THE STATE OF SERUM INSULIN IN MATURITY ONSET DIABETES AND STUDY OF THE MODE OF ACTION OF SULFONYLUREA DRUGS

Thesis

submitted for the fulfilment of the

Ph.D

of Biochemistry

By

Magda Abd El Meguid Amer

M.Sc. of Biochemistry

Supervised by

Prof. Dr Fawzia Refai
Prof. of Biochemistry
Faculty of Science
Ain Shams University

Prof. Dr Ahmed Ghareeb
Prof. of general medicine
Endocrine unit
Ain Shams University

Prof. Dr Hussein El Damassy
Prof. of general medicine
Endocrine unit.
Ain Shams University

Prof. Dr M. Sabry Sallam
Prof. of clinical pathology
Clin. Path. Unit
Ain Shams University

Faculty of Science
Ain Shams University
1987

Printed by TWE. Tomorrow World Engineerig Office.
44-Tawffic city - Nasr City. Tel : 601287-602820

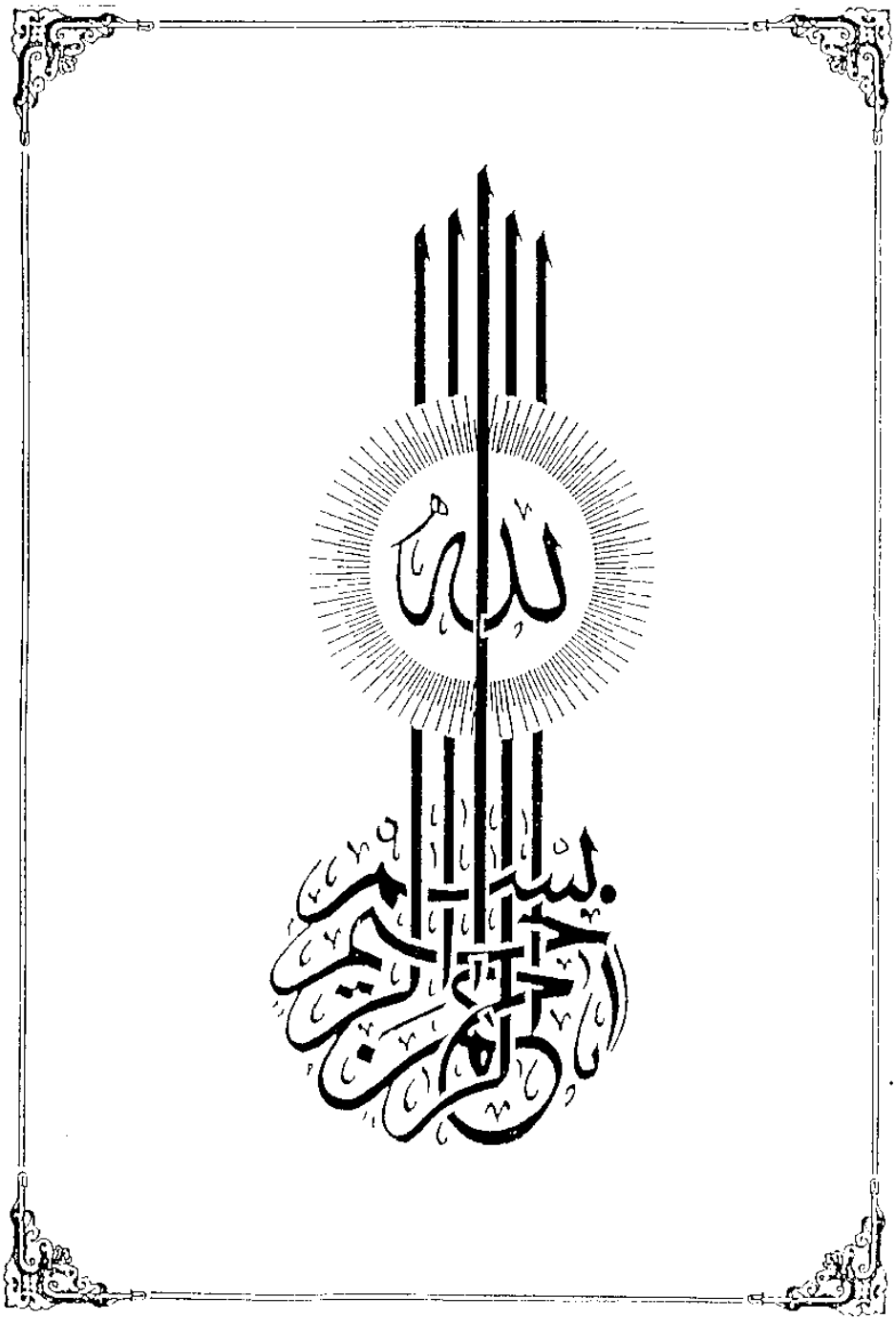
AKNOWLEDGEMENT

I offer my deepest gratitude to Dr Fawzia Mohamed Refai professor of Biochemistry faculty of Science, Ain Shams University, whose helpful criticisms, keen interest and continuous encouragement have been indispensable throughout the writing of this manuscript.

I am greatly indepted to professor Dr Ahmed Ghareeb, professor of general medicine for suggesting this interesting point of research, supervision, marvellous support, objective criticism and valuable directions.

I wish also to express my gratitude to professor Dr Hussein El Damassi professor of general medicine for his precious advice, useful encouragement consistent supervision, care and effort afforded by him.

I would like to pay a special gratitude to Dr Sabry Sallam, professor of clinical pathology for his trustful help, Kindness, unfailing advice , continuous guidance and valuable criticism.



