Study of Some Aspects of Renal Function in Insulin-dependent Diabetes Mellitus (I.D.D.M)

THESIS

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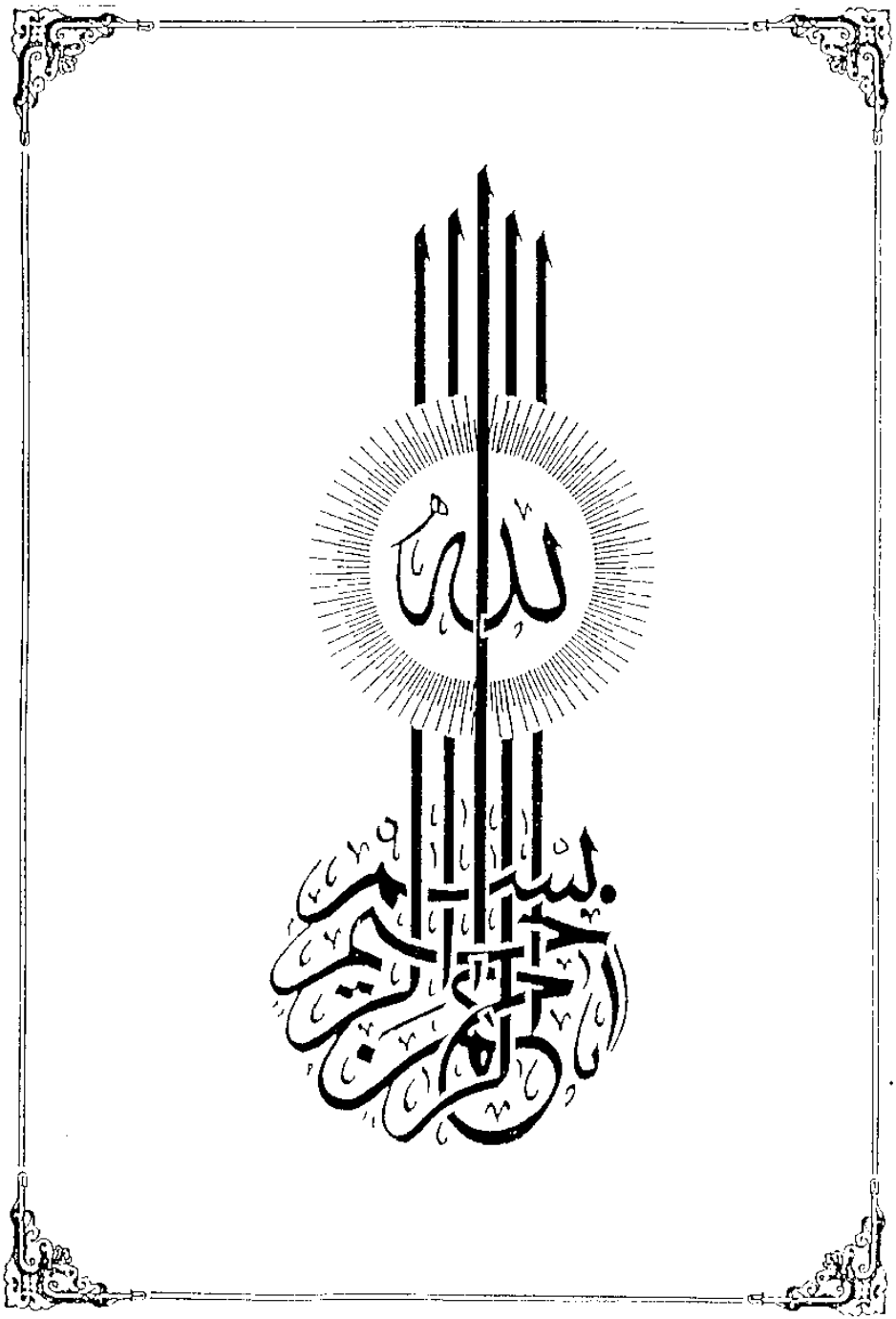
بسم الله الرحمن الرحيم

وما اوتيتم من العلم إلا قليلا

صدق الله العظيم

سورة الإسراء (آية ٨٥)



To My Parents

With Love and Affection

Acknowledgement

Thanks first to God.

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CONTENTS

LIST OF ABBREVIATIONS

BUN	Blood Urea Nitrogen
CFT	Complement Fixation Test
ELISA	Enzyme Linked Immunosorbent Assay
EMC	Encephalomyocarditis virus
GBM	Glomerular Basement Membrane
GFR	Glomerular Filtration Rate
HLA	Histocompatibility loci Antigen
ICAB	Islet-Cell Antibodies
IDDM	Insulin Dependent Diabetes Mellitus
IEC	Ion Exchange Chromatography
IGT	Impaired Glucose Tolerance
NDDG	National Diabetes Data Group
OGTT	Oral Glucose Tolerance Test
PAS	Para Amino Salicylic acid
WHO	World Health Organization

INTRODUCTION & AIM OF WORK

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Type I diabetes is a syndrome characterized by a sudden clinical onset, severe hyperglycaemia, easy appearance of ketoacidosis, and severe insulin deficiency ***(Genuth, 1982)***.

It is estimated that approximately 50 percent of all patients with type I diabetes mellitus develop uremia during the course of their disease, the most prevalent cause of this uremia is diabetic neprhopathy ***(Beyer, 1984)***.

