DIABETIC NEPHROPATHY AS A CAUSE OF CHRONIC RENAL FAILURE AMONG DIALYSIS PATIENTS

Thesis

Submitted for Partial Fulfillment of Master Degree in

General Medicine

By

Ashraf El-Said Mohamed

M.B., B. Ch.

Supervised by

Prof. Dr. Wahid Mohamed El-Said

Professor And Head Of Internal Medicine Department

and Head of Egyptian Society of Nephrology

Dr. Dalia Helmy Farag

Lecturer of Clinical Pathology

Dr. Mahmoud Mohamed Zaki

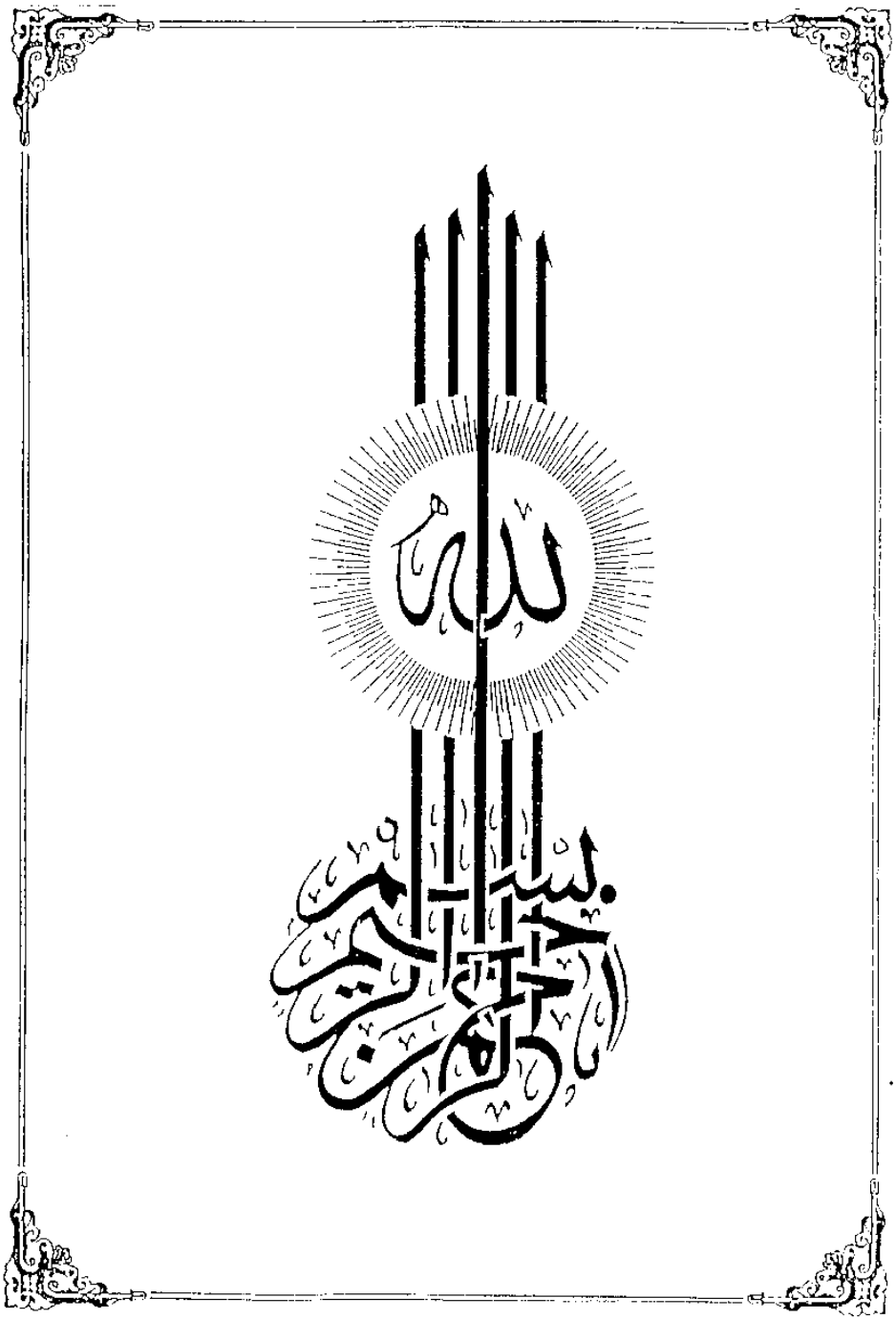
Lecturer of Internal Medicine and Nephrology

Faculty of Medicine

Ain Shams University

1994

TABLE OF CONTENTS



INTRODUCTION AND AIM OF WORK

INTRODUCTION AND AIM OF WORK

INTRODUCTION

Diabetes mellitus is one of the leading causes of end stage renal disease. Its contribution to the dialysis population in literature varies from less than 10% to more than 30% depending on many geographical, genetic, economical and other factors, as well as on the admission strategies of various centers *(Burton, 1987)*.

