VALUE OF MICROALBUMINURIA IN DIABETES MELLITUS

THESIS

Submitted for the Partial Fulfilment of the Master Degree

in Internal Medicine

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1988

DEDICATED TO:

MY WIFE

For her magnificent devotion, love and sacrifice to her family.

MY CHILDREN

For making everything worthwhile

MY BROTHER

For his uncompromising principles that guided him and myself

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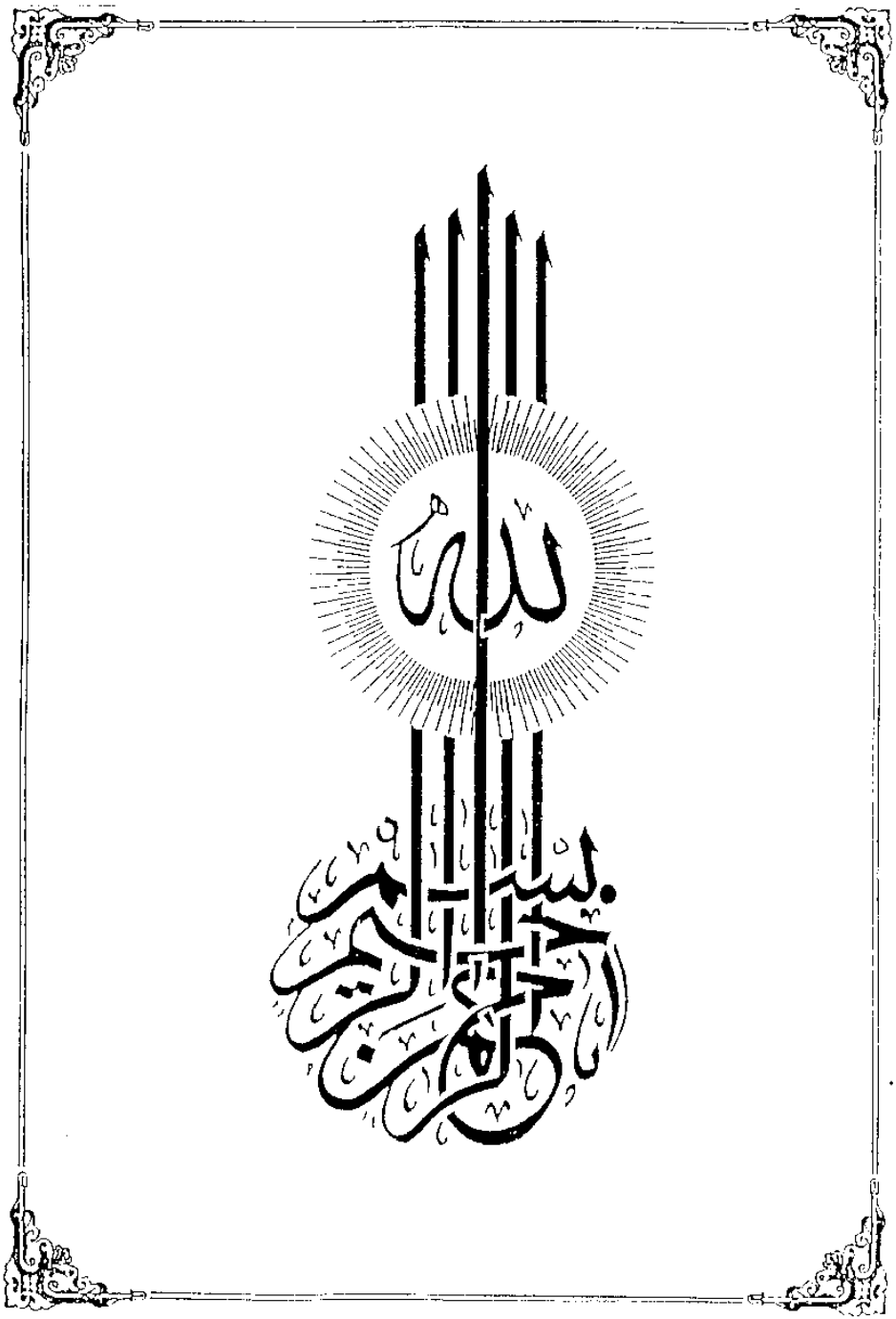

بسم الله الرحمن الرحيم

ACKNOWLEDGEMENT

I would like to express my deepest appreciation to **Prof. Dr. Badawy Labib Mahmoud**, Professor of Internal Medicine, Ain Shams Faculty of Medicine, for his enormous efforts, sincere guidance and much patience in supervising this work.