So, it is important to study some aspects of renal function in insulin dependent diabetic children in order to detect early cases of diabetic nephropathy that require early management.

REVIEW OF LITERATURE

HISTORICAL REVIEW

Diabetes mellitus has been known since antiquity. The first accurate clinical description of the disease was made by Aretaeus of Cappadocia in the second century A.D., who stated that diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine ***(George and Cahill, 1985)***.

Now insulin dependent diabetes mellitus (IDDM) is defined as a syndrome characterized by sudden clinical onset, severe hyperglycemia, easy appearance of keto-acidosis and severe insulin deficiency ***(Gorsuch et al., 1981)***.

Insulin dependent diabetes mellitus (IDDM) defines a group of patients who are usually, but not necessarily, under 30 years of age at the time of diagnosis. They generally present with an accelerating history of glucosuric symptoms for less than three months. They are thin and almost invariably exhibit weight loss. Only rarely such patients are discovered by testing for diabetes when they are asymptomatic ***(Fajans et al., 1976)***.

Though a positive family history of diabetes may be present, only 10% of such patients have either a diabetic parent or a diabetic sibling ***(Fajans et al., 1978)***.

Anatomically, the islets are small and devoid of beta cells, though hyperplasia of other islet cells that produce glucagon, somatostatin and pancreatic polypeptide is often seen ***(Gepts et al., 1977)***. Ultimately, the beta cell function disappears as shown by low plasma levels of the connecting peptide molecule (c. peptide) which normally co-secreted with insulin ***(Malmquist et al., 1982)***.

Functionally, IDDM is characterized by insulinopenia. Fasting plasma insulin levels are low, and there is little or no response to challenge with glucose, aminoacids, talbutamide, glucagon or other beta cell stimulants ***(Genuth, 1982)***.

It was reported that IDDM is the commonest endocrine disorder in childhood with frequent secondary complications ***(Porte and Halter, 1981)***.

A well defined subgroup of youthful-onset diabetics, sometimes known as MODY (maturity-onset diabetes of youth) or NIDDY (non-insulin dependent diabetes of youth), may be diagnosed in their teens. Though these patients are usually treated with insulin, they are able to survive without it ***(Tattersall, 1974 and Fajans et al., 1978)***.

GENETIC SUSCEPTIBILITY AND INHERITANCE OF IDDM

The discovery of ***Singal and Blajchman (1973),*** and of ***Nerup et al., (1974),*** that insulin dependent diabetes mellitus is associated with HLA-B_8 and HLA-B_{15} was an important step forward towards understanding the genetics of diabetes mellitus. First of all, these studies showed clearly that these associations hold only for the insulin dependent form of diabetes and not for the non-insulin dependent form which usually occurs at a later age, and thus proved that the genetic backgrounds of these two disorders are different.

Numerous studies have confirmed the association between HLA and insulin dependent diabetes mellitus ***(Ryder et al., 1979 and Christy et al., 1979).***

In ***1975, Thomsen et al.,*** provided evidence that the associations with HLA-B_8 and B_{15} are secondary to stronger associations with the HLA-D antigens, DW_3 and DW_4 respectively, and this has been confirmed both by HLA-D and DR typing ***(Svejgaard et al., 1979).***

Svejgaard et al., (1980) studied a large number of insulin dependent diabetic patients represent the three major ethnic groups of the world, caucasians, blacks and orientals provided HLA data and he found that:

- HLA-DR_2 antigen occurs with decreased frequency and the DR_3 and DR_4 antigens with increased frequencies in all the three ethnic groups of IDDM patients.
- The DR_8 antigen has increased frequencies in Japanese and blacks.

So, from these results ***Svejgaard, (1980)*** concluded that there is one or more genes conferring susceptibility to IDDM within the HLA system which must be of major effect in the development of the disease. These genes may be the DR_3, DR_4, and DR_8.

Platz et al., (1981) concluded that 93% of IDDM patients are DR_3 and/or DR_4 as compared to only 57% of controls.

Rotter et al., (1983) concluded that there are complex modes of inheritance of HLA-linked IDDM susceptibility such as the presence of two different diabetogenic alleles or multiple loci. He also found that within families where one or more member had IDDM, HLA typing can identify those members at greatest risk of developing IDDM.

Salah El Din, (1981), studied HLA-A and B antigens in Egyptian IDDM patients. He reported that the relative risk of HLA-B_{15} and B_{18} were significantly high in IDDM patients.

AUTOIMMUNITY AND DIABETES

Freytag et al., (1974), stated that there are several mechanisms by which a virus infection may produce the subsequent development of immunologic events in the pancreas and other organs. These mechanisms include:

1. Formation of new antigenic sites in cellular proteins.
2. The production of cell-specific antibodies directed against pancreatic islets.
3. A non specific action of virus infection that may lead to loss of immunologic tolerance.

Lendrum et al., (1975) reported that 48 percent of children with diabetes mellitus of recent onset had pancreatic islet-cell antibodies (ICAB).

These ICAB fix their complement, that react with all known types of endocrine cells within the islet ***(Bottazo et al., 1976)***. These ICAB are directed against cytoplasmic components of islet cells ***(Lendrum et al., 1976)***. At the time of diagnosis of IDDM, ICAB are detectable as high as 85% of patients. The percentage drops to 50 percent by one month and remains at this level for the first year ***(Lendrum et al., 1976)***.

Irvine et al., (1976), found that frequencies of ICAB in insulin-dependent diabetics with or without other clinical organ specific autoimmune disorders were similar