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Research Article

Association Between Human Leukocyte Antigens and Chronic Renal Disease

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Abstract

Objectives: Chronic renal disease is a common clinical problem, the etiology of which has not yet been fully elucidated. Human leukocyte antigen profiling has recently gained popularity as an important new tool for precision medicine approaches. In the present study, directed approaches were applied to understand the distribution of HLA antigens and how different HLA expressions affect the frequency of patients with chronic kidney disease in the Black Sea region.

Methods: A total of 156 patients with end-stage renal disease and 216 healthy participants who were not related to the patients were enrolled in the study.

Results: The frequency of the HLA B*52 and HLA B*58 alleles was significantly lower and the frequency of the HLA B*40, HLA CW*04, HLA CW*05, HLA DRB1*12, and HLA DQB1*03 alleles was significantly higher in end-stage renal disease patients.

Conclusion: The study results indicated that the HLA distribution in end-stage renal disease is different from that of healthy individuals. A significantly larger number of HLA B*40, HLA CW*04 , HLA DRBB1*12 and HLA DQB1*03 and fewer HLA B*52 and HLA B*58 haplotypes were observed in patients with chronic renal disease. More studies on this subject are required.

Keywords: Black Sea region, end-stage renal disease, HLA

According to records of Turkey Renal Diseases Study Group, the prevalence and incidence of chronic kidney disease (CKD) is 17.6% in Turkey,[1] and the morbidity associated with the CRD has become an important public health issue. On the same study it is reported that CKD is more common in women, elder people and patients living in the rural areas. Also the prevalanace of disease is higher in Southeastern and Marmara regions. The causes of CKD among Turkish population are diverse, the most common being diabetes mellitus, hypertension, smoking, hypertension and metabolic syndrome.[2] It is worth noting that 17.8% of late-stage CKD patients, the etiology of the disease is not eluciated.[1] Although chronic renal diseases have an important morbidity, fifth of patients were not known about etiology of disease

The HLA system belongs to the major histocompatibility complex (MHC) family in humans. Which is located on chromosome 6p.[3] HLA genes encode cell surface moleculeswhich is essential to present molecules T cell receptors.[4] Specific HLA types have been known to be associat-

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ed with the pathogenesis of many autoimmune diseases, allergies, and inflammatory bowel disease.[5, 6] The detection of specific HLA types has proven to be a valuable tool for the diagnosis of some important diseases such as ankylosing spondylitis, inflammatory bowel disease and multiple sclerosis.[7, 8] Several emerging studies have described significant correlations between HLA and some renal diseases such as diabetic nephropathy, IgA nephropathy, and glomerulonephritis.[9, 10] However, specific HLA types associated with ESRD have not been well documented. In this study, we aimed to show GHLA distribution in our region and the frequency of HLA allels in patients with chronic renal disease.

Methods

This was an observational prospective study conducted in Nephrology Clinic with the approval of the Local Ethical Committee. We compared the data of 156 patients diagnosed with CRD and referred to the clinic for renal transplantation. Control group was composed from 216 healthy volunteers.

Patients who have chronic malignancies, chronic liver diseases, myeloproliferative or thrombotic disorders, smoking, active alcohol consumption, active or chronic infections were excluded from the study.

Demographic features of study group were recorded. Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki, as reflected in its prior approval by the institution's human Research Committee.

About 10 mL of blood was collected from each patient in Vacutainer tubes (Becton and Dickson, Oxford, UK) with ethylenediaminetetraacetic acid (EDTA) as anticoagulant. The buffy coat was removed and the DNA genome extracted using the PureLinkTM purification system (Invitrogen, Life Technologies, Carlsbad, USA). LAB Type HSSO loci -A, -B and –C (One Lambda Inc., Canoga Park, CA, USA) were employed for the HLA typing. The protocol comprised the DNA amplification process, hybridization, reading on a special device (LABScanTM100) and interpretation by software (HLA FusionTM). All procedures were performed according to the manufacturers' instructions.

