department, Faculty of Medicine, Kuwait University, Kuwait.
5- Immunology Department, Ministry of Health, Kuwait

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Corresponding Author

Youssef Mosaad

Abstract

Objective: The aim was to evaluate the possible effect of HLA-A, B and DR compatibility between patients and their donors on the development of rejection after renal transplantation in Kuwaiti population. ***Patients and Methods:*** HLA-A, -B, and –DR typing was performed by complement-dependent cytotoxicity method for 181 renal transplant patients and 181 donors. ***Results:*** No statistical significant differences were found between patients with rejection and those without for the frequencies of HLA antigens except for HLA-DR17 (OR=2.6, Pc=0.045). HLA incompatibility between patients and their donors was more associated with renal rejection when compared to HLA compatibility (P= 0.003). Also, gender mismatch was more frequent in patients suffering from rejection than patients without rejection (P=0.005) especially if a female patient received kidney from a male donor (P=0.008). ***Conclusion:*** HLA-DR17 antigen, HLA incompatibility between patients and their donors may be risk factors for the development of graft rejection after renal transplantation in Kuwaiti population.

INTRODUCTION

Renal transplantation is the preferred, definitive treatment for end stage renal disease (ESRD). When successful, kidney transplantation offers most ESRD patients improved survival and quality of life compared with maintenance dialysis **(Laupacis et al 1996).**

Despite progress made in the field of immunosuppression, graft rejection remains a major cause of morbidity and mortality of patients after solid organ transplantation. There are several genetic causes which could influence the outcome of renal transplantation. One of the main determining factors of success in renal transplantation is human leukocyte antigen (HLA) compatibility between donor and recipient, particularly at HLA-A, HLA-B and HLA-DR loci. HLA compatibility remains an essential immunological barrier, despite modern immunosuppressive treatments **(Laperrousaz et al 2012).**

The Major Histocompatibilty Complex (MHC) is a highly polymorphic cluster of genes with some of the greatest allelic diversity in the genome. MHC genes are both polygenic (containing multiple genes) and polymorphic (containing multiple variants of each gene) **(Mosaad et al 2014).** This complexity is critical for ensuring sufficient

diversity in MHC molecules to allow for peptide presentation from a wide range of microorganisms. The specific genes and variants that an individual expresses comprise her/his MHC haplotype **(Neefjes et al 2011).** HLA molecule binds and presents peptide to T lymphocytes in cell mediated immune response and plays a key role in shaping the T cell repertoire and is also associated with allograft rejection **(Shiina et al 2004).**

HLA-DR is abundantly expressed on peritubular and glomerular capillary endothelial cells. However, it is not expressed on endothelial cells of larger blood vessels or on tubule cells of normal kidney. HLA class II expression can be induced by proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) in presence of infection or inflammation. Under conditions of renal inflammation, including glomerulonephritis and acute rejection of transplanted kidneys, HLA-DR is also expressed on renal proximal tubule cells **(Hall et al 1984, Muczynski et al 2001,Askar 2009).**

With the dramatic improvement in transplant outcome for both HLA-matched and mismatched kidneys, the role of HLA matching in kidney transplantation has been a hotly debated issue. Many argue that current immunosuppression regimens obviate the benefits of HLA matching altogether, raising the question of whether HLA matching should be used or not before renal transplantation **(Takemoto et al 2004, Askar 2009).**

Therefore, the aim of the present work was to evaluate the possible effect of HLA-HLA-A, -B and -DR antigen matching between patients and their respective donors on the development of renal graft rejection following transplantation among Kuwaiti patients

2. Material and methods:

A retrospective study was conducted using results of serological microlymphocytotoxicity Terasaki test that were obtained from samples submitted to the HLA and Immunology Laboratory, Hamed Al-Essa organ transplant center, Kuwait Ministry of Health for 181 renal transplanted patients and their respective donors.

All patients were suffering from ESRD and were waiting for suitable donors. They were 94 male and 87 female with mean age 42.10±17.56. The donors were either living (175) or cadaveric (6) with mean age 33.91± 7.17 and they were 154 male and 27 females. Post-transplant graft rejection was developed in 52 out of 181 recipients. The gender distribution for transplanted patients was; 82 male - male, 12 male - female , 72 female - male and 15 female - female.

