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LABORATORY STUDY

Association between Human Leukocyte Antigens (HLA-A, -B, and -DR) and end-stage renal disease in Kuwaiti patients awaiting transplantation

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Abstract

The number of patients with end stage renal disease (ESRD) is increasing considerably worldwide. Human Leukocyte Antigens (HLAs) are relevant for the expression of many immunological diseases and contribute to the development of different nephropathies. Therefore, we aimed from the present work to investigate the possible association between the frequency of HLA-A, -B, and –DR antigens and ESRD in Kuwaiti patients awaiting renal transplant. HLA-A, -B, and –DR typing was performed by complement-dependent cytotoxicity (CDC) method for 334 patients with ESRD awaiting renal transplantation and 191 healthy controls. The frequency of HLA-B8 antigen was significantly higher in ESRD patients (OR = 2.62, $p = 0.001$, $p_c = 0.038$), and the frequency of HLA-A28, HLA-DR11 antigens was significantly higher in healthy controls (OR 0.42, $p = 0.0001$; $p_c = 0.0021$, and OR = 0.44, $p = 0.0007$, $p_c = 0.01$ respectively). While the HLA-B8 antigen may be a susceptibility risk factor for development of ESRD, the HLA-A28, and HLA-DR11 antigens may be protective against development of ESRD in Kuwaiti population.

Keywords

ESRD, HLA, Kuwaiti, serology

History

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Introduction

The ultimate consequence of chronic renal failure is end-stage renal disease (ESRD), defined as total, or nearly total, permanent kidney failure. ESRD has become a major health problem because it is a devastating medical condition and the cost of treatment is a huge economic burden. ESRD is managed by dialysis until a suitable donor for renal transplantation is available.[1–3]

The number of patients with ESRD is increasing faster than the number of renal transplantations performed per year worldwide. In Kuwait the incidence rate for ESRD was reported to be 72 (adults) and 38.2 (children) patients per million of population per year.[2,4,5]

Age, gender, genetics, race, proteinuria, lipids, hypertension and smoking are among the factors associated with ESRD.[6,7] The role of the immune system in renal diseases must also be considered because it could be the origin or cause of the disease and its progression.[8] These observations resulted in the search for positive associations between Human Leukocyte Antigens (HLAs) and a wide range of renal diseases.[9]

The MHC (Major Histocompatibility Complex) 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). 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.[10] HLA molecules bind and present 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.[11]

The role of the HLA system in the pathophysiology of ESRD is intriguing, but not completely resolved. Numerous associations and non-associations of HLA with ESRD have been reported in the medical literature but with controversial results.[3,12–17]

Our aim was to evaluate the possible associations of HLA class I (HLA-A, and -B) and HLA class II (HLA-DR) antigens with ESRD independent of other factors among Kuwaiti patients waiting for renal transplant.

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Material and methods

A retrospective study was conducted using results of serological microlymphocytotoxicity Terasaki test, obtained from samples submitted to the HLA and Immunology Laboratory, Hamed Al-Essa organ transplant center, Kuwait Ministry of Health and included 334 Kuwaiti patients with ESRD (194 male and 140 female) with mean age ± SD 44.59 ± 14.89, and 191 healthy Controls (115 male and 76 female) with mean age ± SD 40.86 ± 10.67.

Peripheral blood mononuclear cells from patients and controls were isolated from 10 ml of heparinized blood using lymphoflot (Biotest AG, Dreieich, Germany). Serological testing for HLA Class I and II antigens (HLA-A, -B and -DR) for patients and controls were performed with a standard complement-dependent microlympho-cytotoxicity assay.[18] Identification of HLA-Class I or II was done using ready prepared micro test tray containing regent grade class I or II anti sera. Each well of Terasaki plate contain specific type of anti-HLA class I/II antibodies (Biotest, Landsteinerstr, D-63303 Dreieich, Germany) organized as a panel to identify a complete HLA type for A, B, and DR loci. If the added lymphocytes have the specific HLA expressed on their surface, then the antigen–antibody complex will be formed during first incubation. During second incubation, complement will be added and complement will lyse cells with antigen- antibody complex only. Vital dye will penetrate and stain dead cells red and live cells green. The pattern of reactivity is then interpretable from the provided sheets as the HLA type of the subject.

The healthy control group consisted of 191 unrelated healthy age and sex matched subjects. Written informed consent was obtained from the patients and controls.

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.

