STUDY OF IMMUNOGLOBULIN IgD IN DIABETES MELLITUS

THESIS

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BY Hussain

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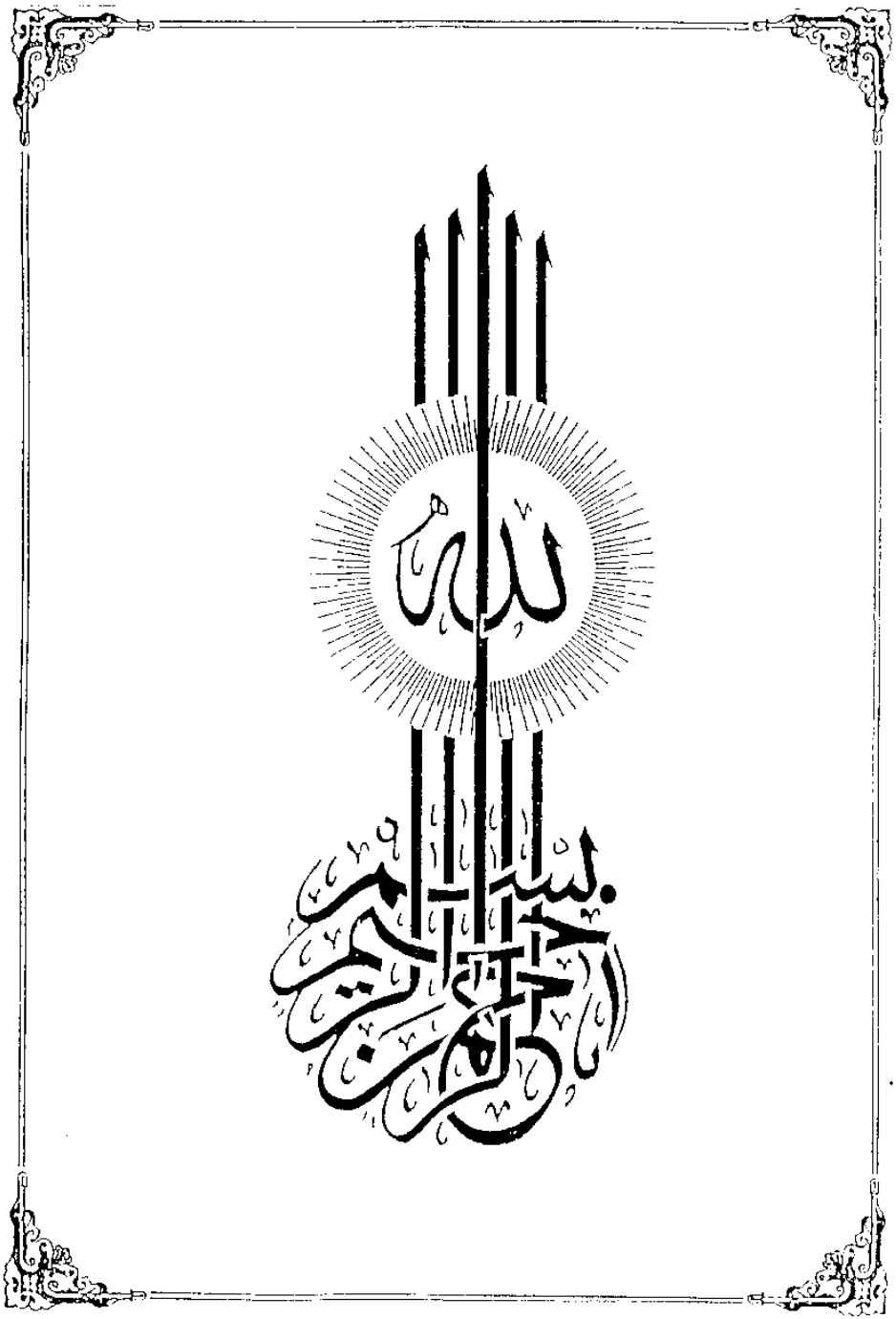
THIS WORK IS DEDICATED TO
MY HOMELAND



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CONTENT

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Introduction
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AIM OF WORK

INTRODUCTION AND AIM OF THE WORK

The relation between diabetes mellitus and the immune system was under investigation for the last two decades, Boitt (1983). Many articles and research works were devoted to point out in strong clear cut the relation between the different types of diabetes (insulin dependent or type I and insulin independent type II) and the immune system. Search for immunoglobulin level (IgG, IgA and IgM) was heavily studied in both types. The immune complex abnormalities and islet cells antibodies were still included in this heavy exhaustive works.