It is a great pleasure to express my gratefulness and appreciation to **Prof. Dr. Rifaat Gab Alla**, Assistant Professor of Clinical Pathology, Ain Shams Faculty of Medicine and **Dr. Hany Rifaat**, Lecturer of Internal Medicine, Ain Shams Faculty of Medicine who paid much of their valuable time to supervise the study and without their close counsel and support, this study would never have succeeded.

Much thanks to **Dr. Alaa Abd El Rohman**, Lecturer of Internal Medicine, Ain Shams Faculty of Medicine, for his kind help.

I also acknowledge the real help of Egypt Air Hospital staff during the progress of this work.

Ahmed Galal
1988

CONTENTS

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ABBREVIATIONS

GFR	Glomerular Filtration Rate.
IDD	Insulin-Dependent Diabetes.
NIDD	Non-Insulin Dependent Diabetes.
RPF	Renal Plasma Flow.
GBM	Glomerular Basement Membrane.
AER	Albumin Excretion Rate.
SI	Selectivity Index.
DN	Diabetic Nephropathy.
I.V.P.	Intravenous Pyelography.
Albu. Conc.	Albumin Concentration.
r	Correlation Coefficient.
S.Cr.	Serum Creatinine.
FPG	Fasting Plasma Glucose.
PPPG	Post Prandial Plasma Glucose.
ID	Insulin Dependent.
NID	Non Insulin Dependent.
CSII	Continuous Subcutaneous Insulin Infusion.
DM	Diabetes Mellitus.

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INTRODUCTION AND AIM OF WORK

Introduction and Aim of Work

Renal failure in diabetes results from renal lesions that develop over many years. Overt proteinuria in diabetics is the earliest indicator of a progressive decline in glomerular function which is refractory to treatment and essentially irreversible.

Before this drammatic event occurs, some abnormalities develop in the kidney of diabetics very early in the course of the disease. One of these abnormalities is "Microalbuminuria" which is detected only by the use of sensitive assays for urinary albumin. This early microalbuminuria can be reversed by strict metabolic control of the diabetic state.

The aim of this work is to find out the diagnostic value of microalbuminuria in diabetes and hence identifying the diabetic patients at risk to develop clinically significant renal disease. Also, grouping these risky patients and identifying which type of diabetes is at higher risk to develop microalbuminuria and whether or not this microalbuminuria is related to the duration of the diabetes.

REVIEW OF LITERATURE

DIABETES MELLITUS

DEFINITION:

Diabetes Mellitus is one of the common metabolic disorders of humans. (Foster 1980)

The word diabetes derives from the greek meaning siphon. (Hostetter 1986).

It may be defined as a metabolic disorder in which chronic hyperglycemia with or without glucosuria is the essential feature. (Drury 1986)

CLASSIFICATION:

Diabetes mellitus could no longer be considered as a single disease entity (Alford 1986). We should really think of DM as the diabetic syndrome (Drury 1986). Previously, several attempts had been made to classify diabetes according to age of onset, insulin requirements, degree of glucose intolerance and predisposition to develop ketosis. The most logical classification of the diabetic syndrome would be based on knowledge of its pathogenesis but in most instances this is not known, thus, no classification is completely satisfactory (Bennett 1983).

The classification recommended by the NATIONAL DIABETES DATA GROUP and subsequently adopted by WHO EXPERT COMMITTEE ON DIABETES is:

1) Insulin-dependent ketosis-prone type of DM (Type - 1 diabetes).
2) Non-insulin-dependent non ketosis - prone type (type - 2 diabetes).
3) Diabetes associated with certain conditions and syndromes e.g. pancreatic diseases, hormonal imbalance, certain genetic syndromes, drugs and chemicals.

4) Gestational diabetes which is restricted to women who develop glucose intolerance during pregnancy.

5) Impaired glucose tolerance which is a term restricted to individuals, their plasma glucose levels between normal and those considered diabetic.

6) Individuals with normal glucose tolerance who have experienced transient hyperglycemia be classed as "previous abnormality of glucose tolerance".

7) Individuals who are at high risk to develop DM, be classed as potential abnormality of glucose tolerance. (National diabetes data group 1979, Bennett 1983, Welborn 1984, Drury 1986).