Result

The frequency of HLA-A28 was higher in healthy controls than its frequency in ESRD Kuwaiti patients, and the difference was statistically significant (OR 0.42; $p = 0.0001$; $p_c = 0.0021$). Although, a statistical significance difference was observed between patients and controls for the frequency of HLA-A1 (8.4 vs. 11.7, OR = 0.62, $p = 0.026$), HLA-24 (5.8 vs. 9.9, OR = 0.54, $p = 0.007$), HLA-A26 (7.6 vs. 3.9, OR = 2.02, $p = 0.008$) and HLA-A68 (10.2 vs. 5.4, OR = 2.11, $p = 0.004$), however, when performing correction of the p value for multiple comparisons using Bonferroni formula, the significance observed was lost ($p_c > 0.05$), Table 1.

Table 1. Comparison of HLA-A frequency in ESRD patients and healthy controls.

HLA-A	ESRD ($n = 334$) No/%	Control ($n = 191$) No/%	OR (95% CI)	p/p_c value
1	56/8.4	45/11.7	0.62 (0.39—0.97)	0.0260/NS
2	145/21.7	74/19.4	1.36 (0.93–1.98)	>0.05/NS
3	70/10.5	28/7.3	1.39 (0.86–2.24)	>0.05/NS
11	17/2.5	13/3.4	0.83 (0.38–1.82	>0.05/NS
23 (9)	19/2.8	18/4.7	0.55 (0.27–1.11)	0.07/NS
24 (9)	39/5.8	38/9.9	0.54 (0.33–0.87)	0.007/NS
2403	3/0.45	1/0.3	1.72 (0.16–43.25)	>0.05/NS
25 (10)	1/0.15	1/0.3	1.14 (0.08–32.08)	>0.05/NS
26 (10)	51/7.6	15/3.9	2.02 (1.17–4.24)	0.008/NS
28	1.0/0.15	10/2.6	0.42 (0.06–0.42)	0.0001/0.0021*
29 (19)	14/2.1	9/2.3	0.77 (0.33–1.84)	>0.05/NS
30 (19)	21/3.1	24/6.2	0.56 (0.30–1.06)	0.05/NS
31 (19)	53/7.9	23/6.0	1.31 (0.77–2.23)	>0.05/NS
32 (19)	15/2.3	12/3.1	0.69 (0.31–1.56)	>0.05/NS
33 (19)	34/5.1	14/3.7	1.24 (0.65–2.37)	>0.05/NS
34 (10)	3/0.45	0.0/0.0	–	–
36	0.0/0.0	1/0.3	–	–
66 (10)	2/0.3	1/0.3	1.14 (0.08–32.08)	>0.05/NS
68 (28)	68/10.2	20/5.4	2.11 (1.21–3.69)	0.004/NS
69 (28)	5/0.8	1/0.3	2.89 (0.33–65.80)	>0.05/NS
74 (19)	4/0.6	5/1.3	0.45 (0.10–1.96	>0.05/NS
Ax	47/7.1	29/7.6	–	–

Note: HLA = human leukocyte antigen; OR = odds ratio; 95% CI = 95% confidence interval. p_c value = p value corrected for 21 comparisons; ESRD = end stage renal disease; NS = nonsignificant; Ax = homozygous A.
*Significant p value if ≤ 0.05.

Analysis of the frequency of HLA-B in patients with ESRD and healthy controls revealed that HLA-B8 was higher in patients than controls (9.1 vs. 3.9) and the difference was significant statistically before and after Bonferroni correction (OR = 262, $p = 0.001$, $p_c = 0.038$). On the other hand, HLA-B18 was more frequent in controls than ESRD patients (3 vs. 8.4) and the significant P value retain its significance after correction (OR = 0.32, $p = 0.0001$, $p_c = 0.0038$) (Table 2).

On examining the frequency of HLA-DR in ESRD patients in comparison to healthy controls, HLA-DR 11 was present more frequently in controls than in patients and the difference between them was statistically significant (OR = 0.44, $p = 0.0007$, $p_c = 0.01$). Although, the frequencies of HLA-DR12, HLA-DR-16, HLA-DR-17, and HLA-DR-18 showed a trend for association with ESRD in Kuwaiti patients (OR = 2.92, 2.13, 1.53, and 2.34, respectively), however, none of them reached the statistical significance ($p > 0.05$) (Table 3).

Discussion

Chronic kidney disease (CKD) is a general term for heterogeneous disorders affecting the structure and function of the kidney. CKD have shifted from being recognized as a life-threatening disorder affecting few people to a worldwide public health problem that should be managed at early stages.[19]

Kidney failure is traditionally regarded as the most serious outcome of chronic kidney disease and symptoms are usually caused by complications of reduced kidney function.

