Pattern of HLA types in renal transplant patients in Sohag Governorate: a cross-sectional study

Emad A.M. Yossef[a], Eman M. Salama[b], Ahmad M.M.A. Elsharif[c]

Objective This study aimed to assess the pattern of HLA types in Egyptian renal transplant patients in the Sohag governorate.

Materials and methods A retrospective chart review was conducted on all patients and their donors, who were scheduled to undergo renal transplantation at Sohag University Hospital through the period from January 2010 to December 2019. We retrieved the following data from eligible patients' files: age of the recipient and donor, gender of the recipient and donor, consanguinity, blood group, cross-matching, HLA classes A and B, and DR alleles.

Results Overall, a total of 26 recipients (70.3%) and 25 donors (67.6%) had HLA-A alleles, while 22 recipients (59.5%) and 26 donors (70.3%) had HLA-B alleles. In terms of the pattern of HLA-A distribution among recipients, the most frequent alleles were A*01/02 (8.1%), A*02/23 (5.4%), A*02/32 (5.4%), and A*02 (5.4%). On the other hand, the most frequent HLA-A alleles in the donors' group were A*01/02 (5.4%), A*02/03 (5.4%), and A*26/68 (5.4%). Regarding HLA-B allele distribution, all recipients had different alleles. While B*41/52 was the most frequent allele in the donors' group. All recipients, except two patients, had HLA-DR alleles, most commonly DR*11/13 (13.5%) and DR*13/15 (8.1%). Negative cross-matching was present in 59.5% of the cases. Among female recipients, only A*13/15 and B*27/51/53 alleles were detected.

Conclusion In conclusion, our findings were very similar to the results from other local and global studies. Different populations and ethnicities are the main dependent variables of the major differences in terms of HLA allele distribution.

Egypt J Haematol 2023 47:316–320

Egyptian Journal of Haematology 2023 47:316–320

Keywords: chronic kidney disease, HLA alleles, kidney transplantation

[a]Department of Internal medicine, Faculty of Medicine, Sohag University, Sohag, Egypt, [b]Department of Clinical Pathology, Faculty of Medicine, Sohag University, Sohag, Egypt, [c]Department of Urology, Faculty of Medicine, Sohag University, Sohag, Egypt

Correspondence to Emad A.M. Yossef, Institution:lecturer of internal medicine and nephrology, sohag university hospital, sohag naser city, Sohag, Egypt. Mob: +20 110177 9988;
e-mail: emadabokhabar@gmail.com

Received: 07 April 2021 **Revised:** 12 April 2021
Accepted: 13 April 2021 **Published:** 09 March 2023

Introduction

Globally, the risk of cardiovascular and all-cause mortality is very high in patients with chronic kidney disease (CKD) [1]. According to the recent World Health Organization, Egypt ranked the 20th in the world in 2017, the death toll of kidney disease in Egypt was 20 433 (3.98%) of the total deaths [2]. The end stage of renal failure is uremia, which induces a variety of clinical symptoms and affects almost all body systems [3,4]. Moreover, it can progress and eventually result in death [5]. Kidney transplantation is the most appropriate treatment for uremia, but it is limited to the severe scarcity of compatible renal sources [6]. The immunological response of the recipient to organ or tissue graft is a significant restriction on transplantation effectiveness [7]. The recognition of transplanted cells, as self or not, is detected by human leukocyte antigens (HLA) [8].

The HLA system is an important marker of transplant organ survival and plays a vital role in the biological system rejection process [9]. For both the donor and the recipient, the pretransplant evaluation involves HLA typing tests as the amount of HLA variations can be associated with decreased graft survival [10]. Greater compatibility between the donor and recipient enhances immune system tolerance and improves the survival of the graft in case of a compatible live donor transplant as well as a deceased donor [11,12].

