International Journal of Sciences: Basic and Applied Research (IJSBAR)

ISSN 2307-4531
(Print & Online)

http://gssrr.org/index.php?journal=JournalOfBasicAndApplied

Human Leucocyte Antigens (DRB1*03, DRB1*04 and DQB1*02) Associated with Type 1 Diabetes Mellitus among 269 Kidney Graft Donors and Recipients in Kenya

Dr. Samuel K. Kabinga[a]*, Dr. Anthony Jude O.[b], Prof. Kirana M. Bhatt[c], Prof. Joshua K. Kayima[d], Prof. Seth O. McLigeyo[e]

[a]*Maralal county referral hospital, P.O. Box 18882-00100 Nairobi.*

[b,c,d,e]*Consultant Physician/Nephrologist. Senior lecturer University of Nairobi, College of Health Sciences, School of Medicine, Department of Internal Medicine and Therapeutics. P.O. Box 30197-00100, Nairobi.*

[a]*Email: Kabingas@yahoo.com*

[b]*Email: ajowere@gmail.com*

[c]*Email: kirna.bhatt@uonbi.ac.ke*

[d]*Email: joshuakayima@yahoo.com*

[e]*Email: mcligeyo@yahoo.com*

Abstract

This was a descriptive study which utilized the medical records for the kidney donors and recipients who had been followed up in the kidney transplantation programme in Kenyatta National Hospital, Nairobi, Kenya. Tissue typing is rarely performed routinely among our patients partially due to cost. It is with this in mind that we engaged in extraction of more information from the tissue typing data which have been used in kidney transplantation programme in Kenyatta National Hospital, Nairobi Kenya. The data were extracted from the medical records of patients who had undergone tissue typing for renal transplantation and were on follow up at Kenyatta National Hospital. The study had been cleared by the Kenyatta National Hospital/University of Nairobi Ethics Research Committee, number, P485/9/2013.

---

* Corresponding author.

The medical records had tissue typing done from 2008 and 2013. A total of 269 individuals' human leucocyte antigen typing were utilized. They comprised 134 kidney graft recipients and 135 donors records. The typing had been performed using serology for class I and polymerase chain reaction for Class II respectively. The data were analysed using Statistical Program for Social Sciences, calculating the frequencies of each individual for HLA specificity and expressing it as a percentage of the total population of 269 individuals. For some genes and alleles associated with type 1 diabetes (DRB1*03, DRB1*04 and DQB1*02), there were 184/269 (68.4%) of individuals who carried genes and alleles. Eighty four (84) individuals had HLA-DRB1*03 allele, 22 had DRB1*04 while 78 had DQB1*02. Among 135 kidney graft donors, 39 (28.90%) carried HLA-DRB1*03 and 14 (10.40%) carried DRB1*04. Among 134 kidney graft recipients, 45 (33.57%) had HLA-DRB1*03 and 13 (9.70%) had HLA-DRB1*04. Thirty-six (26.87%) had HLA-DQB1*02.

There is increase in the prevalence of diabetes mellitus among other non-communicable conditions world over. Diabetes has both nature and nurture as players for its causation. Genetics which include human leucocyte antigens have been liked with diabetes. Among our study population, HLA-DRB1*03, HLA-DRB1*04 and HLA-DQB1*02 were prevalent and this may guide surveillance and care for both donors and recipients, as well as inform the care of our wider population.

Keywords: Type 1 diabetes mellitus; Human leucocyte antigens.

1. Introduction

1.1 Type 1 diabetes

Type 1 diabetes mellitus (T1DM) previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes" results from the body's failure to produce insulin, and currently requires the person to inject insulin or wear an insulin pump. There are multifactorial interactions of the genetic, environmental and immunological factors with resultant destruction of the pancreatic beta cells. Individuals with a genetic susceptibility have normal beta cell mass at birth but begin to lose beta cells secondary to autoimmune destruction that occurs over months to years. The temporal development of type 1 DM is a function of beta cell mass. Features of diabetes do not become evident until a majority of beta cells are destroyed (70–80%). At this point, residual functional beta cells exist but are insufficient in number to maintain glucose tolerance [1].

1.2 Human leucocyte antigens and type 1 diabetes mellitus (T1DM)

The major genetic determinants of T1DM are polymorphisms of human leucocyte antigens (HLA) class II genes encoding DQ and DR. Additional moderate HLA risk haplotypes may help identify the majority of children with T1DM before the onset of the disease [2]. Type 1 diabetes mellitus has been associated with Human Leucocyte Antigen (HLA)-DRB1*03, -DRB1*04, -DQB1*02 among others [3]. Howson *et al* found unique diversity of the African HLA region among African-American diabetics, which supports a specific and major role for HLA-DRB1 in HLA-DRB1*03 haplotype-associated T1DM risk [4]. The pattern of HLA distribution was studied in 70 Nigerian diabetics by Famuyiwa *et al*. Comparison of the data with those in other black populations revealed that the over-all pattern of HLA distribution in black diabetics is rather disparate and still relatively ill-defined

and the pattern of HLA and diabetes association in Nigerian diabetics appeared to be different from that in most other racial groups including North American and South African blacks [5].