Table 2. Comparison of HLA-B in ESRD patients versus control.

HLA-B	ESRD ($n = 334$) No/%	Control ($n = 191$) No/%	OR (95% CI)	p/p_c value
7	51/7.6	24/6.3	1.25 (0.71–2.18)	>0.05/NS
8	61/9.1	15/3.9	2.62 (1.4–4.98)	0.001/0.038*
13	13/2.0	10/2.6	0.73 (0.29–1.84)	>0.05/NS
14	1/0.15	3/0.8	0.19 (0.01–2.04)	>0.05/NS
15	3/0.45	2/0.5	0.86 (0.12–7.38)	>0.05/NS
18	20/3.0	32/8.4	0.32 (0.17–0.59)	0.0001/0.0038*
27	6/0.9	3/0.8	1.15 (0.25–5.85)	>0.05/NS
35	54/8.1	32/8.4	0.95 (0.58–1.59)	>0.05/NS
37	5/0.8	4/1.0	0.71 (0.16–3.19)	>0.05/NS
38 (16)	26/3.9	11/2.8	1.44 (0.67–3.17)	>0.05/NS
39 (16)	11/1.7	8/2.1	0.78 (0.28–2.16)	>0.05/NS
41	22/3.3	17/4.5	0.72 (0.36–1.47)	>0.05/NS
42	6/0.9	4/1.0	0.86 (0.21–3.65)	>0.05/NS
44 (12)	20/3.0	16/4.2	0.7 (0.34–145)	>0.05/NS
45 (12)	6/0.9	6/1.6	0.56 (0.16–2.0)	>0.05/NS
47	1/0.15	1/0.3	0.57 (0.02–2.97)	>0.05/NS
48	0/0.0	1/0.3	–	–
49 (21)	12/1.8	11/2.9	0.61 (0.25–1.52)	>0.05/NS
50 (21)	88/13.2	39/10.2	1.39 (0.89–2.19)	>0.05/NS
51 (5)	89/13.3	47/12.3	1.11 (0.72–1.71)	>0.05/NS
52 (5)	14/2.1	11/2.9	0.72 (0.30–1.73)	>0.05/NS
53	26/3.9	9/2.6	1.65 (0.72–3.89)	>0.05/NS
55 (22)	13/2.0	8/2.1	0.93 (0.35–2.49)	>0.05/NS
56 (22)	1/0.15	0.0/0.0	–	>0.05/NS
57 (17)	18/2.7	16/4.2	0.62 (0.29–1.32)	>0.05/NS
58 (17)	17/2.5	7/1.8	1.41 (0.54–3.82)	>0.05/NS
60 (40)	7/1.0	5/1.3	0.80 (0.22–2.93)	>0.05/NS
61 (40)	9/1.3	4/1.0	1.29 (0.36–5.06)	>0.05/NS
62 (15)	4/0.6	0.0/0.0	–	–
63 (15)	15/2.2	3/0.9	2.95 (0.79–12.97)	>0.05/NS
64 (14)	1/0.15	2/0.5	0.28 (0.01–4.01)	>0.05/NS
65 (14)	12/1.8	8/2.1	0.85 (0.32–2.33)	>0.05/NS
70 (70)	1/0.15	2/0.5	0.28 (0.01–4.01)	>0.05/NS
71 (70)	2/0.3	0.0/0.0	–	–
72 (70)	6/0.9	3/0.8	1.15 (0.25–5.85)	>0.05/NS
73	3/0.45	3/0.8	0.57 (0.09–3.55)	>0.05/NS
75 (15)	0.0/0.0	2/0.5	–	–
77 (15)	1/0.15	0.0/0.0	–	–
Bx	23/3.4	13/3.1	–	–

Note: HLA = human leukocyte antigen; OR = odds ratio; 95% CI = 95% confidence interval. Significant P value if ≤ 0.05. p_c value = P value corrected for 38 comparisons; ESRD = end stage renal disease; NS = nonsignificant; Bx = homozygous B.
*Significant p value.

Table 3. Comparison of the frequency of HLA-DR in ESRD patients and control.

