STUDY OF THE LUPUS ANTICOAGULANT IN THE EGYPTIEN DIABETICS

THESIS SUBMITTED FOR PARTIAL FULFILLMENT OF THE MASTER DEGREE IN GENERAL MEDICINE

PRESENTED BY

ABD EL MOANIS ALI KHALIFA

SUPERVISORS

PROF.DR.MOOTASSEM SALAH AMER
PROF.OF GENERAL MEDICINE

PROF.DR.IBRAHIM KHALIL ALI
PROF.OF CLINICAL PATHOLOGY

CO-SUPERVISOR

DR.NEHAD AHMED AMER
LECTURER OF GENERAL MEDICINE

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

1992

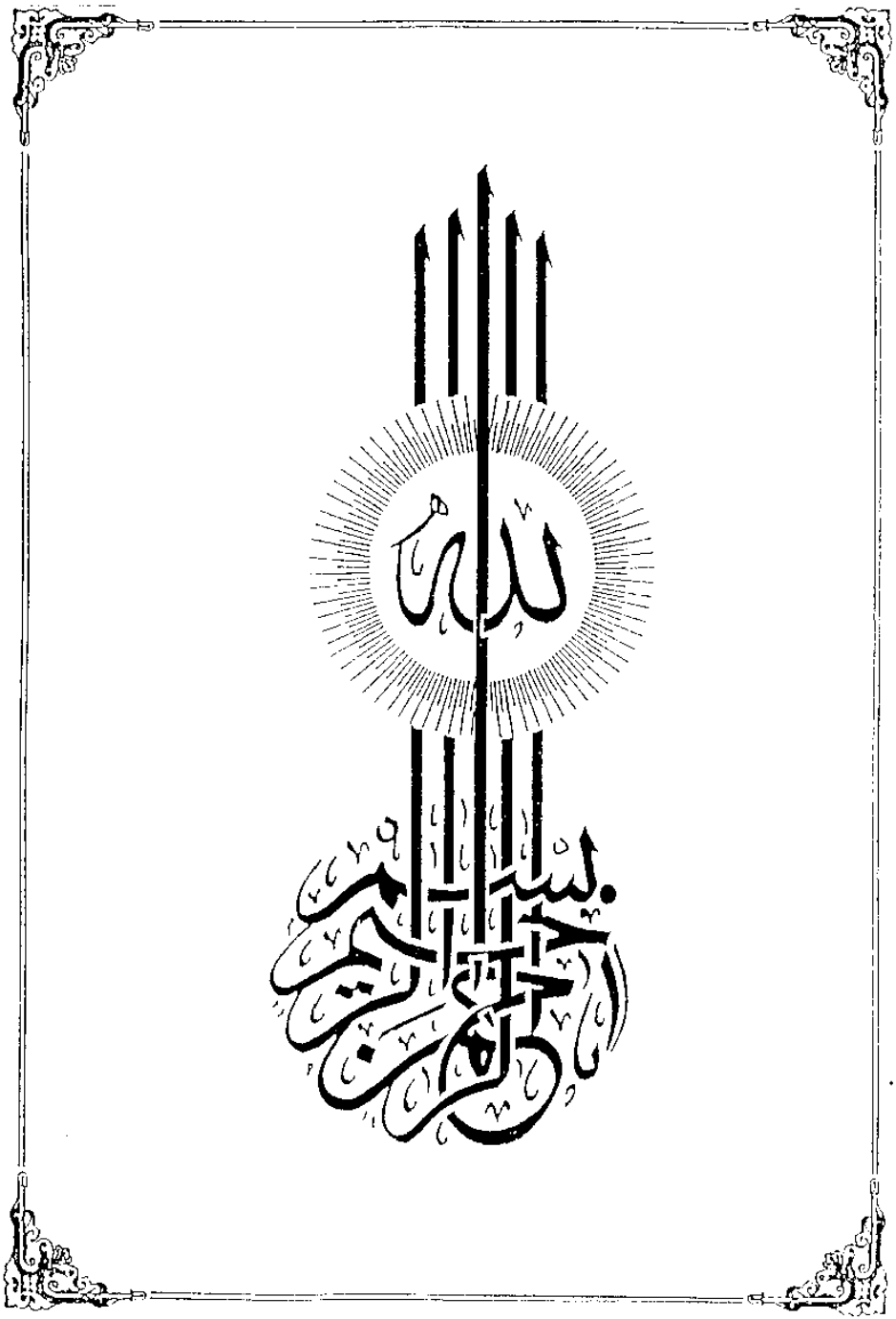
ACKNOWLEDGEMENT

I would like to express my deep thanks and gratitude to prefessor Dr. Mootassem Salah Amer , professor of general medicine ;Faculty of medicine ,Ain Shams University for giving me the honour of working under his supervision , for his continuous encouragement , his patience and fruitful guidance throughout the whole work .

I would also like to express my deep thanks and gratitude to professor Dr . Ibrahim Khalil Ali , professor of clinical pathology ; Faculty of medicine, Ain Shams University for the great effort he did , for the very helpful hints and his continuous encouraging to me .

I would also like to thank Dr. Nehad Ahmed Amer , lecturer of general medicine ; Faculty of medicine, Ain Shams University for her great help and effort done with me.

Lastly , I would like to express my deepest thanks to the very kind Dr. Nevine Nabil Kassem , lecturer of clinical pathology , Faculty of medicine, Ain Shams University for the great support she had given me in the practical part and creative ideas which helped me a lot .



ABBREVIATIONS

JOD	Juvenile onset diabetes .
MOD	Maturity onset diabetes .
MODY	Maturity onset diabetes of the young .
IDDM	Insulin-dependent diabetes mellitus .
NIDDM	Non - insulin dependent diabetes mellitus.
MRDM	Malnutrition - related diabetes mellitus .
IGT	Impaired glucose tolerance .