For many decades, there had been a general agreement that for diabetes to damage the kidneys, it should be insulin dependent *(Rettig and Tentsch, 1984)*. however, in recent years; several reports were published, suggestive of an even more aggressive course of non insulin-dependent diabetes leading to relatively rapid development of renal failure *(Cowie et al., 1989)*.

AIM OF WORK

The aim of this work is to find out the proportional contribution of diabetics (insulin and non insulin dependent) among the Egyptian dialysis population.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetes mellitus is a heterogenous primary disorder of carbohydrate metabolism with multiple etiologic factors that generally involve absolute or selective insulin deficiency, insulin resistance or both. All causes of diabetes ultimately lead to hyperglycemia; which is the hallmark of this disease syndrome.

Diagnosis of Diabetes

The symptoms of increased thirst, polyuria, polyphagia, and weight loss coupled with elevation of the plasma glucose level are pathognomonic. When diabetes is suspected in an asymptomatic patient, the primary diagnostic test is to measure the fasting plasma glucose concentration. If the value is not elevated, an oral glucose tolerance test can be done.

Fasting Plasma Glucose

The gold standard for the diagnosis of diabetes is an elevated glucose concentration in the plasma after an over night fast. The diagnostic value usually cited is 7.8 mmol/L (140 mg/dL) or above on at least two occasions *(National Diabetes Data Group, 1979).*

Oral Glucose Tolerance Test

A sample of blood is taken to measure the fasting plasma glucose level, 75 g glucose disolved in 300 ml of water is then

given by mouth. Thereafter samples of blood are collected at hourly intervals for at least two hours and their glucose content is estimated. The diagnostic criteria for diabetes mellitus and normality recommended by *WHO in 1985* are shown in Table (1):

Table (1): Diagnostic criteria for diabetes mellitus (WHO 1985).

	Venous plasma glucose concentration	
	Normal	Diabetic
Fasting	<6.1 mmol/L (110 mg/dL)	≥7.8 mmol/L (140 mg/dL)
2 hours after glucose	< 8.9 mmol/L (160 mg/dL)	≥ 11.1 mmol/L (200 mg/dL)

Glycosylated Hemoglobin

Glycosylated hemoglobin is produced by nonenzymatic condensation of glucose molecules with free amino groups on the globin component of hemoglobin. The major form of glycohemoglobin is termed hemoglobin A1c which normally comprises only 4-6% of the total hemoglobin. In persons without hemoglobinopathy, an increased level of hemoglobin A1c constitutes presumptive evidence of diabetes. A normal hemoglobin A1c does not exclude impaired glucose tolerance or mild diabetes. Hemoglobin A1c determinations for diagnostic purposes correlate well with the fasting serum glucose level *(Singer et al., 1989)*.

The hemoglobin A1c levels of patients with impaired glucose tolerance are intermediate between those of normal individuals and diabetic patients. A value greater than 3 standard deviations

above normal mean is more than 99% specific for diabetes *(Singer et al., 1989)*.

Nomenclature and Definitions

Diabetes mellitus can be divided into two major categories depending on whether endogenous insulin secretion is sufficient to prevent diabetic ketoacidosis. Insulin-dependent diabetes mellitus is applied to all forms of diabetesin which exogenous insulin is required to prevent diabetic ketoacidosis, regardless of etiology.

The term type I is applied only to diabetes resulting from autoimmune destruction of beta cells. Non-insulin dependent diabetes mellitus is applied to any form of diabetes, regardless of etiology, in which endogenous insulin production is sufficient to prevent diabetic ketoacidosis.

The term type II diabetes will be restricted to patients with NIDDM who do not have: a) Autoimmune destruction of beta cells, b) diabetes secondary to pancreatic disease, c) other rare causes of hyperglycemia. Thus, in this formulation IDDM and NIDDM indicates only the absence or presence of beta cell function, whereas type I and type II distinguish between autoimmune and non autoimmune forms of diabetes *(Keen, 1982)*.