Serological testing for HLA Class I antigens A and B and HLA Class II DR for patients and controls were performed with a standard complement-dependent microlympho-cytotoxicity assay **(Terasaki and Park 1980).** This detection method uses well-characterized HLA antisera that are placed into individual wells on commercial lymphotype HLA-ABC 144 (2x72) and HLA-DR/DQ well tray with pre-dropped anti-HLA-ABC/DR reagents (BioRad Medical Diagnostics ,Landsteinerstr, D-63303 Dreieich, Germany, Lot 3128145) organized as a panel to identify a complete HLA type for A, B, and DR loci. In the presence of exogenous complement, HLA antibodies are cytotoxic to lymphocytes expressing the corresponding antigen. After further incubation, cell death was determined by trypan blue vital stain exclusion. The pattern of reactivity is then interpretable as the HLA type of the subject.

2.2 Statistical Analysis

The statistical analysis of data was done by using SPSS (SPSS, Inc, Chicago, IL) statistical package for social science version 16. The description of the data was done in form of mean (+/-) SD for quantitative data and frequency and percent for qualitative data. For qualitative data Chi square test with Yates correction or Fisher's exact test was used; as appropriate. P value is significant if ≤ 0.05, strength of associations was assessed by computing OR and their 95% confidence intervals. Significant probability values obtained were corrected for multiple testing using Bonferroni formula.

3. Result:

Distribution of HLA-A,-B and -DR antigens in patients and their donors was described in tables 1-3. No significant differences between patient and their donors were found for the distribution of different HLA antigens expect for the increased frequency of HLA-B8 (OR=3.32, P=0.0002, Pc=0.0068), HLA-DR17 (OR=2.21, P=0.0030, Pc=0.048) and decreased frequency of HLA-B18 (OR=0.26, P=0.0002, Pc=0.0068) in patients when compared to the donors.

The frequency of HLA-A antigens in patients with renal rejection and those without rejection showed no significant differences. However, HLA-A11, A30 and A32 showed a trend for association with renal rejection but without statistical significance (OR=2.1, 1.84, and 1.52 respectively). Also, the distribution of HLA-B antigens in patients with renal rejection and patients without renal rejection revealed no significant differences. Table 4 & 5

Patients suffering from rejection after renal transplant had a higher frequency of HLA-DR17 when compared to patients without rejection and the difference in distribution is statistically significant before and after correction of p value (OR=2.66 ,P=0.003 , Pc=0.045). Table 6

HLA incompatibility between patients and their donors was more associated with renal rejection (P=0.003). Also, gender mismatch was more frequent in patients suffering from rejection than patients without rejection (P=0.005). When analyzing the types of gender mismatch in patients with and without rejection, it was observed that the frequency of female patients receiving kidney from a male donor was significantly higher in patients with rejection than those without rejection (P=0.008). Table 7

Table 1: Comparison of HLA-A antigens distribution in patients and donors

HLA-A	Patients (n=181) No / %	Donors (n=181) No / %	OR (95% CI)	P /PC value
1	34 / 9.4	47 / 12.9	0.66 (0.39 – 1.12)	0.13/NS
2	83 / 22.9	64/ 17.7	1.55(0.99 – 2.4)	0.04/NS
3	29 / 8.0	38/ 10.5	0.72(0.42 – 1.27)	0.28/NS
11	12 / 3.3	14 / 3.9	0.85(0.36 – 2.1)	0.83/NS
23(9)	9 / 2.5	12 / 3.3	0.8(0.17 – 4.3)	0.72/NS
24(9)	28 / 7.7	38 / 10.5	0.69(0.39 – 1.22)	0.22/NS
2403	2 / 0.55	2 / 0.55	1.0(0.1 – 10.0)	0.68/NS
25 (10)	0.0	1 / 0.3	-	-
26(10)	27/ 7.5	10 / 2.8	3.0 (1.34 - 6.87)	0.003/NS
28	0.0	10 / 2.8	-	-
29(19)	9 / 2.5	13 / 3.6	0.68 (0.26 – 1.74)	0.5/NS
30(19)	11 / 3.0	21 / 5.8	0.49 (0.22-1.1)	0.09/NS
31(19)	26 / 7.2	19/ 5.3	1.43(0.73-2.82)	0.33/NS
32(19)	13 / 3.6	13 / 3.6	1.0(0.42- 2.37)	0.8/NS
33(19)	16 / 4.4	15 / 4.1	1.07(0.48-2.4)	1.0/NS
66(10)	2 / 0.55	1 / 0.3	2.01(0.14-56.5)	0.5/NS
68(28)	32 / 8.8	20/ 5.5	1.73 (0.91 – 3.3)	0.09/NS
69	0.0	1/ 0.3	-	-
74(19)	2 / 0.55	3/ 0.8	0.66(0.08-4.9)	0.5/NS
Ax	27 / 7.5	20 / 5.5	-	-

