EFFECT OF ALCOHOLISM ON GLUCOSE, LIPIDS AND INSULIN IN MATURITY ONSET DIABETES MELLITUS

THESIS

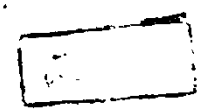
Submitted in partial fulfilment

of master degree in internal medicine

By

SAMEH FOUAD SELIM

M.B., B.Ch.



Supervisors

Professor

SAYED MOHAMMED

RAAFAT

[illegible]

[illegible]

[illegible]

Prof.

GOHAR

GAMAL EL-DIN

[illegible]

[illegible]

[illegible]

Dr.

MOHAMMED

ALA'A EL-DIN HAMED

Assist. Prof. of Int. Medicine

and Endocrine Unit

Ain Shams University

Dr.

FADIA

EMAD-ALLAH

Lecturer of Int. Medicine

and Endocrine Unit

Ain Shams University

Faculty of Medicine

Ain Shams University

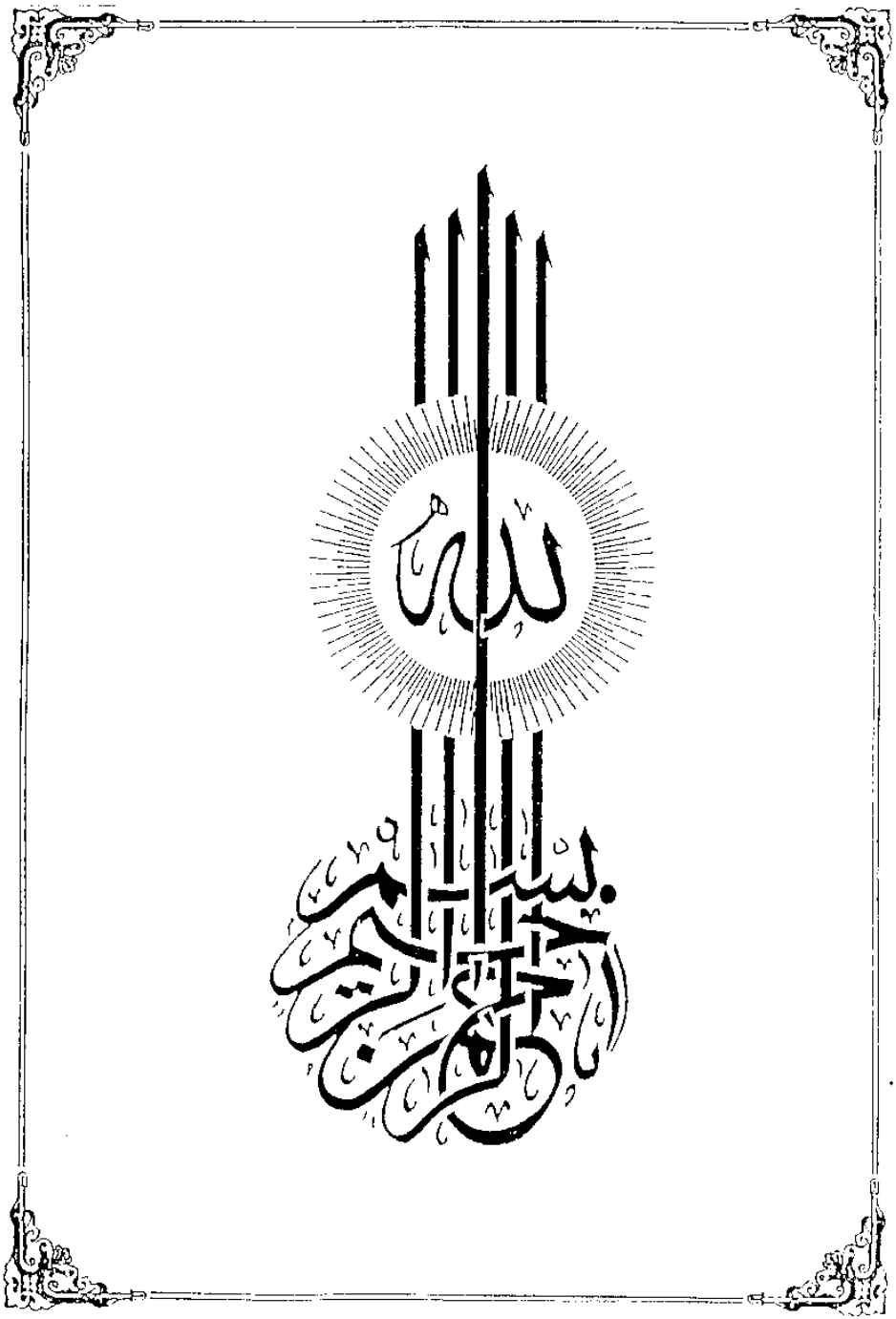
1989

To the soul of my father

"The one who gave me everything he had"

To my mother, wife & daughters

"My life and future"