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 15.0 package of programs (SPSS Inc., Chicago, Illinois, USA). Data were presented as mean±SD unless otherwise noted. Nonparametric Wilcoxon's and x^2 tests assessed differences between case and control patients in baseline characteristics and allele and genotype frequencies. A p value of less than 0.05 was considered statistically significant.

Results

Overall Characteristics of the Cohort

A total of 372 patients were enrolled in Nephrology Unit. Subjects who given renal tissue samples for detecting HLA serotypes. One hundred and fifty-six patients were evaluated as chronic renal disease according to KDIGO-2012 guidelines. Controls were subjects who had renal function tests (n=156). Mean age was 40.6±15.7 years in patients; 41.5±12.6 years in controls. No significant difference was observed according to gender and age.

Characteristics of the Study Group about HLA Allele Levels

The most common HLA A allels in patient group were HLA A02 and A24 (39.7%, 37.2% in order) similar to controls (40.3%, 32.9%) (Fig. 1) displays the characteristics of the study group according to the HLA- A levels.

Distribution of HLA-B antigens was %31.4 B*35, %30.1 B*51, %14.7 B*18, %10.9 B*15 and %9.6 B*44 in patient group. Figure 2 shows HLA-B ranges between the groups HLA B*52 and HLA B58 were significantly more frequent in controls (p=0.013 and p=0.016) and HLA B40 was significantly more frequent in patient group (p=-0.013).