2. Materials and method

Tissue typing is rarely performed routinely among our patients partially due to cost. It is done in routinely among the kidney donors and recipients for the purposes of guiding the donors and recipients selection. However, the data obtained from the tissue typing have not been utilized in other ways apart from in transplantation. It is with this in mind that we engaged in extraction of more information from the tissue typing data which have been used in kidney transplantation programme in Kenyatta National Hospital, Nairobi Kenya The data were extracted from the medical records of patients who had undergone tissue typing for renal transplantation and were on follow up at Kenyatta National Hospital, a teaching and referral hospital in Kenya, East Africa. The hospital had been performing living-related kidney graft transplantation from 1980s, but the performance had been slow until 2010 when the hospital established a kidney transplant programme in collaboration with a partner. The study had been cleared by the Kenyatta National Hospital/University of Nairobi Ethics Research Committee, number, P485/9/2013.

The medical records had tissue typing done from 2008 and 2013. A total of 269 individuals' human leucocyte antigen typing were got. They comprised 134 kidney graft recipients and 135 donors records were available. The donors were living-related to the recipients. The HLA-A, -B, DRB1 and DQB1 alleles groups at both loci were extracted. The typing had been performed using serology for class I and polymerase chain reaction for Class II respectively. The data were analysed using Statistical Program for Social Sciences, calculating the frequencies of each individual for HLA specificity and expressing it as a percentage of the total population of 269 individuals.

3. Results

Three hundred and three medical records for the kidney transplant donors and recipients were perused for the tissue typing laboratory reports. Thirty four were excluded due to incomplete tissue typing reports and 269 individuals records were used (Figure 1).

*Some genes and alleles associated type 1 diabetes (DRB1*03, DRB1*04 and DQB1*02)*

There were 184/269 (68.4%) of individuals who carried genes and alleles associated with type 1 diabetes mellitus. Eighty four (84) individuals who had HLA-DRB1*03 allele, 22 had DRB1*04 while 78 had DQB1*02. None of the individual had homozygous HLA-DRB1*03 or HLA-DRB1*04. Two (2) of the individuals had homozygous HLA-DQB1*02. Among 135 kidney graft donors, 39 (28.90%) carried HLA-DRB1*03 and 14 (10.40%) carried DRB1*04. (Table 1). Among 134 kidney graft recipients, 45 (33.57%) had HLA-DRB1*03 and 13 (9.70%) had HLA-DRB1*04. Thirty-six (26.87%) had HLA-DQB1*02. Among the 134 kidney graft recipients, 30 had diabetes mellitus as a documented co-morbidity.

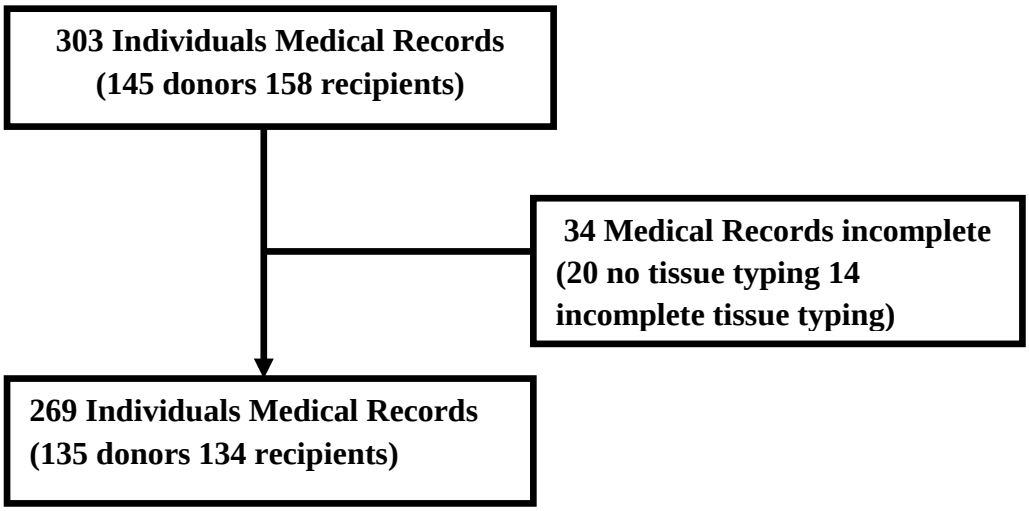

Figure 2: Recruitment flowchart

Table 1: Some genes and alleles associated with type 1 diabetes

S/No	HLA-Gene and Allele	Locus	Sex		Total	
			Male	Female		
1	**DRB1*03**	First	45	22	**67**	
		Second	14	3	**17**	
						84
2	**DRB1*04**	First	12	3	**15**	
		Second	5	2	**7**	
						22
3	**DQB1*02**	First	40	20	**60**	
		Second	11	9	**20**	
						78‡
	Total		**127**	**59**	**186**	**184**