Owing to the significant variation of HLA alleles and haplotypes among the different populations, it is considered highly polymorphic [13]. There are many types of HLA alleles: intracellular molecules (HLA-A, -B, and -C) and extracellular molecules (HLA-DRA, -DRB1, -DPA1, -DPB1, -DQA1, and -DQB1) [14]. The matching of HLA-A, -B, and -DRB1 loci has been shown to be very important to the assignment of kidney transplants as they contribute to the majority of the immunogenicity of the antigens [15]. In order to decide which donor is the best possible match, the determination of the HLA polymorphism and distribution is extremely important for a national registry's strategic planning. Therefore, this study aimed to assess the pattern of HLA types in Egyptian renal transplant patients in the Sohag governorate.

 DOI: 10.4103/ejh.ejh_33_21

Materials and methods

A retrospective chart review was conducted on all patients and their donors, who were scheduled to undergo renal transplantation at Sohag University Hospital through the period from January 2010 to December 2019. Only adults patients aged more than 16 years, of both sexes, were included. We excluded patients with incomplete data and/or patients on hemodialysis due to temporary or permanent failure of transplantation. The study was initiated after the approval of medical research ethics committee of Sohag University Hospital, Sohag, Egypt. Due to the retrospective nature of the present study, written informed consents were not required. Written informed consent was obtained from eligible patients before the beginning of the study.

Data collection and HLA typing

We retrieved the following data from eligible patients' files: age of the recipient and donor, gender, consanguinity, blood group, cross-matching, HLA classes A and B, and DR alleles.

A 10 ml of whole blood was withdrawn from all patients for HLA typing and stored until DNA extraction at −80C The polymerase chain reaction–sequence-specific primer (PCR–SSP) technique was used for HLA typing. After DNA extraction by QIAamp DNA Mini Ki and PCR was done, the DNA was separated by agarose gel electrophoresis in order to obtain the gel picture by UV gel documentation machine. The identification of different classes of HLA was done according to the pattern of DNA distribution within the gel.

Statistical analysis

Data were analyzed using IBM-SPSS, version 20 (IBM, Chicago, Illinois, USA). Quantitative data were expressed as mean±SD and range. Qualitative data were expressed as frequency and percentage. The association between HLA typing distribution and patients' characteristics was examined using Chi-square or Fisher exact tests.

Results

The data of 37 renal transplant recipients and their donors were retrieved for analysis. The mean age of the recipients and donors was 28.45 ± 8.1 and 41.3 ± 10.7 years old, respectively. Thirty recipients (81.1%) were males compared to only 16.2% in the donor group. In addition, 21.6% of the donors were the mothers of the recipients. The most common blood group was A +ve (29.7%), followed by O +ve (10.8%) (Table 1).

Table 1 Characteristics of the study's participants

Variables	Recipents (*n*=37)	Donor (*n*=37)
Age in years, mean±SD	28.45 ± 8.1	41.3 ± 10.
Male, No. (%)	30 (81.1%)	6 (16.2%)
Consanguinity, No. (%)		
Brother	—	2 (5.4%)
Father		3 (8.1%)
Mother		8 (21.6%)
Sister		7 (18.9%)
Wife		1 (2.7%)
Blood group, No. (%)		
A +ve	11 (29.7%)	—
AB +ve	2 (5.4%)	
B +ve	2 (5.4%)	
O +ve	4 (10.8%)	

Overall, a total of 26 recipients (70.3%) and 25 donors (67.6%) had HLA-A alleles, while 22 recipients (59.5%) and 26 donors (70.3%) had HLA-B alleles. In terms of the pattern of HLA-A distribution among recipients, the most frequent alleles were A*01/02 (8.1%), A*02/23 (5.4%), A*02/32 (5.4%), and A*02 (5.4%). On the other hand, the most frequent HLA-A alleles in the donors' group were A*01/02 (5.4%), A*02/03 (5.4%), and A*26/68 (5.4%). Regarding HLA-B allele distribution, all recipients had different alleles. While B*41/52 was the most frequent allele in the donors' group (Table 2). All recipients, except two patients, had HLA-DR alleles, most commonly DR*11/13 (13.5%) and DR*13/15 (8.1%). The distribution of HLA-DR alleles among donors is shown in Table 2. Negative cross-matching was present in 59.5% of the cases.