HLA = human leukocyte antigen; OR = odds ratio; 95%CI = 95% confidence interval. *Significant P value if ≤ 0.05. Pc value = P value corrected for 19 comparisons; NS= nonsignificant; Ax= homozygous A.

Table 2: Comparison of HLA-B antigens in patients and donors

HLA-B	Patients (n=181) No / %	Donors (n=181) No / %	OR (95% CI)	P /PC value
7	27 / 7.5	23 / 6.4	1.2 (0.62 – 2.29)	0.64/NS
8	37 / 10.2	12 / 3.3	3.32 (1.74 – 7.65)	**0.0002/0.0068***
13	6 / 1.7	11 / 3.0	0.53 (0.17 – 1.59)	0.32/NS
14	1 / 0.3	5.0 / 1.4	0.2 (0.01 – 1.74)	0.11/NS
15	2 / 0.55	2.0 / 0.55	1.0(0.1 – 10.03)	0.68/NS
18	10 / 2.8	33 / 9.1	0.26 (0.12- 0.58)	**0.0002/0.0068***
27	3 / 0.8	6.0 / 1.7	0.49 (0.1 – 2.26)	0.25/NS

35	29 / 8.0	34 / 9.4	0.82(0.46 – 1.47)	0.58/NS
37	1 / 0.3	2.0 / 0.55	2.01(0.14-56.5)	0.5/NS
38(16)	16 / 4.4	18 / 5.0	0.88(0.41- 1.88)	0.85/NS
39(16)	6 / 1.7	7.0 / 1.9	0.85(0.25- 2.89)	1.0/NS
41	15 / 4.1	16 / 4.4	0.93 (0.42- 2.06)	1.0/NS
42	3 / 0.8	4.0 / 1.1	0.75 (0.13 -4.0)	0.5/NS
44(12)	11 / 3.0	16 / 4.4	0.67(0.28- 1.57)	0.42/NS
45(12)	4 / 1.1	5.0 / 1.4	0.8 (0.18 -3.48)	0.5/NS
49(21)	10 / 2.7	10 / 2.8	1.0 (0.37- 2.68)	0.81NS
50(21)	46 / 12.7	32 / 8.8	1.59(0.93 - 2.72)	0.09/NS
51(5)	56 / 15.5	40 / 11	1.58 (0.96 - 2.6)	0.07/NS
52(5)	6 / 1.7	9.0 / 2.5	0.66 (0.2 -2.06)	0.59/NS
53	12 / 3.3	7.0 / 1.9	1.77(0.63 - 5.09)	0.35/NS
55(22)	9 / 2.5	8.0 / 2.2	1.13 (0.39 – 3.3)	1.0/NS
57(17)	5 / 1.4	14 / 3.9	0.34 (0.1 - 1.04)	0.03/NS
58(17)	11 / 3.0	5.0 / 1.4	2.28 (0.71-7.7)	0.2/NS
60(40)	1 / 0.3	4.0 / 1.1	0.25 (0.01 – 2.35)	0.19/NS
61(40)	4 / 1.5	3.0 / 0.8	1.34 (0.25 – 7.6)	0.5/NS
63(15)	7 / 1.2	1.0 / 0.3	0.29(0.05-1.59)	0.1/NS
64	0.0	3.0 / 0.8	-	-
65(14)	6 / 1.7	8.0 / 2.2	0.74(0.22 - 2.41)	0.78/NS
70	0.0	3.0 / 0.8	-	-
71	2 / 0.55	1.0 / 0.3	2.01(0.14-56.5)	0.5/NS
72(70)	2 / 0.55	2.0 / 0.55	1.0(0.1 – 10.03)	0.68/NS
73	3 / 0.8	4.0 / 1.1	0.75 (0.13 – 4.0)	0.5/NS
75	0.0	1.0 / 0.3	-	-
76	0.0	1.0 / 0.3	-	-
Bx	11 / 3.0	12 / 3.3	-	-

HLA = human leukocyte antigen; OR = odds ratio; 95%CI = 95% confidence interval. Significant P value if ≤ 0.05. Pc value = P value corrected for 34 comparisons; NS= nonsignificant; *Using Chi Square,**Fisher Exact test, Bx=homozygous B.

