HLA-A2 ANTIGEN AS A RISK FACTOR FOR DIABETIC NEPHROPATHY.

thesis

Submitted for partial fulfillement of master degree in internal medicine

By

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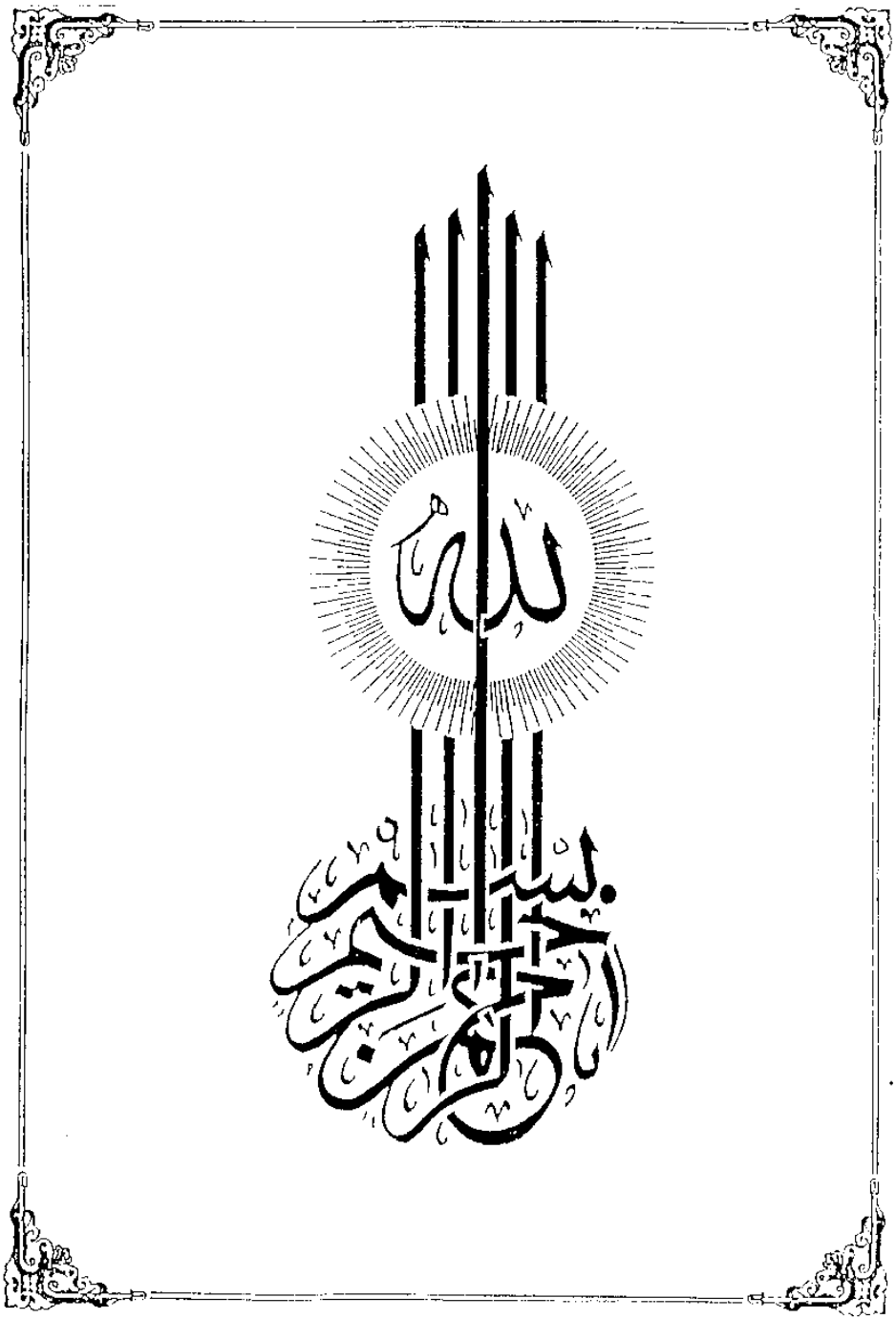
Abreviation

1. *C= Complement*
2. *DM= Diabetes mellitus.*
3. *DN= Diabetic nephropathy.*
4. *ESRF= End stage renal failure.*
5. *FAB= antigen binding fragment.*
6. *FC= Crystallizable fragment.*
7. *F.H= Family history.*
8. *GFR= Glomerular filteration rate.*
9. *HLA= Human leucocyte antigen.*
10. *ICA= Islet cell antibody.*
11. *IDDM= Insulin dependent diabetes mellitus.*
12. *M.HC= Major histocompatibility complex.*
13. *MODY=Maturity anset diabetes of young.*
14. *NIDDM=Non insulin dependent diabetes mellitus.*
15. *PPBS=Post- prandial blood sugar.*
16. *RBF=Renal blood flow.*
17. *UAE= Urinary Albumin excretion.*
18. *WHO= World Health Organization.*



Acknowledgment

I would like to express my deepest gratitude to ***Prof.Dr. Mohamed Fayed,*** *Assistant professor of internal medicine and nephrology, Faculty of medicine, Ain Shams University, for his great help and continuous valuable advice throughout the work.*

