STUDY OF THE LOCAL IMMUNOGLOBULINS IN GASTRIC ANTRAL MUCOSA IN DIABETIC PATIENTS

THESIS

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BY

AMANY TALAAT KAMAL HANNA
M.B.B.Ch.

616.46233
A.T

Supervisors

Prof. Dr. Soheir Shoeir
Head of Department of
Gastroenterology
Faculty of Medicine
Ain Shams University

Prof. Dr. Motasseim Amer
Prof. of Internal Medicine

Faculty of Medicine
Ain Shams University

Prof. Dr. Samia Amar
Prof. of Pathology

Faculty of Medicine
Ain Shams University

Dr. Emad Barkat
Assistant Prof. of
Internal Medicine
Faculty of Medicine
Ain Shams University

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

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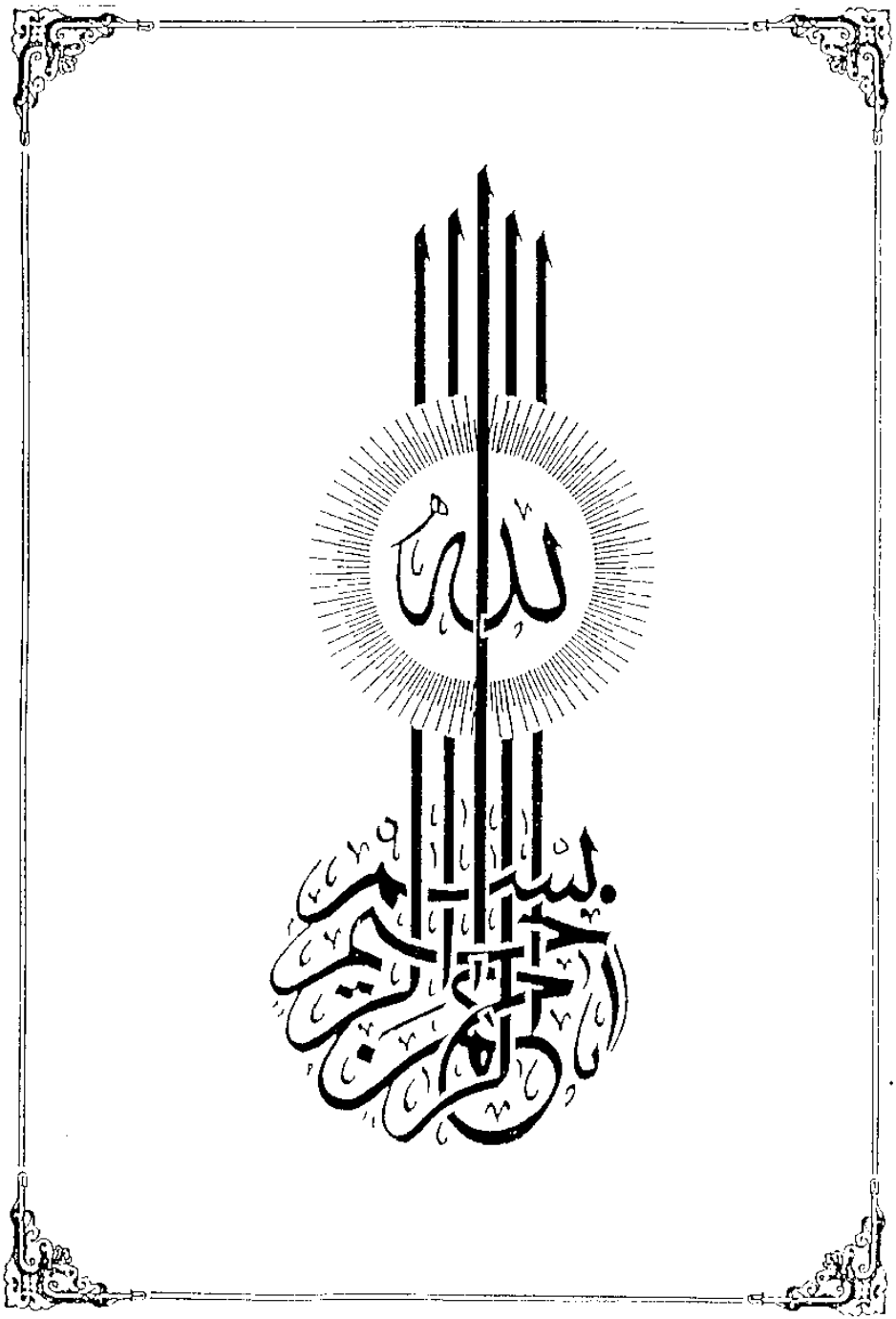

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INTRODUCTION

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INTRODUCTION

Diabetes mellitus is the most common of the serious metabolic diseases of humans. It is a heterogenous primary disorder of carbohydrate metabolism with multiple oetiologic factors that generally involve absolute or relative insulin deficiency or insulin resistance or both. All causes of diabetes ultimately lead to hperglycemia, which is the hallmark of this disease syndrome (Olefsky, 1988).