Among female recipients, only A*13/15 and B*27/51/53 alleles were detected.

Discussion

In this retrospective study, we proposed to evaluate the pattern and distribution of HLA alleles in the Egyptian population. HLA-DR was the most frequent allele in the recipients, followed by HLA-A and HLA-B. The most frequent alleles of HLA-A were A*01/02, A*02/23, A*02/32, and A*02. While different HLA-B alleles are distributed in all recipients. In terms of the donor, the distribution of HLA-B alleles was larger than HLA-A alleles. The most frequent HLA-A alleles in the donors' group were A*01/02, A*02/03, and A*26/68, while B*41/52 was the most frequent allele in the donors' group.

Survival of HLA-identical siblings living-donor kidney transplants has been recognized for a long time to be higher than that of a less-matched relative or well-matched deceased donors [16]. Cheigh *et al.* [17] conducted a study to compare the outcomes in identical

Table 2 Distribution of HLA alleles

Variables	Recipents (*n*=37)	Donor (*n*=37)
HLA-A, No. (%)		
01&02	3 (8.1%)	2 (5.4%)
01&03	1 (2.7%)	1 (2.7%)
01&30	1 (2.7%)	1 (2.7%)
01&32	1 (2.7%)	1 (2.7%)
01&33	0	1 (2.7%)
02&02	0	1 (2.7%)
02&03	1 (2.7%)	2 (5.4%)
02&23	2 (5.4%)	0
02&26	1 (2.7%)	0
02&30	1 (2.7%)	1 (2.7%)
02&32	2 (5.4%)	1 (2.7%)
02&66	0	1 (2.7%)
02&68	0	1 (2.7%)
03&29	1 (2.7%)	0
1	0	1 (2.7%)
1&2	0	1 (2.7%)
11&23	0	1 (2.7%)
2	2 (5.4%)	0
2&3	0	1 (2.7%)
23&24&29	0	1 (2.7%)
23&80	0	1 (2.7%)
24&68	1 (2.7%)	0
26&32	1 (2.7%)	0
26&68	0	2 (5.4%)
30&30	0	1 (2.7%)
30&69	0	1 (2.7%)
30&74	1 (2.7%)	0
35&41	0	1 (2.7%)
35&57	1 (2.7%)	0
68&68	1 (2.7%)	1 (2.7%)
68&69	1 (2.7%)	0
HLA-B, No. (%)		
03&04	0	1 (2.7%)
04&07	1 (2.7%)	0
07&15	1 (2.7%)	0
07&18	0	1 (2.7%)
07&41	0	1 (2.7%)
13&13	1 (2.7%)	1 (2.7%)
14&35	0	1 (2.7%)
14&51	0	1 (2.7%)
15&18	1 (2.7%)	0
15&50	1 (2.7%)	2 (5.4%)
15&58	1 (2.7%)	0
18&50	1 (2.7%)	1 (2.7%)
27&35	1 (2.7%)	0
27&51&53	1 (2.7%)	0
35&44	0	1 (2.7%)
38&51	1 (2.7%)	0
38&53	0	2 (5.4%)
39&42	0	1 (2.7%)
40&58	1 (2.7%)	1 (2.7%)
41&27	1 (2.7%)	0
41&44	1 (2.7%)	0
41&47	1 (2.7%)	0
41&52	0	2 (5.4%)
41&53	0	1 (2.7%)
41&58	1 (2.7%)	0
42&49	0	1 (2.7%)
44&49	0	1 (2.7%)
50&52	1 (2.7%)	0
51	1 (2.7%)	0
51&35&53	0	1 (2.7%)
51&52	1 (2.7%)	0
51&52&53	0	1 (2.7%)
51&58	0	1 (2.7%)
52	1 (2.7%)	1 (2.7%)
52&51	0	1 (2.7%)
52&53	1 (2.7%)	0
63&51	1 (2.7%)	0
7&52	0	1 (2.7%)
7&53	1 (2.7%)	0
71&44	0	1 (2.7%)
HLA-DR, No. (%)		
01&01	1 (2.7%)	0
01&01&10	0	1 (2.7%)
01&03	1 (2.7%)	0
01&04	0	2 (5.4%)
01&08	0	2 (5.4%)
01&31	0	1 (2.7%)
03&03&10	1 (2.7%)	0
03&04	1 (2.7%)	0
03&11	0	1 (2.7%)
03&13	2 (5.4%)	2 (5.4%)
03&16	1 (2.7%)	1 (2.7%)
04&04	0	3 (8.1%)
04&08	1 (2.7%)	0
04&13	1 (2.7%)	0
04&15	1 (2.7%)	0
04&16	1 (2.7%)	0
07&01	0	1 (2.7%)
07&03	1 (2.7%)	0
07&11	1 (2.7%)	1 (2.7%)
07&15	2 (5.4%)	0
08&08&10	0	1 (2.7%)
10&15	1 (2.7%)	0
11&13	5 (13.5%)	3 (8.1%)
11&15	1 (2.7%)	2 (5.4%)
13	0	1 (2.7%)
13&13	2 (5.4%)	1 (2.7%)
13&15	3 (8.1%)	5 (13.5%)
15	0	1 (2.7%)
15&15	1 (2.7%)	1 (2.7%)
15&15&14	0	1 (2.7%)
15&15&16	2 (5.4%)	1 (2.7%)
15&16	1 (2.7%)	1 (2.7%)
17&04	2 (5.4%)	1 (2.7%)
3&13	1 (2.7%)	0
3&4	0	1 (2.7%)
4&13	0	1 (2.7%)
4&15	0	1 (2.7%)
8&11	1 (2.7%)	0