The HLA system has not escaped from these massive studies and significant relation could be proved in some of these studies between the HLA - B8 and Bl5 with type I diabetes,. Nerup, et al. (1974).

The role of IgD in these studies was not clearly studied if ever and so it becomes the aim of this work.

Review

DIABETES MELLITUS

Diabetes mellitus has been known since antiquity (Wrenshall et al., 1982). Reference is made in the Papyrus Ebers (1500 B.C.) to "A medicine to drive away the passing of too much urine". The first accurate clinical description of the disease was made by Aretaeus of Cappadocia in the second century A.D. who stated. "Diabetes is a wonderful affection, not very frequent among men, being a melting down of flesh and limbs into urine". The early references to diabetes most certainly were to the ketoacidotic form of the disease. Thomas Willis described the sweet character of the urine in diabetes in the later part of the seventeenth century. He recognized that diabetes was rare among ancients "but in our age given to good fellowship and guzzling down chiefly unallayed wine, we meet with examples and instances enough". He undoubtedly was describing the increasing frequency of a nonketotic form of the disease. Throughout the course of history, diabetes mellitus was thought to be a single disease entity. The concept nowadays is that diabetes mellitus is not a single disease, but rather a clinical syndrome characterized by inappropriately elevated fasting and/or postprandial blood glucose and the development of longterm microvascular, macrovascular, and neuropathic changes is of very recent origin and stems for numerous

investigation into the epidemiology, genetics, etiology and pathogenesis of clinical states (Harold E. Leboritz, 1984).

Classification:

The traditional classification of clinical diabetes mellitus is based on age of onset and recognizes juvenil-onset (J.O.D.) and maturity-onset diabetes (M.O.D.) varieties. A further presentation of diabetes in young described maturity onset diabetes of young (M.O.D.Y.), Tattersal and Fajans, (1975). This condition may be more common than we realize. The onset is early in life, serious ketosis does not occur and long term complication are infrequent although not absent. Obesity is a characteristic feature and insulin is probably not required in treatment. The MODY varient is inherited as an autosomal dominant trait, where as inheritance of the classic varieties of diabetes is multifactorial. A few rare syndromes has been described in which a JOD type of disease associated with other conditions is inherited as an autosomal recessive trait (Page M.M. et al., 1976). The DIDMOAD syndrome is one example of this group and comprises diabetes insipidus dibetes mellitus, optic atrophy and deafness. Another is the association of diabetes mellitus with Friederich's ataxia, where the inheritance is again

recessive. These syndromes are of considerable interest because they provide an opportunity to study patients with diabetes in whom heredity seems to be the sole aetiological factor. However the pathogenesis of these disorders remain unknown.

The term "Juvenile" and "Maturity" onset are now regarded as unsatisfactory and misleading. Some patients, mature in years, may develop diabetes that is insulin dependent and the presentation of a maturity onset in the young is refered to above. Cudworth and Woodrow (1976) have pointed out that insulin-dependent diabetics over the age of thirty at the time of diagnosis are genetically similar to insulin-dependent diabetics diagnosed before that age at least in respect of HLA haplotype.New information on genetic and immunological mechanism in diabetes mellitus have led to the need for a revised classification. Furthermore the terms previously used to describe the various types of subclinical diabetes (Prediabetes, potential-diabetes, latent diabetes) need to be more clearly defined. Cudworth (1976) proposed the term "Type I" to describe all insulin-dependent patients, regardless of age. Bottazzo and Daniach (1976) further subdivided type I diabetes into IA and IB. Both of these sub-groups show the presence of circulating pancreatic islet cell antibodies (ICA) immediately after