Table (2): Classification of Diabetes Recommended by the National Diabetes Data Group (1979)

I-	Idiopathic diabetes mellitus
	1- Insulin-dependent or type I.
	2- Non-insulin-dependent or type II
	a- Nonobese
	b- Obese
II-	Gestational diabetes. (Glucose intolerance with onset during pregnancy).
III-	Impaired glucose tolerance (Oral glucose tolerance test is between 140 mg/dL and 200 mg/dL).
IV-	Previous abnormality of glucose tolerance.
V-	Potential abnormality of glucose tolerance.
VI-	Secondary diabetes (Diabetes secondary to conditions causing insulin resistance "e.g. acromegaly, Cushing's syndrome").

Etiology

Etiology of Type I (IDDM)

The corner stone in pathogenesis of type I IDDM is the interplay between genetic, environmental and immunological factors.

1- Genetic Factor:

Genetic influences are important in IDDM, about 36% of identical twins of diabetic patients and about 10% of non identical twins and siblings of diabetic patients develop the disease. *(Leslie et al., 1989).*

Association Between HLA Antigens and Type I (IDDM):

Approximately 95% of white patients type I (IDDM) have either DR3 or DR4 antigens *(Nerup et al., 1987)* and 55% to 60% have both DR3 and DR4. It was previously thought that a susceptibility gene was linked to the DR3 and the DR4 loci. Furthermore, it is thought that the alleles of HLA-DQ beta chain primarily determine susceptibility and resistance to autoimmune destruction of beta cells. If an aspartic acid residue occupies position 57 in both alleles of that chain, autoimmune diabetes will not occur. Full susceptiblity requires that both alleles be Asp-57 negative *(Todd et al., 1987)*. The combinations of DR and DQ alleles was found to be associated with higher risk for type I IDDM than either alone *(Sheehy et al., 1989)*.