HLA-DR	ESRD ($n = 334$) No/%	Control ($n = 191$) No/%	OR (95% CI)	p/p_c value
1	22/3.3	12/3.1	1.05 (0.48–2.32)	>0.05/NS
2	2/0.3	1/0.3	1.14 (0.08–32.08)	>0.05/NS
3	49/7.3	28/7.3	0.92 (0.55–1.53)	>0.05/NS
4	87/13.0	55/14.4	0.89 (0.59–1.35)	>0.05/NS
7	106/15.9	57/14.9	1.18 (0.79–1.75)	>0.05/NS
8	10/1.5	5/1.3	1.15 (0.35–3.92)	>0.05/NS
10	20/3.0	13/3.4	0.75 (0.36–1.58)	>0.05/NS
11 (5)	42/6.3	47/12.3	0.44 (0.27–0.69)	0.0007/0.01*
12 (5)	10/1.5	2/0.5	2.92 (0.59–19.48)	>0.05/NS
13 (6)	88/13.2	46/12.1	1.07 (0.70–1.64)	>0.05/NS
14 (6)	16/2.4	14/3.7	0.59 (0.27–1.29)	>0.05/NS
15 (2)	64/9.6	33/8.6	1.2 (0.73–1.78)	>0.05/NS
16 (2)	23/3.4	7/1.8	2.13 (0.85–5.52)	>0.05/NS
17 (3)	72/10.8	29/7.6	1.53 (0.96–2.45)	>0.05/NS
18 (3)	11/1.6	3/0.8	2.34 (0.60–10.56)	>0.05/NS
DRx	46/6.9	30/7.9	–	–

Note: HLA = human leukocyte antigen; OR = odds ratio; 95% CI = 95% confidence interval. p_c value = p value corrected for 15 comparisons; ESRD = end stage renal disease; NS = nonsignificant, DRx = homozygous DR.
*Significant p value if ≤ 0.05.

When symptoms are severe they can be treated only by dialysis and transplantation; kidney failure treated this way is known as ESRD. Kidney failure is defined as a GFR of less than 15 mL/min per 1·73 m2 (stage 5 of CKD), or the need for treatment with dialysis or transplantation.[19,20]

The number of patients with ESRD is increasing faster than the number of renal transplantations performed per year worldwide. Incidence is now as high as 200 cases per million per year in many countries. It is nearing 400 cases per million in the USA, Taiwan, and some regions in Mexico.[19] In Kuwait the incidence rate for ESRD was reported to be 72 (adults) and 38.2 (children) patients per million of population per year.[2,5,21]

The most common cause of CRF in Kuwaiti adults is glomerulonephritis (including systemic lupus erythematosus and vasculitis), followed by diabetic glomerulosclerosis, tubule-interstitial disease, nephro-angiosclerosis, reno-vascular / ischemic disease, obstructive nephropathy, and adult polycystic kidney disease.[21] Etiological factors for chronic renal failure in children include congenital urological malformation, chronic glomerulopathies, hereditary nephropathies, multi-system disease, chronic pyelonephritis, tumors, ischemic renal disease and unknown etiology.[5]

The primary function of HLA molecules is the participation in antigen presentation leading to T cell activation and B cell antibody production to clear infectious agents and malignant self-tissue and prevent autoimmunity by negative selection of autoreactive T cells. Population studies have shown that predisposition to almost all human autoimmune diseases is linked to HLA genes, primarily the class II genes, playing key role in the specific immune response and in parallel associated with several autoimmune diseases.[22]

HLA-B8 was the only HLA of the three studied loci to be significantly higher in ESRD Kuwaiti patients when compared to healthy controls (OR = 262, $p = 0.001$, $p_c = 0.038$) suggesting that these antigen may be a susceptibly risk factor for the development of ESDR in Kuwaiti population. On the other hand, a statistical significant higher frequencies of HLA-A28 (OR 0.42; $p = 0.0001$; $p_c = 0.0021$), HLA-B18 (OR = 0.32, $p = 0.0001$, $p_c = 0.0038$), and HLA-DR11 were found in healthy controls than those in ESRD Kuwaiti patients suggesting that HLA-28, B18 and DR11 may be protective factors against the development of ESRD in Kuwaiti population (Tables 1–3).

The identification of HLA-associated diseases parallels increased understanding of the genetic complexity of the HLA system and its extensive polymorphism. With the passage of time, several hundred diseases have now been reported to occur more frequently in individuals with particular HLA genotypes. These diseases include a broad spectrum of immune-mediated diseases involving all major organ systems, certain malignancies, infectious diseases and more recently, adverse reactions to particular drugs. Despite the longevity of

this area of immunogenetics research, clear identification of a causative role for HLA polymorphism in the molecular immunopathogenesis of HLA-associated diseases remains the exception rather than the rule. What mechanisms might underlie a clearly established HLA association with a given disease? In terms of the role of HLA molecules in peptide presentation to T cells, a causative role of HLA in terms of presentation of a disease-triggering self-peptide, non-self-peptide or altered-self-peptide at the site of disease is clearly an attractive hypothesis. Alternatively, HLA may play a causative role via influence on the T-cell repertoire, including Treg cells, resulting in potential autoreactivity. Other aspects of HLA biology may additionally or alternatively influence the disease process. Finally, the associated HLA polymorphism may play no direct role, and the actual disease-predisposing polymorphism may be in linkage disequilibrium with the initially reported HLA association, which merely acts as a marker.[23]