WHO	World Health Organization .
NB	Notcia brevia (short note).
HLA	Human leucocyte antigen .
DNA	Deoxyribonucleic acid .
MHC	Major histocompatibility complex.
FCDP	Fibrocalculus pancreatic diabetes .
PDPD	Protein deficiency pancreatic diabetes .
NDDG	National Diabetic Data Group .
OGTT	Oral glucose tolerance test .
SI	System international .
mmol	Milli mole .
2HSS	Two - hour blood sugar screen .
LDL	Low density lipoprotein .
AGES	Advanced glycosylation end products .
ARIS	Aldose reductase inhibitors .
GFR	Glomerular filtration rate .
BBrat	Biobreeding rat .
NODmice	Non abese diabetic mice .
Tc cells	Cytotoxic T cells .
Th cells	Helper T cells .
APC cells	Antigen - presenting cells .
SLE	Systemic lupus Erythematosus .
IL-2	Interlevkin - 2.
NK cells	Natural Killer Cells .

RNA	Ribonucleic acid .
ICA	Islet cell cytoplasmic antibodies .
ICSA	Islet cell surface antibodies .
CF-ICA	Complement - fixing islet cell antibodies .
IAA	Insulin autoantibodies .
Fc	Crystalizable fragment .
C_3	The third component of the complement .
Ts cells	Suppressor T cells .
ng	Nano gram .
LAC	Lupus anticoagulant antibodies .
ACA	Anticardiolipin antibodies .
APLA	Antiphospholipid autoantibodies .
TM	Thrombomodulin .
Pc	Protein C.
Ps	Protein S .
APC	Activated P.C.
APS	Activated P.S.
Ec	Endothelial cells .
IIa	Activated coagulation factor 2.
t-PA	Tissue plasminogen activator .
t-PAI	Tissue plasminogen activator inhibitor .
AECA	Anti - endothelial cell antibodies .
VDRL	Venereal Disease Research Laboratory.
PTTK	Partial thromboplastin time .
APTT	Activated partial thromboplastin time with Kaolin .
dsDNA	Double strand Deoxyribonuleic acid .
HUVEC	Huamn Umbilical vein endothelial cells .
PGI2	Prostaglandin inhibitor 2 .
Fab	Antigen - binding fragment .
RIA	Radio immunoassay .
PE	Phosphatidylethanolamine .
FPA	Fibrinopeptide A.