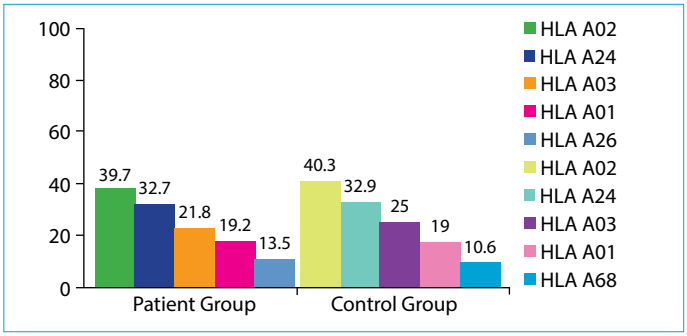

Figure 1. Distribution of HLA-A alleles between patient and control groups

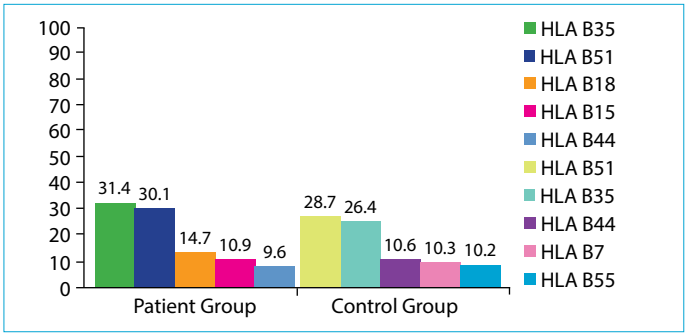

Figure 2. Distribution of HLA-B alleles between patient and control groups

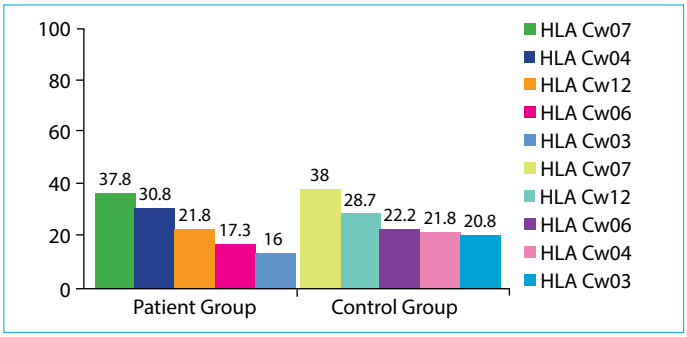

Figure 3. Distribution of HLA-C alleles between patient and control groups

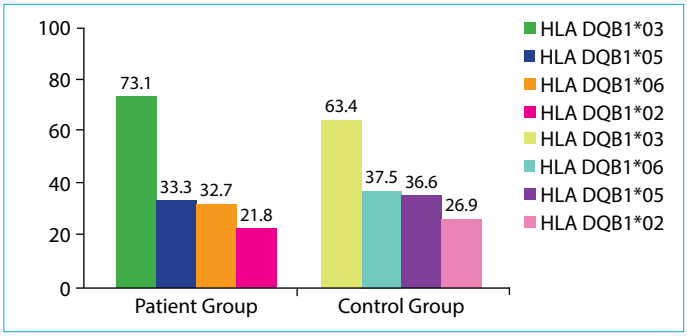

Figure 4. Distribution of HLA-DQ alleles between patient and control groups

HLA Cw*04 and HLA Cw05 were significantly higher in patients with CRD (p=0.033 and 0.041 in order, Fig. 3)

HLA DRB1*12 and HLA DQB1 were significantly different between the groups. 8,3% of patients had HLA DRB1 (n=13) whereas 3.2% of controls (n=13, p=0.028). HLA DQB1*03 was higher in %73.1 of patients (n=114) and %63.4 of controls (n=137, p=0.032) This was statistically significant. Figure 4 and 5 displays HLA DQB1 and HLA DRB 3-4-5 between the groups.

Discussion

Because of host community to different cultural groups, Turkey have nonhomogenous dispersion about ancestries. Because of that, genetic dispersion is very different between geographical regions.In our country, some studies were reported about HLA distribution in Mediterranean, Thracian, Eastern and Central Anatolia regions of Turkey. [11-14] Also there is a study about HLA dispersion of overall Turkey.[15] But there is no study about Blacksea region. Because of location and patient population of our hospital, we aimed to determine HLA range of our region and compare between patient and control group.

When we examined HLA-A alleles, we found that HLA A02 group was significantly frequent than the other HLA-A groups (40.3%). This result was similar to other study

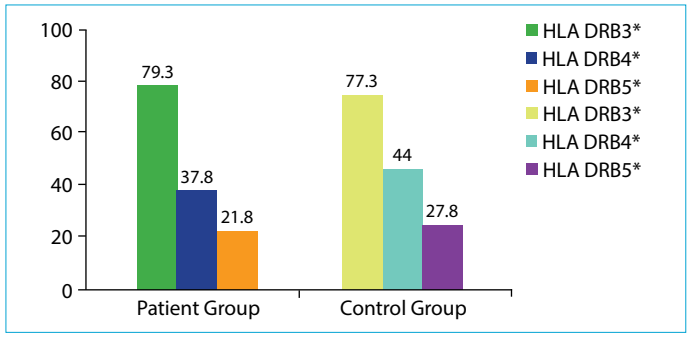

Figure 5. Distribution of HLA-DR alleles between patient and control groups

groups.[13, 14, 16] But our B group results were different from the other reports. The frequence of B51 allele was significantly higher fron pther B alleles (28, 7%). Previous reports showed that B51 was the second frequent allele in thracian region.[13] Our results were similar to Thracian and central anatolia regions; but different from the report made in Mediterranean region.[13-16] The ranking in our HLA A locus (A02, A24 and A03 in order) was similar to Chinese and Japonese population data.[17, 18]

When we compered HLA DR allels, we showed that HLA DRB11 allee was the most frequent seen HLA DR allel type in all regions similar to our results.[12, 13] According to overall studies, we can say that HLA DRB11 is the most recurring HLA DR allel group in Turkish population. Another society where this allel is most frequently seen is the Greeks. [19] Also, DRB11 rate was found 29% in Macedonians[20] and 15% in Croatians.[21] Temiz et al.[14] reported that HLA Cw04 is the most and HLA cw 07 IS THE SECOND FREQUENT ALLELE IN their population but we found that Cw07 is the most (28.7%) and Cw 04 is the second one (21.8%). Also, DQ allele results showed some dşffereneces with pur study. In mediterranean region, DQ7 is on the fist line (28.6%) but we found that DQ 03 was the most seen type DQ group (63%).