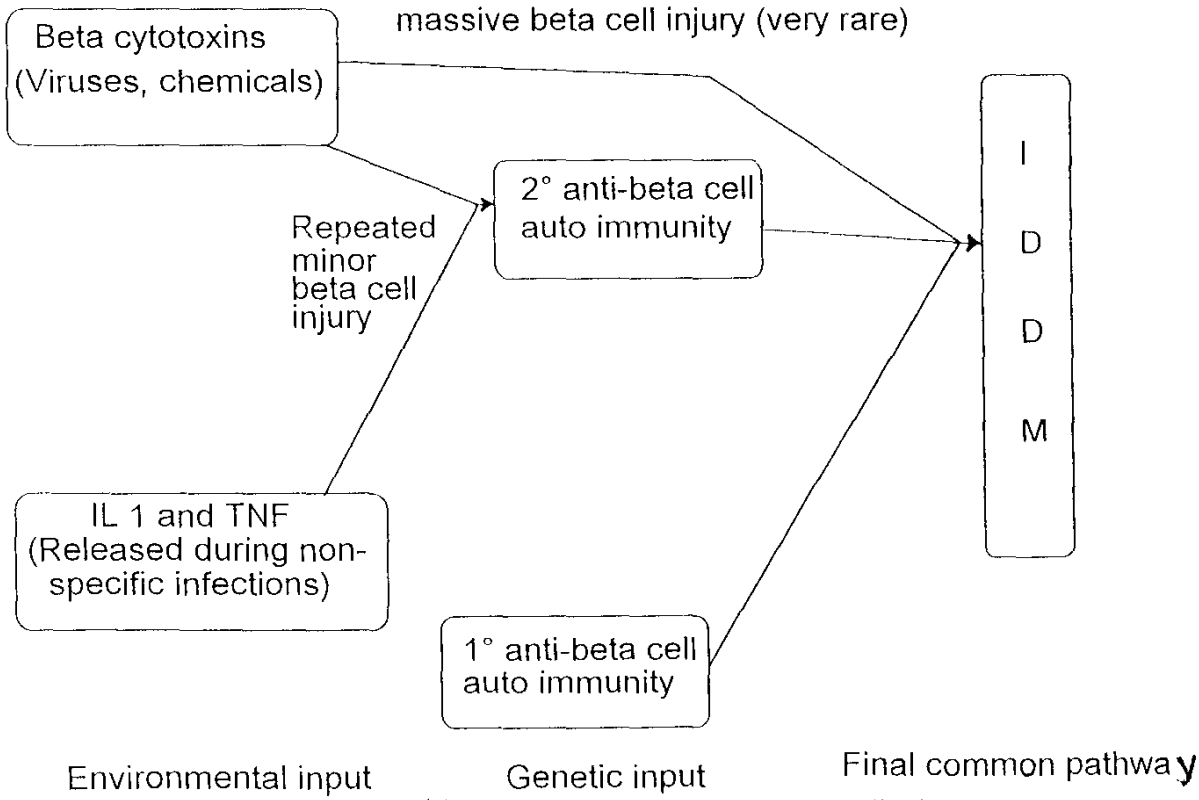


Fig. (1): Putative pathogenic pathways to IDDM
Adopted from *Williams Textbook of Endocrinology, 8th Edition, 1992, p: 1261.*

2- ENVIRONMENTAL FACTOR:

The lack of 100% concordance for type I diabetes in identical twins has been used to argue that environmental factors must contribute to the development of the disease, Fig. (1). A variety of environmental events are thought to play a role in triggering the onset of type I diabetes *(Blom et al., 1989)*. The onset of type I sometimes coincides with or follow infection with mumps, rubella, cytomegalic, measles, influenza, encephalitis, polio, and Ebstein-barr viruses *(Yoon and Ray, 1985)*.

Astonishingly, high risk of type I diabetes was associated with congenital rubella infection especially if the child is DR3 or DR4 *(Menser et al.,1978)*. On the other hand, coxsackie virus B4 infection was found to be associated with fulminant beta cell destruction rather than a virally triggered autoimmune disorder *(Yoon et al., 1979)*.

Other non viral environmental factors can cause non autoimmune destruction of beta cells by high doses of streptozocin or alloxan in animals or by poison vacor in humans *(Karam, et al., 1980)*.

3- Immunological Factor:

Evidence that type I IDDM is an immune mediated disease can be summarized as follows:

1- Familial aggregation of type I diabetes and other autoimmune conditions, such as pernicious anemia, vitiligo, myasthenia gravis, rheumatoid arthritis and collagen disease *(Nerup et al., 1977)*.

2- Coexistence of type I (IDDM) with autoimmune endocrinopathy (e.g., thyrotoxicosis, Hashimoto thyroiditis, Addison's disease) *(Nerup et al., 1977).*

3- Presence of islet cell antibodies in a high proportion of type I diabetic subjects at the time of diagnosis *(Bottazzo et al., 1982).*

4- Lymphocytic insulitis in the islets of langerhans of type I diabetic subjects dying soon after diagnosis *(Gepts, 1987).*

5- Pancrease transplanted from non diabetic to diabetic monozygotic twin develops insulitis without graft rejection accompanied by return of diabetes after initial reversal of hyperglycemia *(Bach and Sachs, 1987).*

6- Linkage of type I (IDDM) to specific class II antigens known to be associated with autoimmune disease *(Bach and Sachs, 1987).*

Etiology of type II (NIDDM):

1- Genetic Factor

The genetic basis of NIDDM is strong, although environmental factor usually contributes to the time of the onset of the disease *(Taylor, 1989).*

No HLA association of NIDDM have been identified although some weak association with HLA-A2 have been reported in some population *(Zimmet, 1982).*

The pattern of diabetes in the families indicated that diabetes was likely to be due to combinations of several genetic defects rather than to a single responsible gene. This made the search for a genetic cause even more difficult *(Zimmet, 1982)*.

2- Pancreatic B-cell Dysfunction:

It is not clear whether the impaired insulin secretion results from decreased pancreatic B-cell mass, from abnormal function of individual B-cells, or from both of these defects, *(Leahy et al., 1984)*.

3- Insulin Resistance In Pathogenesis of Type II Diabetes:

Many studies have shown that established type II diabetes is almost invariably associated with tissue insulin resistance *(Bergman et al., 1985)*.

The mechanism for the development of insulin resistance in type II diabetes is multifactorial. Obesity appears to be a major factor inducing insulin resistance *(Andrews et al., 1984)*. Insulin is less effective in obese than in non-obese subjects in stimulating glucose uptake *(Prager and Wallace, 1986)*. Although antilipolytic action in obese subjects may be normal *(Howard, 1984)*.

Insulin resistance in diabetes may in part be due to deficient insulin receptor binding *(Prager and Wallace, 1986)*.