DIAGNOSIS:

Diagnosis of symptomatic diabetes is not difficult, a patient presents with polyuria, polydipsia, weight loss, fatigue and is found to have hyperglycemia (Foster 1980). However, many patients are asymptomatic and only come under suspicion when glucosuria is noted on routine examination (Drury 1986).

The diagnosis of diabetes may be established solely on the basis of fasting venous plasma glucose concentration when the level of which is greater than 7.8 mmol/L (140 mg/dl) on more than one occasion (National diabetes data group 1979).

In certain situations when a considerable doubt exists about patients glucose tolerance, fasting level is less than 140 mg/dl, these cases exhibit sustained elevated venous plasma glucose values during an oral glucose tolerance test using 75 gm oral carbohydrate load (National

diabetes data group 1979). Values ≥ 200 mg/dl at 2 hs after ingestion of carbohydrate dose and also at some other time point between time 0 and 2 hs, are diagnostic (Bennett 1983, Welborn 1984, Heine 1985, Drury 1986).

With strict application of the above criteria, there will be a group of patients in whom the values, whilst not diagnostic of DM, lie outside the normal range, this is the group of Impaired glucose tolerance (IGT) (Drury 1986).

The WHO criteria for diagnosis of IGT specify that the fasting blood glucose should be normal and the 2 h. blood glucose is greater than 140 mg% but less than 200 mg% (Heine 1985, Drury 1986).

Specific criteria for diagnosis of Gestational DM, based on the study of O'Sullivan and Mahan in 1964, have been adopted by national diabetes data group (NDDG 1979).

An oral glucose tolerance test is performed over 3 hs. using 100 gm oral glucose load with sampling at zero, 1,2,3, hours. The test is abnormal when any two of the following values are equalled or exceeded.

Fasting venous plasma glucose value	105 mg%	
1-h value	189 mg%	
2-h value	165 mg%	
3-h value	146 mg%	(Drury 1986)

AETIOLOGY AND PATHOGENESIS:

Type 1 DIABETES:

The prime aetiological factor in IDD is absolute or near absolute insulin deficiency (Andreani 1984). This insulin deficiency results from corresponding degrees of B-cell malfunction (Drury 1986). 90% of the B-cell mass has to be destroyed before chronic hyperglycemia develops (Drury 1986).

The cause of B-cell mass destruction is unknown (Doniach 1983). It is possible that a genetic susceptibility interacts with environmental agents and immunological factors producing the typical clinical syndrome (Andreani 1984).

1) Genetic Factors:

Studies of the HLA antigens have provided new evidence for the existence of genetic heterogenity in diabetes (Pyke 1979). There is clear evidence of an association between certain HLA antigens and IDD with increased relative risk when possessing certain HLA-A and HLA-B antigens (Cudworth 1978). The strongest association with the disease lie with the DR antigens, HLA-DR_3 (Sachs et al., 1980), and HLA-DR_4 (Deschamps et al., 1980).

58% of IDD patients were found to be DR_3 positive and 42% DR_4 positive, this suggests that the diabetogenic genes may be closer to the HLA-D locus than the HLA-A,B,C loci (Cudworth 1978).

Several studies have shown in siblings of IDDs, a statistically significant association between the sharing of identical haplotypes and the development of IDD, this could support the existence of HLA linked predispoing genes (Barbosa 1977).

In identical twins, the concordance for DM when age of onset is less than 45 y. is about 50% in contrast with the concordance of about 100% when age of onset is greater than 45 y. (Pyke 1979, Barnett 1981). Current evidence supports the possibility of two diabetogenic genes on the 6 $\frac{th}{}$ chromosome in linkage disequilibrium with either DR_3 or DR_4 (Nelson 1975). It is not yet clear whether it is the DR antigens themselves which confer susceptibility to DM or they are juxtaposed with diabetogenic genes which have not yet been isolated (Drury 1986).

2) **Immunological Factors:**

Several studies have been made to show the role of immunological factors in the pathogenesis of IDD based on the observation that IDD may be associated with other autoimmune endocrinopathies (Nerup et al., 1971).

In 1974, islet cell antibodies were described in some diabetics with other autoimmune disorder (MacCuish et al., 1974). These antibodies are found in a high percentage of IDDs and appear to have a close relationship in time with B-cell damage (Irvine 1977).

Other antibodies that are found to react with the surface of islet cells namely islet cell surface antibodies appear to be separate from islet cell antibodies and found in 50% of newly diagnosed cases of IDD (Lernmark 1978).

Very recently insulin autoantibodies have been found in newly diagnosed untreated IDDs but their significance is not yet clear (Drury 1986).