CONTENTS

PART I

INTRODUCTION AND AIM OF WORK

Diabetes mellitus is the most common of the serious metabolic diseases of humans. It is a heterogenous primary 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 hyperglycaemia , which is the hallmark of this disease syndrome [Olefsky ,1988].

The presence of circulating antibodies to islet cells and insulin at the time of diagnosis may be an additional evidence of immune activation potentially mediating beta cell destruction [Lernmark et al.,1987:Palmer,1987]. Several types of antibodies have been described. Islet cell cytoplasmic antibodies (ICA) bind to islet cell cytoplasmic antigens and are detected by immunofluorescence using cryostate secretions of pancreas. ICA are islet specific, but not beta cell specific, and are of the Ig G and Ig M classes. Islet cell surface antibodies (ICSA) bind to surface antigens on the plasma membrane, and are detected using cultured living cells. They react mainly with islet beta cells and can mediate complement dependent lysis (complement dependent, antibody - mediated cytotoxicity or C AMP) of islet cells in vitro, and also inhibit insulin secretion in vitro. Complement - fixing islet cell antibodies (CF-ICA) have been described and may be more specific than conventional ICA , although it would seem that CF-ICA merely represent high titres of conventional ICA . There are also anti-insulin antibodies (insulin autoantibodies or IAA) present at the onset of IDDM , Prior to adminstration of exogenous insulin . The presence of IAA suggests that insulin itself may serve as a surface antigen stimulating the immune system (presumably in association with aberrantly exprssed class II antigens) , or that insulin release

(presumably in a damaged form) as a consequence of beta cell detruction may induce antibody formation [Palmer et al..1983].

The lupus anticoagulant was first decribed by Conely and Hartmann at 1952 as a spontaneously acquired inhibitor of blood coagulation that interfers with the activation of prothrombin by the activator complex (Factor Xa. V, calcium and phospholipid) [Feinestein et al.,1972]. This inhibitor is an immunoglobulin of the IgG or IgM appears with autoimmune disorders including SLE but has also been described in patients with disorders not directly associated with the immune system [Schleilder et al.,1976]. The classic lupus anticoagulant is an immunoglobulin that reacts in vitro with negatively charged phospholipids resulting in an inhibition of the generation of prothrombin activator complex and prolongation of the partial thromboplastin time . The term lupus anticoagulant is misnomer , since the factor seldom interferes with homeostasis and is found more often in individuals without SLE than in those with this diagnosis . It is one of the related family of anti-phospholipid antibodies which includes the reaginic antibody of treponemal infections and anticardiolipin antibodies [Virigil et al..1989]. Recently , it appears that the most frequent clinical manifestation observed in those patients who have the lupus anticoagulant is an increased tendency to display thrombotic complications [Mueh et al.. 1989].

As diabetes mellitus is a syndrome with multiple autoimmune disorders and frequent thrombo-emboiic complications so the aim of this work is to study if there is any change in lupus anticoagulant in diabetics as it may be related aetiologically to the thrombo-emboiic complications in diabetics .

Chapter 1

DIABETES MELLITUS
THE CLINICAL SYNDROME

(I) INTRODUCTION

Diabetes mellitus is a heterogenous primary group of disorders of carbohydrate metabolism with muitiple aetiologic factors that generally involve absolute or relative insulin deficiency or insulin resistance or both. All causes of diabetes ultimately lead to hyperglycaemia.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 areatequal 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,1988].

Recently,studies of the mechanisms causing DM have yielded valuable information which is anticipated to be of importance in the prevention and treatment of the disease in the future,e.g immuno-modulation for IDDM [Foster,1987:Keen 1989].