Also, I would like to express my deep appreciation to ***Prof.Dr. Alaa El-Din Ali Abdul-Rahman,*** *Assistant professor of internal medicine and nephrology, Faculty of medicine, Ain Shams University, for his help, advice, and valuable supervision.*

I am honoured to be supervised by ***Prof.Dr. Narges Mohamed Elaish,*** *Assistant professor of microbiology and immunology, Faculty of medicine, Ain Shams University, for her encouragement and guidance.*

I wish to thank ***Prof.Dr. Fadila Gad-Allah,*** *assistant prof of internal medicine and endocrinology, Faculty of medicine, Ain Shams University for her valuable advice throughout this work.*

Also thanks to ***Dr. Mohamed Abdul-Ghany,*** *Lecturer of internal medicine, Ain Shams University for his help and encouragement.*

Content

INTRODUCTION AND AIM OF THE WORK

Introduction

Diabetic nephropathy is a devastating complication of diabetes **(Jennies et al., 1987)** *and is one of the leading indication for dialysis and kidney transplantation* **(Friedman, 1985)**.

Natural history studies suggest that diabetic nephropathy, develop in 30 to 50 percent of diabetic persons **(Krolewski et al., 1985)**. *A patient usually has diabetes for several years before the clinical manifestations of nephropathy are apparent. Why some diabetic persons are susceptible to diabetic nephropathy and others are not.*

Many believe that hypertension **(Andersen et al., 1983)** *and poor glycemic control lead to nephropathy, but attention has recently turned to factors that can not be altered b y therapy* **(Seaquist et al., 1989)**. *In a study of familial clustering of nephropathy, seaquist et al., 1989 found that the prevalence of nephropathy was 83% in diabetic siblings to patients who had already developed diabetic nephropathy, while the prevalence was only 17% in diabetic siblings to normoalbuminuric diabetic patients. The inheritance of the susceptibility to diabetic nephropathy may be independent of the inheritance of factors that put a patient at risk for development of diabetes itself. Recent work showed that there is high incidence of HLA - A2 in patients with diabetes and microalbuminuria* **(Watts et al., 1992)**.

Aim of this work

The aim of this work is to study the role of HLA -A2 in pathogenesis of diabatic nephropathy.

REVIEW OF LITERATURE

Major Histocompatibility System

The HLA system is the major histocompatibility system or complex in man, which is localized on the short arm of chromosome number 6 **(Lamm, et al., 1974)**. *Three types of molecules are associated with MHC class I molecules, class II molecules and some complement components (class III molecules) as shown in Figure I.*

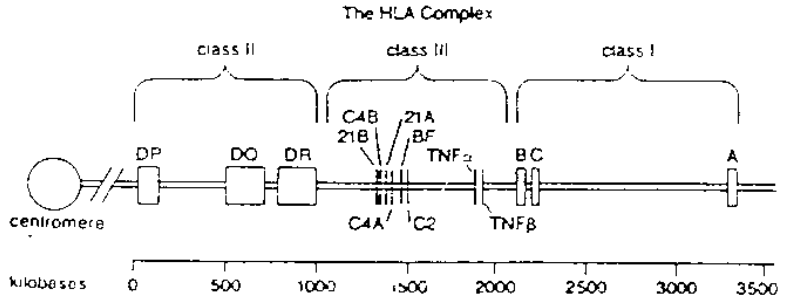


Figure I : Genetic makeup of the HLA region

The HLA complex is found on the short arm of chromosome 6. 21A and 21B are 21-hydroxylase A and B, respectively. BF is properidin factor, and BG is the alternative complement pathway. C2, C4A, andC4B are complement components. TNFα and TNFβ are tumor necrosis factor α and β, respectively. The DP, DQ and DR subregions each contain multiple loci.

Class I antigens:

These antigens are coded for the A, B and C molecules and were the first series of HLA antigens to be detected, the A and B loci were detected in 1968

(Kissmeyer - Nielsen et al., 1968) *while the C locus was detected in 1970* **(Sandberg et al., 1970)**. *Class I molecules consist of two polypeptide chains in monovalent association on cell surfaces. The heavy (44,000 daltons) chain is inserted into the plasma membrane and contain the antigenic portions while the light (12.000 dalten) chain is B-micro-globulin.*

Class I antigens are expressed on all cells except mature erythrocytes in man **(Hart et al., 1981)**.

In the kidney, by the use of monoclonal antibodies antigens have been shown to be expressed on the endothelium of all blood vesseles, on the tubules, on the mesangium and dendritic cells **(Braun, 1983)**. *Class I molecules are serologically detected (S.D) utilizing the whole blood lymphocytes, human allo antisera specific for each of the antigen to be detected and rabbit complement. Antibodies against the HLA, A B and C specificities are commonly found in the sera of women who have several pregnancies, or in individuals receiving an organ transplant or numerous transfusions. Most commonly, sera are collected from multigravida women.*

Class II antigens:

Class II molecules consists of two membrane- inserted and noncovalently associated glycosylated polypeptides, called α (34,000 daltons) and B (28,000 daltons).