CONTENTS

ABBREVIATIONS

A.F.P.	:	feto protein
Apo	:	Apolipoprotein
B	:	Beta
C.AMP	:	Cyclic adenosine monophosphate
Ca	:	Calcium
COA	:	Coenzyme A
Conc=	:	Concentration
CRP	:	C reactive protein
D.M	:	Diabetes mellitus
E.C.F.	:	Extracellular fluid
F	:	Free insullin
FFA	:	Free fatty acid
F	:	Fasting
GIF	:	Gastro intestinal factor
GIP	:	Gastric inhibitory polypeptide
GTT	:	Glucose tolerance test
HDL	:	High density lipoprotein
HLA	:	Histocompatibility lymphocytic antigen
ICA	:	Islet cell antibody
IRI	:	Immunoreactive insulin
IDDM	:	Insulin dependent diabetes mellitus
Ig	:	Immunoglobulin

I.V : Intravenous

L.D.L : Low density lipoprotein

M.O.D : Maturity onset diabetes

mRNA : Messenger ribonucleic acid

NIDDM : Non insulin dependent diabetes mellitus

OGTT : Oral glucose tolerance test

P : Probability test

r : Correlation coefficient

S : Significant (+ increase, - increase)

SE : Standard error

T.G : Triglyceride

T : Total insulin

T.C.A. : Tricarboxylic acid cycle

t : Test of significance

VLDL : Very low density lipoprotein

$\bar{X}$: Mean

Ins. resist. D. : insulin resistant diabetics

Ins. non resist. D.: insulin non resistant diabetics

D. resp to sulf : Diabetics responsive to sulfonylurea drugs

D. unresp to sulf : Diabetics unresponsive to sulfonylurea drugs

newly diagn. D. : Newly diagnosed diabetics

healthy ctrl subj. : Healthy control subjects

Aim of Work

AIM OF WORK

There is increasing evidence that maturity onset diabetes starts by insulin resistance.

Himsworth and Kerr (1942), were the first to demonstrate conclusively the presence of insulin resistance in non insulin dependent diabetic patients.