Table (3): Comparison of HLA-DR antigens frequency in patients with donors

HLA-DR	Patients (n=181) No / %	Donors (n=181) No / %	OR (95% CI)	P /PC value
1	11 / 3.0	13 / 3.6	0.92(0.38 – 2.21)	1.0/NS
2	1.0 / 0.55	1.0 / 0.3	2.01(0.14-56.5)	0.5/NS
3	27 / 7.5	34 / 9.4	0.76 (0.42- 1.37)	0.39/NS
4	52 / 14.4	57/ 15.7	0.88(0.55 - 1.4)	0.65/NS
7	46 / 12.7	48/ 13.3	0.94(0.57-1.55)	0.9/NS
8	8.0 / 2.2	4.0/ 1.1	2.05(0.55 - 8.24)	0.38/NS
9	0.0	3.0 / 0.8	-	-
10	10 / 2.8	12/ 3.3	0.82(0.32- 2.11)	0.82/NS
11(5)	34 / 9.4	49/ 13.5	1.34(0.56- 3.36)	0.61/NS
12 (5)	5.0 / 1.4	3.0 / 0.8	1.62(0.17-38.5)	0.55/NS
13 (6)	38 / 10.5	49/ 13.5	0.62(0.37 - 1.05)	0.06/NS
14 (6)	11 / 3.0	12/ 3.3	0.91(0.36 – 2.28)	1.0/NS
15 (2)	32 / 8.8	35/ 9.7	0.9(0.51- 1.57)	0.78/NS
16 (2)	16 / 4.4	5.0 / 1.4	3.41 (1.14 – 10.9)	0.01/NS

17 (3)	42 / 11.6	20/ 5.5	2.21(1.2 - 4.0)	**0.003/0.048***
18 (3)	9 / 2.5	5.0 / 1.4	1.84 (0.55- 6.4)	0.41/NS
DRx	21 / 5.8	12 / 3.3	-	-

HLA = human leukocyte antigen; OR = odds ratio; 95%CI = 95% confidence interval. *Significant P value if ≤ 0.05. Pc value = P value corrected for 16 comparisons; DRx=homozygous DR; NS= nonsignificant.

Table 4: Comparison of distribution of HLA-A antigens in patients with renal rejection versus those without rejection

HLA-A	Rejection (n=52) No / %	No Rejection (n=129) No / %	OR (95% CI)	P /PC value
1	9 / 8.6	25 / 9.7	0.88 (0.37 - 2.1)	0.91/NS
2	26 / 25	57 / 22.1	1.16 (0.66 – 2.05)	0.67/NS
3	9 / 8.6	20 / 7.8	1.12 (0.45 – 2.7)	0.94/NS
11	2 / 1.9	10 / 3.9	0.48 (0.07 – 2.4)	0.27/NS
23(9)	3 / 2.8	6 / 2.3	1.24 (0.24 – 2.46)	0.58/NS
24(9)	8 / 7.7	20 / 7.8	0.98 (0.38 – 2.46)	0.85/NS
2403	0.0 / 0.0	2 / 0.8	-	-
26(10)	9 / 8.6	18 / 7.0	1.25 (0.5 -3.07)	0.75/NS
29(19)	0.0 / 0.0	9 / 3.5	-	-
30(19)	2/ 1.9	9/ 3.3	0.54 (0.08- 2.37)	0.34/NS
31(19)	9 / 8.6	17 / 6.6	1.33 (0.53 – 3.3)	0.65/NS
32(19)	6 / 5.8	7 / 2.7	2.18 (0.63 – 7.3)	0.13/NS
33(19)	6 / 5.8	10 / 3.9	1.5 (0.47 - 4.64)	0.3/NS
66(10)	1 / 0.9	1 / 0.4	2.48 (0.0 – 91.4)	0.49/NS
68(28)	7 / 6.9	25 / 9.7	0.67 (0.29 – 1.69)	0.48/NS
74(19)	1 / 0.9	1 / 0.4	2.48 (0.0 – 91.4)	0.49/NS
Ax	6 / 5.8	21 / 8.1	-	-

HLA = human leukocyte antigen; OR = odds ratio; 95%CI = 95% confidence interval. *Significant P value if ≤ 0.05. Pc value = P value corrected for 21 comparisons; NS= nonsignificant; Ax= homozygous A.