In the early 1973, the determinant (HLA-D) responsible for the initiation of the mixed lymphocyte culture (MLC) response were identified **(Dupont et al., 1973)**. *These determinants, which are found on B but not on resting T lymphocytes, stimulate cells from individuals who do not possess the same determinant (S).*

The DR antigens were serologically detected and organized into a system of allelic antigens in 1977 **(Bodmer et al., 1977)**. *The DC (also called MT or MB) system of antigens were recognized in 1979* **(Duquesnoy et al., 1979)**. *The SB antigens were initially defined by the primed lymphocyte typing (PLT) test* **(Shaw et al., 1980)** *and only some of them have been detected serologically* **(Van leeuwen et al., 1982)**. *Class II MHC molecules are expressed on B lymphocyte cells, macrophages, monocytes, various antigen-presenting cells and activated T lymphocytes. The class II (D-region) antigens are coded for three loci, DP (formerly SB), DQ (formely DC, MB, MT) and DR. A separate locus (formly D) coding for determinants*

responsible for stimulation in the mixed lymphocyte culture reaction probably does not exist and stimulation is caused by antigens of the DQ and DR systems.

C. Class III antigens:

A number of the complement system components, including C2, C4 and factor B, are encoded within the MHC and located between class I and class II loci. These are referred to as class III molecules.

Other genes within the HLA region:

The enzyme steroid 21- hydroxylase placed between class I and class II, the deficiency of which produces congenital adrenal hyperplasia (Dupont et al., 1977). The second, genes for the two tumor necrosis factors, TNF-α (Tumor necrosis factor α), and TNF-B (Tumor necrosis factor B are adjacent to HLA-B **(Spies et al., 1986)**.

Table (1): Complete listing of recognized HLA specificities

(Bodmer et al., 1989).

A	B		C	D	DR	DQ	DP
A1	B5	B51(5)	CW1	DW1	DR1	DQW1	DPW1
A2	B7	BW52(5)	CW2	DW2	DR2	DQW2	DPW2
A3	B8	BW53	CW3	DW3	DR3	DQW3	DPW3
A9	B12	BW54(W22)	CW4	DW4	DR4	DQW4	DPW4
A10	B13	BW55(W22)	CW5	DW5	DR5	DQW5(W1)	DPW5
A11	B14	BW56(W22)	CW6	DW6	DRW6	DQW6(W1)	DPW6
AW19	B15	BW57(17)	CW7	DW7	DR7	DQW7(W3)	
A23 (9)	B16	BW58(17)	CW8	DW8	DRW8	DQW8(W3)	
A24 (9)	B17	BW59	CW9(W3)	DW9	DR9	DQW9(W3)	
A25 (10)	B18	BW60(40)	CW10(W3)	DW10	DRW10		
A26 (10)	B21	BW61(40)	CW11	DW11(W7)	DRW11(5)		
A28	BW22	BW62(15)		DW12	DR W12(5)		
A29(W19)	B27	BW63(15)		DW13	DRW13(W6)		
A30(W19)	B35	BW64(14)		DW14	DRW14(W6)		
A31(W19)	B37	BW65(14)		DW15	DRW15(2)		
A32(W19)	B38(16)	BW67		DW16	DRW16(2)		
AW33(W19)	B39(16)	BW71(W70)		DW17(W7)	DRW17(3)		
AW34(10)	B40	BW70		DW18(W6)	DRW18(3)		
AW36	BW41	BW72(W70)		DW19(W26)			
AW43	BW42	BW73		DW20	DRW52		
AW66(10)	B44(12)	BW75(15)		DW21	DRW53		
AW68(28)	B45(12)	BW67(15)		DW22			
AW69(28)	BW46	BW77(15)		DW23			
AW74(W19)	BW47			DW24			
	BW48	BW4		DW25			
	B49(21)	BW6		DW26			
	BW50(21)						

Numbers in parentheses indicate parent HLA antigen from which these antigens split.

Table (2): Splits of HLA specificities **(Bodmer et al., 1989).**

Original Broad Specificities	Splits
A9	*A23, A24*
A10	*A25, A26, AW34, AW66*
AW19	*A29, A30, A31, A32, AW33, AW74*
A28	*AW68, AW69*
B5	*B51, BW52*
B12	*B44, B45*
B14	*BW64, BW65*
B15	*BW62, BW63, BW75, BW76, BW77*
B16	*B38, B39*
B17	*BW57, BW58*
B21	*B49, BW50*
B21	*B49, BW50*
BW22	*BW54, BW55, BW56*
B40	*BW60, BW61*
BW70	*BW71, BW72*
CW3	*CW9, CW10*
DR2	*DRW15, DRW16*
DR3	*DRW17,DRW18*
DR5	*DRW11, DRW12*
DRW6	*DRW13, DRW14*
DQW1	*DQW5, DQW6*
DQW3	*DQW7, DQW8, DQW9*
DW6	*DW18, DW19*
DW7	*DW11, DW17*