siblings at HLA-A and HLA-B loci and recipients of transplants from “semi-identical” donors. They found that the identical group had superior graft survival (85% vs. 53%) and patient survival (95% vs. 85%) compared to the semi-identical group. In 100 patients undergoing HLA-identical sibling transplants, a contemporaneous study also found excellent renal allograft (88%) and patient survival (92%) [16].

There was also an analysis of the relative importance of matching HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DP [18–21]. HLA-DR matching was linked to an improvement in graft survival in the 1985 Collaborative Transplant Study. The findings of the study of Euro-transplant that analyzed data from 39,205 transplantations have confirmed the salutary effect of HLA-DR matching on the survival of grafts [19]. A positive effect was also observed in the graft results of matching HLA-B. Australia and New Zealand Dialysis and Transplant Registry indicated that mismatching of HLA-DQ is associated with an increased risk of rejection [20].

Interestingly, Shang and colleagues compared uremic patients and healthy controls in terms of HLA alleles. They found that HLA-B62 and HLA-DRB1-15 alleles were more common in controls compared with patients, indicating that these two alleles have a protective effect for uremia. On the other hand, HLA-DRB1-4, HLA-DRB1-11, HLA-DRB1-10, HLA-B54, HLA-B15, and HLA-B40 were significantly more prevalent in the group of patients, which may be risky alleles for uremia [14]. They suggest that these six alleles may increase the difficulty in the allocation of kidney transplantation; therefore, more attention should be paid for these alleles. Pan *et al.* [15] demonstrated that HLA-A*11:01, HLA-A*31:01, HLA-B*55:02, HLA-B*39:05, HLA-DRB1*03:01, HLA-DRB1*04:03, HLA-DRB1*04:04, HLA-DRB1*04:05, HLA-DRB1*11:01, and HLA-DRB1*12:02 indicated a substantial positive association with ESRD and appeared as susceptible alleles to ESRD.