Table 5: Comparison of HLA-B antigens in patients with renal rejection and patients without rejection

HLA-B	Rejection (n=52) No / %	No Rejection (n=129) No / %	OR (95% CI)	P /PC value
7	10 / 9.6	17 / 6.6	1.5 (0.61 - 3.63)	0.45/NS
8	14 / 13.6	23 / 8.9	1.6 (0.73 – 3.7)	0.28/NS
13	0.0 / 0.0	6 / 2.3	-	-
14	0.0 / 0.0	1 / 0.4	-	-
15	0.0 / 0.0	2 / 0.8	-	-
18	1.0/ 0.9	9 / 3.4	0.27 (0.01 - 2.09)	0.16/NS
27	0.0 / 0.0	3 / 1.2	-	-
35	9/ 8.6	20 / 7.8	1.13 (0.46 - 2.72)	0.94/NS
37	0.0 / 0.0	1 / 0.3	-	-
38(16)	3.0 / 2.9	13 / 5.0	0.56(0.12 - 2.14)	0.5/NS
39(16)	0.0 / 0.0	6 / 2.3	-	-
41	3.0 / 2.9	12 / 4.7	0.6 (0.13 - 2.36)	0.33/NS
42	0.0 / 0.0	3 / 1.2	-	-
44(12)	5 / 4.8	6 / 2.3	2. 56 (0.63 - 10.5)	0.13/NS
45(12)	0.0 / 0.0	4 / 1.6	-	-

49(21)	5 / 4.8	5 / 1.9	2.56 (0.63 -10.5)	0.13/NS
50(21)	14 / 13.5	32 / 12.4	1.1 (0.53 – 2.25)	0.92/NS
51(5)	16 / 15.4	40 / 15.5	0.95 (0.5 - 1.94)	0.86/NS
52(5)	3.0 / 2.9	3 / 1.2	2.5 (0.4 -15.8)	0.23/NS
53	3.0 / 2.9	9 / 3.5	0.82 (0.17- 3.37)	0.53/NS
55(22)	3.0 / 2.9	6 / 2.3	1.24 (0.24 - 5.7)	0.5/NS
57(17)	2.0 / 1.9	3 / 1.2	1.65 (0.19 – 12.4)	0.45/NS
58(17)	4 / 3.8	7 / 2.7	1.42 (0.34 – 5.5)	0.39/NS
60(40)	0.0 / 0.0	1 / 0.4	-	-
61(40)	0.0 / 0.0	4 / 1.5	-	-
63(15)	4 / 3.8	3 / 1.2	3.37 (0.63 - 19.5)	0.1/NS
65(14)	2.0 / 1.9	4 / 1.5	1.24 (0.15 - 7.9)	0.55/NS
71	0.0	2.0/ 0.8	-	-
73	1/0.9	2.0 /0.8	1.24 (0.11 – 13.5)	0.64/NS
72(70)	0.0 / 0.0	2 / 0.8	-	-
Bx	2.0 / 1.9	9 / 3.5	-	-

HLA = human leukocyte antigen; OR = odds ratio; 95%CI = 95% confidence interval. Significant P value if ≤ 0.05. Pc value = P value corrected for 38 comparisons; NS= nonsignificant; *Using Chi Square,**Fisher Exact test, Bx=homozygous B.