Others investigators described an insulin antagonist attached to albumin or prealbumin called " Synalbumin " (Vallance-owen et al., 1958). (Vallance-owen and Lilley, 1961).

Studies reported by Antoniades et al. (1961), suggested that insulin in human blood circulate in two forms " free & bound ". The " free " insulin was assumed to be the physiologically active form of crystalline insulin while the insulin protein complex termed " bound " insulin was postulated to be physiologically inactive (Antoniades et al ., 1965 a).

The present study was performed in an attempt to demonstrate the state of serum insulin and its

fractions " free " and " bound " in maturity onset diabetes and its role in the pathophysiology of insulin resistance ,as well as the mode of action of sulfonylurea in current use especially tolbutamide and glibenclamide . Little is known about whether they change bound into free insulin or work in another way.

The presence of insulin antibodies in maturity onset diabetics (Pav et al., 1963) draw our attention to investigate the protein electrophoretic pattern, particularly γ globulin.

This thesis had not been submitted for any degree at this or at any other university

Magda Abd El Meguid Amer

Introduction

HISTORICAL ASPECT OF DIABETES

In accounts of the history of diabetes, it is stated that in the Ebers papyrus (Egypt, about 1500 B. C) there was mention of polyuria and that "honey urine" was noted by Sushrutha in India in 400 B.C. The first good clinical description of the disease was made by Celsus and the name "Diabetes" was introduced by Aretaeus, a Roman physician. Analogous descriptions of a disease suggesting diabetes are said to have appeared in Chinese and Japanese writings of these early centuries. (Poulsen, 1982).

Avicenna (Ibn-Sina) (980-1087), gave a remarkably good description of diabetes, including some of its complications such as gangrene.

Willis (1621-1675), was the first to discover the sweet taste of the urine.

In subsequent studies, Dobson (1775), demonstrated that the sweetness of diabetic urine was due to sugar and that such urine was subject to alcoholic and acetic fermentation.

Furthermore Cawley (1788), discussed the role of the pancreas in the pathology of diabetes .

Rollo, just prior to (1800), was among the first to outline a definite dietary regimen.

Trommer (1841), and Fehling (1848), developed the well known cupric oxide tests for urinary sugar.

In (1869), langerhans discovered the islets which were later given his name.

In (1889), a great landmark was reached when Mering and Minkowski produced diabetes in dogs by total pancreatectomy.

A series of papers published around 1900 by Szobolev gave the clearest explanation of the function of the islets.

The greater step forward came in (1921), when Banting and Best, a Canadian physiologist and a biochemist , succeeded in extracting a substance from the pancreas with hypoglycemic properties "Insulin" and treated the first human diabetic by this substance.

The first crystalline insulin was then prepared and its molecular weight was determined by Svedberg, (1931), using the ultra centrifuge technique.

The introduction of the oral hypoglycemic agents in 1955 by loubatieres (1957), provided another stimulus because studies designed to elucidate the mode of action of these drugs led investigators into a closer examination of the pathophysiology of diabetes and the mode of action of insulin.

In (1968) Steiner et al., discovered the existence of proinsulin, a single chain precursor of insulin.

In the last two or three decades interest in diabetes and related problems has been greatly aroused and remarkably well sustained.

DIABETES MELLITUS

Diabetes Mellitus is not a disease in the classical sense but is more probably a syndrome. Blood glucose concentration is the most common variable used to define diabetes .

In order to group patients for clinical and research purposes , it is of paramount importance to try to subdivide this syndrome according to some features that seem highly relevant .

In the last few years, different classifications of diabetes have been reported (Bottazzo and Doniach 1976, Cudworth and woodrow 1976, Irvine 1977) .

In (1979), The National Diabetes development group developed together with the main associations for the study of diabetes, a new classification of the disease (National Diabetes development group, 1979). This classification divides diabetes according to insulin dependence .

I- Type i insulin dependent diabetes mellitus (IDDM):

The first subclass of diabetes is usually characterized