Since the availability of insulin, deaths from acute metabolic complications have markedly decreased thus leading to increasing, disability and deaths resulting from the degenerative complications of the disease. Traditionally, retinopathy, neuropathy and nephropathy have been designated microvascular complications while atherosclerosis and its sequelae have been called macro-vascular complications (Unger and Foster; 1985).

Ideally, in order to be considered an auto-immune disease, a pathologic process should meet a series of criteria, delineated by Milgrom and Witebsky (1962). Diabetes mellitus fulfills some, but not all of these criteria. Insulinitis, the name used since 1940 to describe the lesion of the islets of langerhans in diabetics, may be the result of an environmental aggressor such as a virus acting either directly or by triggering an auto immune

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reaction resulting in beta cell damage and death. The predisposition to develop this auto-immune reaction may be determined partially by genetic factors. (Kaldany et al., 1982).

The presence in the sera of diabetic patients of many auto antibodies, such as islet cell antibodies (Bottazzo et al., 1973), islet cell surface antibodies (Pujol-Borrell et al., 1982), and isulin auto antibodies (Palmer et al., 1983) was detected by many research works since the early seventies.

The possibility of these antibodies causing B-cell damage ending in the diabetic state or being just a reflection of an ongoing cell damage is still a matter of controversy.

Moreover, circulating auto-antibodies to thyroglobulin, thyroid cells and adrenal gland and other endocrine glands have been found in the serum of some diabetics, usually in conjunction with islet cell antibodies. (Irvine et al., 1977).

Therefore, the aim of this work was to study the normally occurring immunoglobulins of the gastric antral mucosa in diabetics to detect any change in their pattern which may affect the G-cells of the antrum which are considered part of the endocrine system of the body.

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REVIEW OF LITERATURE

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DIABETES MELLITUS

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Definition:

Diabetes mellitus is a heterogenous primary group of disorder of carbohydrate metabolism with multiple aetiologic factors that generally involve absolute or relative insulin deficiency or insulin resistance or both. All causes of diabetes ultimately lead to hyperglycemia, which is the hallmark of this disease syndrome (Olefsky, 1988).

Diabetes tends to run in families. It is associated with accelerated atherosclerosis and predisposes to specific microvascular abnormalities including retinopathy, nephropathy and neuropathy. It doubles the risk for stroke, increases the risk for heart attacks 2-3 folds, and for peripheral vascular problems, particularly in the feet, 50 fold. It wipes out the relative protection that normal young females have against developing coronary artery disease, so that males and females are at equal risk, with the males 2-3 times the non-diabetic males, and the females 20 times the non-diabetic females. There are other problems, such as lessening the resistance to infection, especially if the diabetes is uncontrolled (Cahill, 1985).

Classification and Diagnosis:

The currently accepted classification and criteria for the diagnosis of diabetes mellitus are based on the 1979 report of the National Diabetes Data Group (NDDG, 1979) and

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are comparable to the standards set forth by the world Health organisation (WHO, 1980).

This is shown in the following tables:

Table (1) Classification of Diabetes (NDDG, 1979)

I. *Idiopathic diabetes mellitus.*
   1. Insulin dependent (IDDM) or type I
   2. Non-insulin dependent (NIDDM) or type II
      a. Non-obese
      b. Obese

II. Gestational diabetes

III. Impaired glucose tolerance.

IV. Previous abnormality of glucose tolerance.

V. Potential abnormality of glucose tolerance.

VI. Secondary diabetes.

In the NDDG classification and most previous ones, IDDM and type I diabetes are used synonymously. Similarly, NIDDM and type II diabetes are equivalent terms. Keen (1982) and Foster (1987) criticized this practice since some patients with apparently non insulin dependent diabetes may become fully insulin dependent and ketosis prone. SO, Unger and Foster (1985) suggested that the term insulin dependent diabetes (IDDM) is applied to all forms of diabetes in which exogenous insulin is required to prevent diabetic ketoacidosis irrespective of aetiology, and non-insulin dependent diabetes (NIDDM) is applied to any form of diabetes irrespective of aetiology, in which

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endogenous insulin production is sufficient to prevent diabetic ketoacidosis. On the other hand, the term type I and type II is applied according to the pathogenetic mechanism, where type I refers to the common form of IDDM expressing HLADR3 and/or DR4, while type II is restricted to the NIDDM patients who do not meet the criteria for type I and do not have secondary diabetes.