‡ Two individuals were homozygous

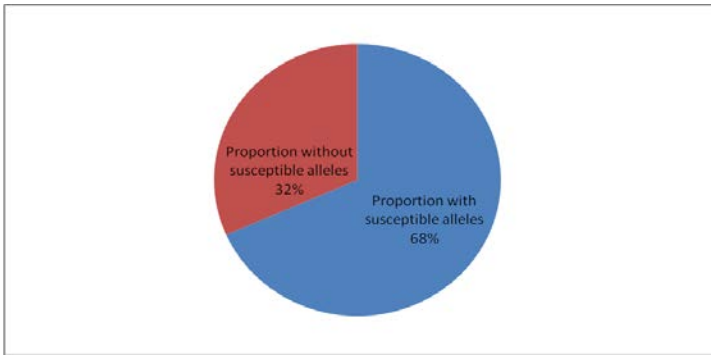

Figure 3: Proportion of the study population who had DRB1*03, DRB1*04 or DQB1*02

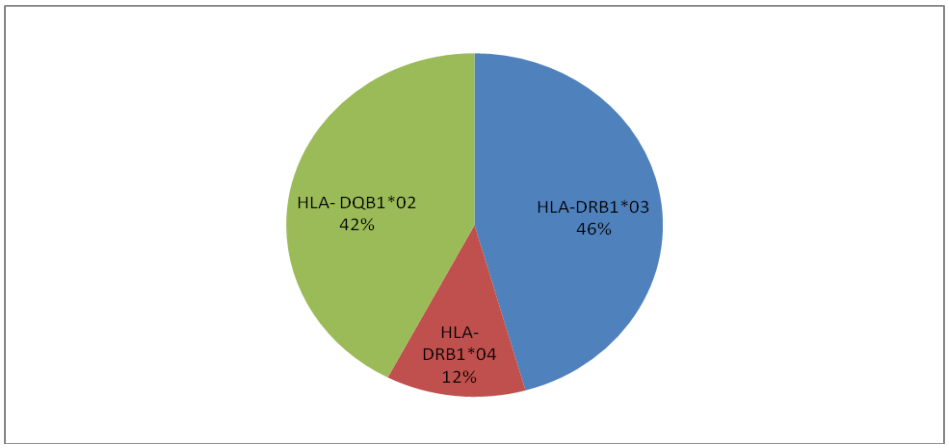

Figure 4: Proportion contributed by each of the three genes and alleles

4. Discussion

Type 1 diabetes mellitus (T1DM) previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes" results from the body's failure to produce insulin, and currently requires the person to inject insulin or wear an insulin pump. There are multifactorial interactions of the genetic, environmental and immunological factors with resultant destruction of the pancreatic beta cells. Individuals with a genetic susceptibility have normal beta cell mass at birth but begin to lose beta cells secondary to autoimmune destruction that occurs over months to years. The temporal development of type 1 DM is a function of beta cell mass. Features of diabetes do not become evident until a majority of beta cells are destroyed (70–80%). At this point, residual functional beta cells exist but are insufficient in number to maintain glucose tolerance [1]. Because the trigger is unknown, the autoimmune process is largely undetected until the point of diagnosis. Some HLA-genes and alleles have been associated with development of Type 1 diabetes. Some of the HLA genes and alleles include HLA-DRB1*03, HLA-DRB1*04 and HLA-DQB1*02. In our study, more than two-thirds, 184/269 (68.4%) of individuals carried these genes and alleles in different combinations. (Figure 2). Among individuals who had any of the three genes and alleles, HLA-DRB1*03 was in 84, HLA-DQB1*02 was in 78 and HLA-DRB1*04 was in 22 individuals.(Figure 3).