In Egypt, EI-Gezawy *et al.* [22] demonstrated that Egyptian ESRD patients had substantially increased frequency of HLA-A*02, HLA-DRB1*3, and HLA-DRB1*11, which was consistent with the studies in Brazil, America, and Turkey [23,24]. In agreement with our findings, in Brazilian renal transplant candidates, the most frequent HLA alleles were HLA-A*01, A*02, A*03, A*24, B*35, B*44, B*51, DRB1*03, DRB1*04, DRB1*11, and DRB1*13 [23]. Similarly, another Brazilian study showed that the most frequent HLA alleles in the renal transplant candidates were HLA-A*02, A*24, A*03, A*01, B*44, B*35, DRB1*13, DRB1*11, DRB1*04, and DRB1*07 [24]. These findings were similar to those of the European population [25,26]. In contrast, the Kuwaiti study of Mosaad *et al.* [27] showed that the frequency of HLA-A*24, HLA-A*28, HLA-B*18, and HLA-DRB1*11 was higher in healthy controls compared with patients, which may suggest that they have a protective effect against uremia. This difference can be explained by the variation between the different populations and races.

In conclusion, our findings were very similar to the results from other local and global studies. Different populations and ethnicities are the main dependent variables of the major differences in terms of HLA allele distribution.

Acknowledgements

FUNDING SOURCE: None (authors confirm that they did not receive any funding to do this work).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 McCullough PA, Li S, Jurkovitz CT, Stevens L, Collins AJ, Chen SC, *et al*. Chronic kidney disease, prevalence of premature cardiovascular disease, and relationship to short-term mortality. *Am Heart J* 2008; versión On-line ISSN 1989-2284 versión impresa ISSN 0211-6995.

2 Barsoum RS. End stage renal disease (ESRD) in Egypt and North Africa. In García-García G, Agodoa LY, Norris KC, editors. *Chronic kidney disease in disadvantaged populations*. Amsterdam: Elsevier; 2017. pp. 113–123.

3 El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. *Kidney International* 2005; **68**:2918–2929.

4 Naicker S. End-stage renal disease in sub-Saharan Africa. *Ethn Dis* 2009; **19**:S1-13-5

5 Prince M, Tafur JD, White CJ. Treatment of non-atheromatous renal artery stenosis. *J Am Coll Cardiol Intv*. 2019;**12**: 505–517.

6 Karlberg I, Nyberg G. Cost-effectiveness studies of renal transplantation. *Int J Technol Assess Health Care* 2018; **18**:1168–1176.

7 Platt JL, Cascalho M. The immunologic barriers to replacing damaged organs. *Curr Top Microbiol Immunol* 2003; **278**:1–21

8 Choo SY. The HLA system: genetics, immunology, clinical testing, and clinical implications. *Yonsei Med J* 2007; **48**:11

9 Mahdi BM. A glow of HLA typing in organ transplantation. *Clin Transl Med* 2013; **2**:6

10 Uffing A, Hidalgo LG, McMullan C, Perry J, Milford EL, Murakami N, *et al*. Preformed donor-specific antibodies against HLA class II and graft outcomes in deceased-donor kidney transplantation. *Transplant Direct* 2019; **5**:e446

11 Alelign T, Ahmed MM, Bobosha K, Tadesse Y, Howe R, Petros B. Kidney transplantation: the challenge of human leukocyte antigen and its therapeutic strategies. *J Immunol Res* 2018; **2018**:1–18

12 Vinson AJ, Kiberd BA, Davis RB, Tennankore KK. Nonimmunologic donor-recipient pairing, HLA matching, and graft loss in deceased donor kidney transplantation. *Transplant Direct* 2019; **5**:e414