Foster (1987) used such a classification to suggest three major forms of primary diabetes:

1. Type I insulin dependent diabetes,
2. Type I non-insulin dependent diabetes,
3. Type II non-insulin dependent diabetes.

Were category (2) can be considered as type I insulin dependent diabetes in evolution i.e. auto immune B-cell destruction occurs slowly.

Table (2) Criteria for the diagnosis of Diabetes

(NDDG, 1979)

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1. Fasting plasma glucose > 140 mg/dl on at least two occasions.
2. Oral glucose tolerance test (OGTT), using 1.75 gm glucose/kg body weight; 75 gm glucose maximum.
   a. Diabetes mellitus: plasma glucose > 200 mg/dl at two hours and one other point in the test.
   b. Impaired glucose tolerance: plasma glucose between 140 and 200 mg/dl at two hours and>200 mg/dl between zero time and two hours.
   c. Gestational diabetes: two or more values greater than:
      Fasting: 105 mg/dl
      1 hour : 190 mg/dl
      2 hour : 165 mg/dl
      3 hour : 145 mg/dl

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Genetics and aetiology of the different types of Diabetes:

Type I (IDDM)

Inheritence:

Evidence regarding the aetiology suggests genetic and environmental factors and abnormal immune response. Although IDDM aggregates in families, the mechanism of inheritance is unclear in mendalian terms. Transmission may be autosomal dominant, recessive or mixed. Genetic predisposition is permissive, not causal, as the concordance rate for diabetes mellitus in identical twins is not more than 50% (Foster, 1987).

Association of IDDM susceptibility and HLA genes:

There are strong associations between susceptibility and specific alleles of HLA genes. The first identified associations of HLA with IDDM susceptibility were positive with class I alleles B8 and B15 and negative with B7. With the definition of the class II specificities, stronger positive associations with DR3 and DR4 and negative associations with DR2, DR5 and DR7 were demonstrated in numerous studies, weaker positive associations with DR1 and possibly with DRw8 have been suggested (Thomson, 1984). Recent data suggest that the primary association may be with DQ rather than DR. DR4 is usually associated with the

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DQw3 specificity, DQw3 has been subdivided, and the DR4-DQw3.2 (DR4-DQR4) subset may be associated with susceptibility to IDDM, whereas the DR4-DQw3.1 (DR4-DQR5) subset is associated with nonsusceptibility (Schreuder, 1986). DR2, DR5, DR7 and B7 alleles have been called protective since they are found with less frequency in diabetics than in the general population. It is likely that they are actually low risk alleles because they are present in inverse relationship with DR3 and DR4 (the high risk alleles) (Foster, 1987).

Heterogeneity within IDDM:

Bottazzo and Doniach (1976) and Macleod (1986) suggested the terms types IA and IB on the basis of whether islet cell antibodies (ICA) positivity was temporary and secondary to viral islet infection (i.e result from pancreatic damage) or permenant and related to polyendocrine heridity and HLA-B8.

The presence of islet cell antibodies has also been used to subdivide type I IDDM into:

Subclass a: with persistant ICA and associated with other auto-immune phenomena.

Subclass b: with transient ICA and absent auto-immune phenomena.

Subclass c: Without ICA or auto-immune phenomena (NDDG, 1979).

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It is now postulated that there are two HLA-related axes for type I IDDM designated S_1 and S_2 which may be related to different forms of the disease, where S_1 pattern reflects a primary auto-immune disorder with increased prevalence of other auto-immune diseases while S_2 pattern is a primary environmental insult with a secondary auto-immune response (Bottazzo et al., 1982). Differences between both types are listed in table (3).

Table 3 Postulated HLA-linked Clinical Heterogeneity with type I IDDM (Unger and Foster, 1985).

	S1 Axis	S2 Axis
HLA	DR3	DR4
Age of onset	Older	Younger
Sex	Female>male	Male>Female
NIDDM phase prior to IDDM	Frequent	Rare
Insulin antibody titre	Low	High
Islet cell antibodies (ICA)	Persistent	Transient
Associated auto-immune endocinopathy	Frequent	Absent
Auto-immune disease in family	Frequent	Absent

Role of Virus Infection:

As stated previously, type I IDDM requires an environmental factor (aggressor) to trigger the initiation of the disease. This environmental factor may be viral in origin (Notkins, 1979). The onset of type I IDDM frequently coincides with or follows infections with mumps, rubella

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