(II) CLASSIFICATION

[1] The traditional classification of diabetes mellitus is based on the age of onset of the disease namly "early onset or juvenile onset diabetes JOD"and "late onset or maturity onset diabetes MOD".JOD has its onset chiefly in children ,adolescents and young adults in whom symptoms are severe and the overall course is aggressive.The other variety occurs chiefly in older persons.It often has an insidious onset with relatively few or no symptoms and a much greater tendency to obesity .Another form of diabetes was described resembling MOD in characteristics,but occurring in young age called maturity onset diabetes of the young (MODY).[Tatter and Fajans.1975]. The terms juvenile and maturity onset are regarded unsatisfactory and misleading because some old patients may develop diabetes that is insulin dependent and the characters of maturity onset diabetes may be present in a young patient as previously mentioned.

[2] The current, essentially clinical, classification put forward by the WHO study group on diabetes mellitus [1985] is as follows :

1- Insulin - dependent diabetes mellitus [IDDM] .

2- Non - insulin dependent diabetes mellitus [NIDDM].

a.Non-obese

b.Obese

3-Malnutrition-related diabetes mellitus [MRDM].

4-Other types of D.M associated with certain conditions and syndromes :

a.Pancreatic diseases[e.g. chronic pancreatitis in alcholics].

b.Diseases of hormonal aetiology [e.g.

pheochromocytoma,acromegaly,and Cuhing s syndrome].

c.Drug-induced or chemically induced conditions.

d.Abnormalities of insulin or its receptors.

e. Certain genetic syndromes [e.g. lipodystrophies,myotonic dystrophy, ataxia telangiectasia].

f.Miscellaneous[i.e any condition not fitting elsewhere in the aetiologic scheme].

5-Gestational DM.

6-Impaired glucose tolerance[IGT].

[2] D.M may be also classified into "primary" and"secondary" types.primary including IDDM and NIDDM.implies that no associated disease is present,while some other identifiable condition causes or allows a diabetic syndrome to develop in the "secondary" type, which is equivalent to "other types " in the WHO classification .[Foster,1987].

N.B: D.M. can be also classified in other dimensions e.g.the geneticists may wish to know about precise HLA type,the molecular biologists about DNA sequences,the immunologists about nutritional status and local toxic hazards.The appearance of abnormal carbohydrate metabolism in association with any of the secondary causes does not necessarily indicate the presence of underlying diabetes although in some cases a mild asymptomatic primary diabetes may made overt by the secondary illness .[Unger & Foster,1987].

IDDM And NIDDM:

IDDM and NIDDM are more descriptive and informative terms which have replaced the old terms juvenile and maturity onset

diabetes mellitus respectively . Insulin dependence is not equivalent to insulin therapy.Rather, the term means that the patient is at risk for ketoacidosis in the absence of insulin . Many patients classified as NIDDM require insulin for control of hyperglycaemia although they do not become ketoacidotic if insulin is withdrawn[Foster,1987,Keen,1989].

The terms'type I"and "type II" diabetes have often been used as synonyms for IDDM and NIDDM respectively . This probably is not ideal since some patients with apparent NIDDM may in fact be destined to become fully insulin-dependent and prone to ketoacidosis. This subset of patients are non-obese subjects who carry the HLA-DR $_3$/DR $_4$ phenotype and exhibit islet cell antibodies in blood.For this reason it has been suggested that the above classification be modified such that terms IDDM and NIDDM describe physiologic states (ketoacidosis-prone and ketoacidosis-resistant respectively),while the terms "type I" and "type II" refer to pathogenetic mechanisms (immune-mediated and non-immune mediated respectively).Using such a classification three major forms of primary diabetes would be recognized :

1.Type I IDDM.

2.Type I NIDDM.

3.Type II NIDDM.

Category 3 can be considered as type I IDDM in evolution,i.e. autoimmune beta cell destruction occurs slowly rather than rapidly with the result that there is a delay in reaching the ketoacidotic threshold of insulin deficiency [Foster,1987].

Type I:(IDDM):

The common characteristics of this form are, a sudden clinical onset, severe hyperglycaemia, the easy appearance of