Table (6): Comparison of HLA-DR antigens frequency in patients with rejection and patients without rejection

HLA-DR	Rejection (n=52) No / %	No Rejection (n=129) No / %	OR (95% CI)	P /PC value
1	3 / 2.9	8 / 3.1	0.93 (0.19 - 3.94)	0.6/NS
2	0.0	1 / 0.4	-	-
3	5 / 4.8	22 / 8.5	0.54 (0.17- 1.5)	0.33/NS
4	17 / 16.3	34 / 13.2	1.29 (0.65 – 2.5)	0.53/NS
7	11 / 10.6	35 / 13.6	0.75 (0.34 -1.61)	0.54/NS
8	1 / 0.9	7 / 2.7	0.35 (0.02 – 2.48)	0.27/NS
10	3 / 2.9	7 / 2.7	1.06 (0.21-4.6)	0.58/NS
11(5)	8 / 7.7	26 / 10.0	0.74 (0.3 – 1.78)	0.61/NS
12 (5)	1 / 0.9	4 / 1.5	0.62 (0.03 – 5.88)	0.55/NS
13 (6)	13 / 12.5	25 / 9.7	1.32 (0.61 – 2.8)	0.54/NS
14 (6)	3 / 2.9	8 / 3.1	0.92 (0.22 – 3.6)	0.61/NS
15 (2)	10 / 9.6	22 / 8.5	1.14 (0.52- 2.5)	0.9/NS
16 (2)	4 / 3.9	12 / 4.7	0.81 (0.22 – 2.8)	0.49/NS
17 (3)	19 / 18.3	20 / 7.6	2.66 (1.35 - 5.2)	**0.003/0.045***
18 (3)	3 / 2.9	6 / 2.3	1.24 (0.24 - 5.7)	0.5/NS
DRx	2 / 1.9	19 / 7.4	-	-

HLA = human leukocyte antigen; OR = odds ratio; 95%CI = 95% confidence interval. *Significant P value if ≤ 0.05. Pc value = P value corrected for 15 comparisons; DRx=homozygous DR; NS= nonsignificant.

Table 7 : Comparison of HLA / gender compatibility between patient-donor pairs and Renal rejection

Data	Rejection (n=52) N / %	No Rejection (n=129) N / %	P value
HLA Compatibility			
HLA-compatible patient – donor	2 / 3.8	30 / 22.5	**0.003***
HLA-incompatible patient – donor	50 / 96.2	99 / 77.5	
Gender compatibility**			
Patient – donor match	19 / 36.5	78 / 60.5	**0.005***
Patient – donor mismatch	33 / 63.5	51 / 39.5	
Type of gender mismatch			
Male patient – female donor (N/N)	4 / 48	8 / 121	0.97
Female patient – male donor (N/N)	29 / 23	43 / 86	**0.008***

*Significant P value, **Gender match= male-male and female-female, Gender mismatch= Male-Female and Female - male

4. Discussion:

The importance of HLA matching has been clearly established in renal transplantation and the extent of HLA mismatches at the A, B and DR loci form an important part in the assessment of the immunological risk of potential transplant candidates. Increasing number of HLA mismatches has been shown to be associated with poorer graft and patient survival following kidney transplantation but the ongoing importance of this association in the era of more potent immunosuppression and improved donor selection remains unclear **(Nguyen et al 2013).**

We compared the distribution of the studied HLA antigens in Kuwaiti patients with renal rejection in relation to patients without renal rejection to find whether presence of certain HLA antigen predispose to the development of renal rejection in transplanted patients and the results were presented in Tables 1-6. While HLA-A and HLA-B antigens showed no statistical significance, the HLA-DR17 antigen was significantly higher in patients suffering from rejection (OR=2.66, Pc=0.045).

While renal transplant against HLA-incompatibility between patients and their respective donors was more associated with renal rejection , HLA-compatible patient –donor pairs were less susceptible to renal rejection and the difference was statistically significant (P=0.003). Furthermore, It was found that gender mismatch was more frequent in patients suffering from rejection than patients without rejection and the differences between their frequencies were statistically significant (P=0.005) especially when female patient receiving a kidney from male donor (P=0.008). Table 4

Large registry reports have consistently demonstrated a strong association between HLA-matching at the HLA-A, B and DR loci and graft and patient outcomes, independent of donor type, initial immunosuppression, transplant era and even the presence of DSA **(Opelz and Dohler 2007 , Dunn et al 2011, Lim et al 2012).**

Recent retrospective single center study of live and deceased donor renal transplants has demonstrated that HLA-mismatches remained an important determinant of acute rejection risk in renal transplant recipients receiving quadruple immunosuppression. In this study, increasing number of HLA mismatches was an independent predictor of acute rejection (OR 1.65 for every single HLA-mismatch; 95% CI: 1.15 to 2.38; P=0.007), with HLA-mismatches at the HLA-DR locus associated with the highest risk of acute rejection compared to mismatches at the HLA-A and HLA-B loci (**Wissing et al 2008).**

Opelz and Dohler 2007 analysis of 135,970 deceased donor renal transplant recipients demonstrated that the effect of HLA-mismatches on acute rejection risk remained highly significant over two consecutive decades (1985-1994 vs 1995-2004), independent of 'intention to treat' immunosuppressive regimen.