Atasoy et al were typed HLA A and B antigens of 973 individuals who are not relative with each other from the various regions of Turkey by the standard two step microlymphocytotoxicity method.[22] It was reported that, there are regional differences in the distribution of leukocyte antigens.

Because of more discriminative and informative features of HLA DR antigens in terms of revealing kinship of differenet communities,this antigens were commonly preferred class II antigens. Machulla et al were typed HLA A, B, CW,DRB1 and DQB1 locuses in mogolian population by PCR-SSP method.[23] They compared results with some societies. Their results were similar to Khalka, Tsactan; but different from Geman and Anatolian Turkish population. Also another reported showed that HLA alleles of Anatolian people werwe similar to other Mediterranean populations, Arme-

nian population also have similar HLA alleles to Turkish and other Middle Eastern populations.[17]

Yasavul et al.[16] studied Hla haplotypes of healthy kidney donors and patients with chronic renal diseases and thye found no significant differenece between the groups. But they didn't perform molecular techniques for tissue molecular typing. Also another group compered molecular ans serologic methods in Chinese populationd and they found 9% mismatch ratio for HLA A and 12.2 % for HLA B.[24] Also Mytilineos et al.[25] found 4.8% mismatch ratio for HLA-A and 13.8% for HLA-B. Another group compared the samples from cord blood and they expressed 13.8% error rate for serologic methods.[26] The reason for the statistically significant differences in our study may be that the number of HLA antigens identified and the number of HLA antigens in those years were scant and / or due to the technique of operation.

Karahan et al.[27] examined distribution and differences of HLA haplotypes between patients with CRD nad healthy controls. They found HLA A 11, 23, 23, 26, 30, 32, 66, 68 and HLA 69 alleles significantly lower in patient group. In our study, HLA A alleles were similar between the groups. HLA A26 allele was higher in our patients with CRD nonsignificantly in our study population. At the study we pointed out above, they showed higher HLA B58 frequency in patient group but our result was exactly oppose to this result. Also, they showed significantlly lower HLA B7, B57 and DRB11 in CRD group. We get lower HLA B7, B57 and higher DRB11 results but they were not statistically significant.

We found higher HLA DR11 and lower HLA B14 allele frequencies in patient with CRD nonsignificantly. These results were similar to anorher study reported by Crispim et al.[28] But they didn't found any statistically significant difference between any HLA allele groups.

A number of studies have investigated the relationship between HLA allels and diabetes mellitus. Gorodezky et al.[29] reported higher risk for diabetik nephropathy in patients have HLA DRB1*1502, HLA DQB1*0501 allles and lower risk in patients carrying higher DRB1*0407 allels. Also in long diabetic patients carrying higher HLA A2 alles have more seriously risk for diabetic nephropathy.[30] Also Freedman et al found higher risk for hypertension in subjects with higher DR3 allele.[31]

In our country, a report showed that microalbuminuri risk was higher in tip 1 diabetic patients have higher HLA A2, B8 and A2+B8 alleles.[32] Because our patient has chronic renal disease with some diseases on admission, we couldn't discriminate etiologic factors. We found significantly higher HLA B40, Cw 04, HLA DRBB1 12 and HLA DQB1 03 and lower HLA B52 and HLA B58 haplotypes in patients with chronic renal disease.

Conclusion

Chronic renal disease is very common and complex condition which etiology is not elucidated completely. Because of serious morbidity and mortality of this disease, fore knowledge is very important for prevention and taking precautions. If disease is associated with HLA alleles, patients may be recognised abd followed before they enmeshed to chronic stages of disease. HLA polymorphism might be a useful clinical tool for screening patients with high risk of ESRD. Larger scale studies are needed, in this subject.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship contributions: Concept – H.K.; Design – H.K.; Supervision – K.C.; Materials – H.K., K.C.; Data collection &/or processing – D.A.; Analysis and/or interpretation – D.A.; Literature search – H.K., D.A.; Writing – H.K., D.A.; Critical review – K.C.

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