13 Shen C, Zhu B, Deng Y, Ye S, Yan J, Yang G, *et al*. Allele polymorphism and haplotype diversity of HLA-A, –B and –DRB1 loci in sequence-based typing for Chinese Uyghur Ethnic Group. *PLoS ONE* 2010; **5**:e13458

14 Shang W, Shen Y, Gao S, Feng G, Feng Y, Wang Z, *et al*. Comparison of HLA-A, –B and –DRB1 loci polymorphism between kidney transplants of uremia patients and healthy individuals in central China. *PLoS ONE* 2016; **11**:1–9

15 Pan Q, Ma X, Chen H, Fan S, Wang X, You Y, *et al*. A single center study of protective and susceptible HLA alleles and haplotypes with end-stage renal disease in China. *Hum Immunol* 2019; **80**:943–947

16 Ascher NL, Simmons RL, Noreen H, VanHook J, Howard RJ, Sutherland DE, *et al*. 100 HLA-identical sibling transplants. prognostic factors other than histocompatibility. *Ann Surg* 1979; **189**:209–216

17 Cheigh JS, Chami J, Stenzel KH, Riggio RR, Saal S, Mouradian JA, *et al*. Renal transplantation between HLA identical siblings: comparison with transplants from HLA semi-identical related donors. *N Engl J Med* 1977; **296**:1030–1034

18 Williams RC, Opelz G, McGarvey CJ, Weil EJ, Chakkera HA. The risk of transplant failure with HLA mismatch in first adult kidney allografts from deceased donors. *Transplantation* 2016; **100**:1094–1102

19 Doxiadis IIN, De Fijter JW, Mallat MJK, Haasnoot GW, Ringers J, Persijn GG, *et al*. Simpler and equitable allocation of kidneys from postmortem donors primarily based on full HLA-DR compatibility. *Transplantation* 2007; **83**:1207–1213

20 Lim WH, Chapman JR, Coates PT, Lewis JR, Russ GR, Watson N, *et al*. HLA-DQ mismatches and rejection in kidney transplant recipients. *Clin J Am Soc Nephrol* 2016; **11**:875–883

21 Leeaphorn N, Pena JRA, Thamcharoen N, Khankin EV, Pavlakis M, Cardarelli F. HLA-DQ mismatching and kidney transplant outcomes. *Clin J Am Soc Nephrol* 2018; **13**:763–771

22 El-Gezawy EM, Baset HAA, Nasif KA, Osama A, AbdelAzeem HG, Ali M, *et al*. Human leukocyte antigens as a risk factor for the primary diseases leading to end stage renal disease in Egyptian patients. *Egypt J Immunol* 2011; **18**: 13–21.

23 Ravazzi-Gauch C, Bajay MM, Caldas HC, Abbud-Filho M. HLA-A, -B, and -DRB1 allele and haplotype diversity in a cohort of Brazilian renal transplant candidates. *Hum Immunol* 2016; **77**:464–469

24 Saito PK, Yamakawa RH, Noguti EN, Bedendo GB, Júnior WV da S, Yamada SS, *et al*. HLA-A, HLA-B, and HLA-DRB1 allele and haplotype frequencies in renal transplant candidates in a population in Southern Brazil. *J Clin Lab Anal* 2016; **30**:258–265

25 Carvalho AS. HLA-A, –B and –C markers in the Portuguese population. *Tissue Antigens* 1983; **21**:39–44.

26 Ribas F, Oliveira LA, Petzl-Erler ML, Bicalho MG. Major histocompatibility complex class I chain-related gene A polymorphism and linkage disequilibrium with HLA-B alleles in Euro-Brazilians. *Tissue Antigens* 2008; **72**: 532–538

27 Mosaad YM, Mansour M, Al-Muzairai I, Al-Otabi T, Abdul-Moneam M, Al-Attiyah R, *et al*. Association between human leukocyte antigens (HLA-A, –B, and –DR) and end-stage renal disease in Kuwaiti patients awaiting transplantation. *Ren Fail* 2014; **36**:1317–1321.