HLA-DR mismatches appear to be of greater importance in predicting graft outcomes compared to HLA-A, B mismatches. Previous studies have demonstrated that allocation based predominantly on HLA-DR matching, as implemented in the United States, may eliminate any advantage of HLA-AB matching but this remains controversial **(Vereerstraeten et al 1999, Doxiadis et al 2007).**

Although, improved immunosuppression has reduced the effect of HLA mismatching on kidney graft survival, however, **Rodrigues et al 2004** demonstrated a clear influence of HLA matching on the graft survival. The continuing impact of HLA matching on long-term graft survival is even more remarkable and survival rates of transplants performed under modern immunosuppression are affected by the number of HLA mismatches to the same degree as transplants performed prior to the introduction of CsA **(Danovitch and Cecka 2003).** In the same time, more aggressive immunosuppression is associated with intolerable and may be life-threatening adverse effects that negatively impact the overall well-being of the recipient and may even lead to patient non-compliance **(Galbraith and Hathaway 2004, Askar 2009).**

On the other hand, the recognition of mismatched donor HLA molecules by recipient alloreactive T cells either directly or indirectly contributes to allograft rejection. It has been suggested that the direct pathway predominates during early acute rejection and that the indirect pathway provides a continuous supply of alloantigen responsible for chronic rejection. Although most donor APCs will disappear soon after transplantation, a small proportion may persist in the recipient **(Womer et al 2001, Askar 2009).**

Explanations for improved kidney allograft survival in HLA well-matched individuals have included: less anti-HLA antibody formation **(Terasaki 2003),** less alloreactive 'direct pathway' CD4+ T-cell response to DR-matched grafts **(Vandekerckhove et al 1990),** and fewer allopeptide epitopes to stimulate T-helper 'indirect pathway' responses that contribute to chronic rejection **(Ciubotariu et al 1998).** An alternative explanation would be that HLA matching for DR (and perhaps also for A and B) increases the likelihood of developing donor antigen-specific T regulatory cells **(Rodrigues et al 2004, Askar 2009).**

Despite conflicting reports of the effect of donor–recipient sex mismatch on renal allografts, the association between acute rejection of renal allografts and the development of human alloantibodies to the male H-Y antigen suggested that donor–recipient sex mismatch deserved re-evaluation. Observations that even in HLA-identical kidney transplants (a) acute rejection is commonly observed and (b) maintenance immunosuppression is required for long-term allograft survival suggest that minor histocompatibility antigens (mHAs) may be the target of immune responses leading to allograft dysfunction and premature loss (**Tan et al 2012).**

Using HLA-identical sibling transplants in the European Collaborative Transplant Study (CTS) registry, **Opelz 2005** showed significantly lower 10-year allograft survival estimates with increasing levels of panel reactive antibody (PRA). Because HLA-identical siblings have no HLA mismatches, this difference in allograft survival would most likely be a result of factors other than immunity to HLA. These findings suggest a clinically significant role for immunity to non-HLA alloantigenic stimuli.

Among the best defined of the mHA candidates are the H-Y antigens encoded by the Y chromosome **(Miklos et al 2005)**. It is demonstrated that de novo anti-H-Y antibody production is associated with acute rejection in female recipients of male donor kidneys **(Tan et al 2008).** This finding suggests how renal allograft survival would be affected by donor–recipient sex mismatch; however, previous studies of donor–recipient sex mismatch effects yielded conflicting results **(Ellison et al 1994, Zeier et al 2002).**

Conclusion*:*

HLA-DR17 antigen, HLA incompatibility and gender mismatch between patients and their donors especially when a female receive kidney from a male may be risk factors for the development of graft rejection after renal transplantation in Kuwaiti population.

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