the onset of the disease, but in type IA they are transient. In type IB ICA may be detected long before the onset and may persist for many years afterward. Autoimmune antibodies to other endocrine tissues are also found in type IB diabetes and it seems certain that although insulinopenia is present in both subtypes, their pathogenesis is entirely different. Type II diabetes (Gudworth, 1976) included those patients previously classified as MOD. These patients are not insulin-dependent and may be controlled by diet alone or with the aid of oral hypoglycaemic agents. Type II diabetes in general, a disease of late life, is usually associated with obesity and has no association with any HLA antigen. Insulinopenia is not present (except in late stages) although there is a blunted or delayed insulin response to a glucose stimulus. The insulin response to Arginine and to tolbutamide is normal in these individuals so the inherited deficiency of B-cell receptor may be specific for glucose. Another major defect seems to be in the biological effectiveness of circulating insulin. This cellular insensitivity is caused mainly by a change in the insulin receptor sites associated with obesity, but may also be related to premature cellular aging.

With all these considerations in mind, a revised classification of diabetes mellitus has been proposed. According to Genuth et al. (1983) diabetes is classified into:

A- Idiopathic:

- Insulin dependent (type I).
- Non-insulin dependent (type II).
- Maturity onset diabetes of youth (MODY).

B- Secondary:

- Pancreatic trauma, disease or resection.
- Hormone-induced.
- Drugs and chemical agents.
- Genetic syndromes.
- Insulin receptor abnormalities.
- Other types.

The medical and sientific section of the British Diabetic Association has suggested another classification (1978). This classification was produced by a workshop of European and North American contributers and is presented in this table.

1. Primary diabetes mellitus:

a) Type I: Insulin-dependent diabetes (IDD) can be further subdivided into:

Type IA: Transient ICA; no autoimmune features.

Type IB: Persistent ICA: other immune features.

Type IC: No ICA or other immune features.

b) **Type II:** Non-insulin dependent (NIDD) can be further subdivided into:

Obese.

Non-obese.

c) Impaired glucose tolerence (I.G.T.).

d) Gestational diabetes mellitus.

e) Latent diabetes.

f) Potential abnormality.

2. **Secondary diabetes mellitus:**

a) Hormonal.

b) Drug-induced.

c) Pancreatic disease.

d) Genetical and chromosomal syndromes.

e) insulin receptor abnormalities.

f) Other types.

Primary diabetes mellitus:

The typical features of the two main clinical syndrome, type I and II are listed in the table No. (1).

Table (I)

Type I	Type II
- Under weight - Young (usually less than 30) - Peak age onset 12-14 years	- Over weight or of normal weight. - Older age groups. - Incidence rises with age, peak age onset more than 50 years.
- Onset usually rapid - Peak incidence autumn and winter - Ketosis prone	- Onset insidious - No seasonal incidence - Ketotic only if acute or severe infection, trauma etc. is present
- Low or absent endogenous Insulin secreation	- Normal or increased endogenous Insulin secretion in earlier stages; in the more advanced stages insulin secration is low
- B-cell mass less than 10% - Treatment with insulin is necessary, but may not be required at the onset	- B-cell mass moderately reduced - Treatment with diet alone or diet and oral drugs. Insulin required only temporarily to cover infections trauma etc.
- Insulin-sensitive	- Tendency to insulin-resistence increases with obesity.
- Anti-pancreatic cell-mediated immunity frequent at onset. Antibodies to islet cell frequent at onset.	- No autoimmune features
- HLA association	- No HLA association

In the early stages of type I diabetes, insulin requirements may fluctuate markedly, and it is not unusual for the daily insulin requirement to fall to very low levels for some weeks or months after the initial acute hyperglycaemic episode has been corrected. This "honeymoon" period reflects in part a reduction of glucagon secretion (high during