Autoimmune and infectious diseases are among the most common causes of ESRD in Kuwaiti patients and the exact explanation for the association of HLA-B with ESRD in Kuwaiti patient is unknown. However, HLA-B8 may be associated with HLA-DR3 more frequently than other HLA-DRB1 types and this point needs to be investigated in Kuwaiti individuals.

The HLA-B8, DR3 haplotype is remarkable for its association with a number of autoimmune diseases such as lupus, Type 1 diabetes mellitus and IgA deficiency.[24] The extended HLA-B8, DR3 haplotype (8.1 AH) is highly conserved[25] and in linkage disequilibrium with the TNF*2 promoter allele which leads to a genetically high setting of TNF-α[26,27] and C4AQ0, which leads to defect in opsonization and clearance of immune complexes.[28] Studies in healthy individuals have revealed an altered balance of cytokines produced in carriers of the haplotype such as an impaired production of IL-2, IL-5, IL-12 and INF-γ after a mitogen stimulus.[29] The immune response is thus skewed towards Th2 cytokine production and the humoral response, although IL-5 production is also depressed.[30] Furthermore, both an increased production of auto-antibodies[31] and an increased blood lymphocyte spontaneous apoptosis are observed resulting in low levels of circulating lymphocytes.[32]

Positive significant association was found between HLA-A11, A33, B49 and ESRD in Iranian patients.[13] Al-Taie et al.[3] reported that HLA-A2 in Arab patients and HLA-B35 in Kurdish patients might be associated with susceptibility to risk of ESRD in Iraqi population. On Egyptian, HLA-B27 was most closely linked with renal disease in children,[33] and El-Gezawy et al.[34] reported that HLA-A2, B8, DRB1*3 and DRB1*11 were significantly correlated with diabetic nephropathy, and concluded that the determination of HLA-A, B and DRB1 as a risk factor for primary diseases leading to ESRD might be beneficial in preventing progression to ESRD and recurrence of the primary disease post-transplantation. On the other hand, no significant differences were observed between Saudi Patients with ESRD and controls in respect of HLA-A2, B50 (21), B51 (5), DRB1*04, and DRB1*07.[35]

Karahan et al.[15] work on Turkish population revealed that HLA-A3, A66 and B18 were associated with ESRD. Chen[36] studied the association between HLAs and ESRD in Caucasian patients and demonstrated a decrease in the frequencies of HLA-B27, B40 and an increase in the frequency of HLA-B35 in patients when compared with healthy controls. Doxiadis et al.[14] pointed out to the significant increase in frequencies of HLA-B35 and DR5 in ESRD European patients, and significant increase in HLA-B7, B8, DR2, and DR3 in controls.

The results of Freedman et al.[37] suggested that HLA-DR3 and HLA-DR5 were positively associated with ESRD in both African–Americans and whites population and HLA-DR7 is negatively associated with ESRD in white population only. Furthermore, HLA-A78 and HLA-DR11 were positively associated and HLA-B14 was negatively associated with ESRD in Brazilian patients[6] and in Mexican population DRB1*1502 contributes to susceptibility to ESRD due to type 2 diabetes mellitus while DRB1*0407 is involved in protection.[38] In the same time, the HLA-B38, B51, B53 and B62 were positively associated with ESRD and the HLA-A9, B12, B17, B40 and B48 were negatively associated in population from Venezuela.[9]

Therefore, the development of ESRD is associated with different HLA in different ethnic population, different races of the same population and sometimes the results may be contradictory. These findings can be explained by the difference in patients and controls number between studies, different techniques used for HLA-typing, different etiologic factors leading to ESRD, different ethnic and genetic background of each population. In the same time, the likelihood of developing ESRD in an individual is determined by interactions between genetic and environmental factors. Further molecular studies may clarify the types and subtypes of alleles involved in ESRD progression.

Conclusion

While the HLA-B8 may be a susceptibility risk factor for the development of ESRD and the HLA-A28, -DR11 may be protective against development of ESRD in Kuwaiti population.

Declaration of interest

The manuscript has not been published elsewhere and has not been submitted simultaneously for publication elsewhere.

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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