There were 84/269 (31.23%) individuals with HLA-DRB1*03 allele. This shows no sex difference in contribution to HLA-DRB1*03 allele. None had homozygous state of this allele. Among the 135 donors, 39 (28.90%) had HLA-DRB1*03. The rest was contributed by the recipients. Among African American patients with Type 1 diabetes J. M. M. Howson *et al* found that HLA-DRB1*03 confers greatest susceptibility to T1D [6]. Areas in the world where HLA-DRB1*03 allele has been found in high frequency include Pakistan Brahui, among rural Asian where Mohyuddin *et al* detected HLA-DRB1*03 at a frequency of 34.5% [7]. The prevalence of diabetes mellitus (DM) and impaired glucose tolerance (IGT) in Parkistan has been reported as glucose intolerance (DM+IGT) was 22.04% in urban and 17.15% in rural areas with major risk factors identified were age, positive family history [8].

There were 22/269 (8.18%) individuals in whom HLA-DRB1*04 was detected in our study. Among the 135

donors, 15 (10.40%) had HLA-DRB1*04. From 134 recipients, 13 (9.70%) had HLA-DRB1*04. The distribution of HLA-DRB1*04 in high frequency compares relatively to areas in the world which have reported highest prevalence of diabetes.

In our study, 78/269 (29.00%) of individuals studied had HLA-DQB1*02 allele. Two (2) of the individuals had homozygous HLA-DQB1*02. Among 134 recipients, 36 (26.87%) had HLA-DQB1*02. From 30 recipients with diabetes mellitus as a documented co-morbidity, 10 (33.33%) had HLA-DQB1*02. HLA-DQB1*02 allele has been reported in frequencies above 25% in several regions of Europe and Asia. It has been reported in frequencies above 25% in few regions in America. In Africa, it has been found in frequencies 36.90% in Aka Pygmies and Bantu Congolese [9] in Ethiopia among the Oromos and Amharas at a frequency of 33.70% [10] and in Arabic-speaking Moroccans it had been reported at 37.80% allelic frequency [11].

5. Conclusion

There is increase in the prevalence of diabetes mellitus among other non-communicable conditions world over. Diabetes has both nature and nurture as players for its causation. Genetics which include human leucocyte antigens have been liked with diabetes. Among our study population, HLA-DRB1*03, HLA-DRB1*04 and HLA-DQB1*02 were prevalent and this may guide surveillance and care for both donors and recipients, as well as inform the care of our wider population.

Acknowledgement

We acknowledge the Kenyatta National Hospital Renal Unit management, the health records and information department for the support they accorded us during the study.

References

[1] Longo, D.L., et al., Harrison's Principles of Internal Medicine. 18 ed. Vol. 1. 2012: The McGraw-Hill Companies.

[2] Noble, J.A. and A.M. Valdes, Genetics of the HLA Region in the Prediction of Type 1 Diabetes. Curr Diab Rep, 2011. **11**(6): p. 533–542.

[3] Guarene, M., et al., Targeting the Immunogenetic Diseases with the Appropriate HLA Molecular Typing: Critical Appraisal on 2666 Patients Typed in One Single Centre. BioMed Research International, 2013.

[4] Howson, J.M.M., et al., HLA class II gene associations in African American Type 1 diabetes reveal a protective HLA-DRB1*03 haplotype. Diabet. Med, 2013. **30**: p. 710 -716.

[5] Famuyiwa, O.O., I.E. Nwabuebo, and A.A. Abioye, Pattern of Histocompatibility (HLA) Antigen Distribution Among Nigerian (West African Black) Diabetics. Diabetes, 1982. **31**: p. 1119-1122.

[6] Howson, J.M.M., et al., HLA class II gene associations in African American Type 1 diabetes reveal a protective HLA-DRB1*03 haplotype. Diabet Med, 2013. **30**: p. 710-716.

[7] Mohyuddin, A., et al., HLA polymorphism in six ethnic groups from Pakistan Tissue Antigens, 2002. **59**(6): p. 492-501.

[8] Lawlor, D.A., et al., Prevalence of diabetes in Pakistan. Diabetes Res Clin Pract, 2007. **76**(2): p. 219-222.

[9] Renquin, J., et al., HLA class II polymorphism in Aka Pygmies and Bantu Congolese and a reassessment of HLA-DRB1 African diversity. Tissue Antigens, 2001. **58**: p. 211-222.

[10] Fort, M., et al., HLA class II allele and haplotype frequencies in Ethiopian Amhara and Oromo populations. Tissue Antigens, 1998. **51**: p. 327-336.

[11] Casado, E.G., et al., HLA genes in Arabic-speaking Moroccans: close relatedness to Berbers and Iberians. Tissue Antigens, 2000. **55**: p. 239-249.

[12] Fokianos, K., I. Sarrou, and I. Pashalidis, Increased radiation exposure by granite used as natural tiling rock in Cypriot houses. Radiation Measurements, 2007. **42**(3): p. 446-448.