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ABBREVIATIONS

1- Ab :Antibody
2- ACOD :Acyl Co A oxidase
3- ADA :American Diabetic Association
4- ADP :Adenosine diphosphate
5- Alc :Alcohol
6- AMP :Adenosine monophosphate
7- ANOVA :Analysis of variance
8- Apo :Apolipoprotein
9- C :Rank of the mean
10- CE :Cholesterol esterase
11- Chol :Cholesterol
12- CO :Cholesterol oxidase
13- Co-A :Coenzyme A
14- CP :C-peptide
15- DEA.HCl/APP :N,N-diethylanilin HCl/4-aminoantipyrine
16- DM :Diabetes mellitus
17- ECG :Electrocardiography
18- F :Variance ratio
19- F.CP :Fasting C-peptide
20- Fcr :Crystallisable fraction
21- F.G :Fasting glucose
22- F.ins :Fasting insulin
23- F.Prob :F.Probability
24- GDH :Glycerol dehydrogenase
25- -GPNA.HCl :Samma glutamyl-p-nitroanilide hydrochloride
26- GGT :Samma glutamyl transferase
27- GO :Glucose oxidase
28- gr :Group
29- GTT :Glucose tolerance test
30- H :Hormone
31- 1H :First hour
32- 2H :Second hour
33- HDL :High density lipoproteins
34- HPO :Horseradish peroxidase
35- ICA :Islet cell cytoplasmic antibodies
36- ICSA :Islet cell surface antibodies
37- IDDM :Insulin dependent diabetes mellitus

38- IDL :Intermediate density lipoproteins
39- ins :Insulin
40- IRI :Immunoreactive insulin
41- K :Number of groups
42- LCAT :Lecithin-cholesterol acyl transferase
43- LDL :Low density lipoproteins
44- MEHA :3-methyl-N-ethyl-(B-hydroxy ethyl)-aniline
45- MHC :Major histocompatibility
46- MODY :Maturity onset diabetes of the young
47- MSA :Mean square among sample
48- MSW :Mean square within sample
49- n :Number of observations
50- NADH :Reduced form of nicotinamide adenine dinucleotide
51- NADPH :Reduced form of nicotinamide adenine dinucleotide phosphate
52- NIDDM :Non insulin dependent diabetes mellitus
53- No :Number
54- OGTT :Oral glucose tolerance test
55- O-MODY :Offspring of maturity onset diabetes of the young
56- P :Level of significance
57- PNL :Polymorphonuclear leucocytes
58- POD :Peroxidase
59- PPi :Pyrophosphate
60- RIA :Radio-immuno-assay
61- S^2 :Residual mean square in ANOVA table
62- SSA :Sum of squares among sample
63- SST :Sum of sqares in the total
64- SSW :Sum of squares within sample
65- STD :Standard deviation
66- t :Student test value
67- Tgl :Triglycerides
68- TPD :Tropical pancreatic diabetes
69- VLDL :Very low density lipoproteins
70- WHO :World Health Organization
71- X :Individual value
72- $\bar{x}$:Mean
73- Σ :Sum of
74- $>$:More than
75- $<$:Less than

CONTENTS

AIM OF THE WORK

The aim of this work is to study the effects of alcoholism on the metabolism of the maturity onset diabetic patients regarding the effectiveness of pancreas to secrete insulin, the level of the blood glucose and the levels of blood cholesterol,triglycerides,high density lipoproteins and free fatty acids. High density lipoproteins (HDL) level gives an impression about the possible cardiovascular complications.

Free fatty acids (FFA) are readily metabolised mainly by muscles and heart,as a preferential substrate for oxidation; therefore determination of FFA as a parameter of the metabolic state is very useful(Mayer et al.,1981).

[PART I]

REVIEW OF LITERATURE

A] DIABETES MELLITUS

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[1] GENERAL CONSIDERATIONS

Diabetes mellitus is a diagnostic term applied to a constellation of anatomic and biochemical abnormalities which have in common , as part of a syndrome,a disturbance in glucose homeostasis , which is secondary to a deficiency in the beta cells of the endocrine pancreas.This bulky and vague definition cannot be more specific owing to the marked variability in the disorder.As was once said for syphilis , knowledge of diabetes and its sequelae touches on all areas of medicine.[Cahill,1982].

The syndrome can be completely asymptomatic,or it can appear as an isolated disorder of any organ or system.Fulminant ketoacidosis,fatal unless immediately treated,may be the first sign.Often it is manifested by one of the long term complications,such as foot ulcer,retinopathy or proteinuria. Other pathologic states noted to be more frequent in diabetics as compared to the general population may be the clue.For example,the presenting event may be of myocardial infarction in a young male,an unexpectedly large newborn or pruritis vulvae in the female,recurrent skin infections , or many other phenomena which at first glance appear unrelated.Diabetes mellitus is protean in its manifestations,and this variability is central to its diagnosis and treatment.Furthermore,it tends to be familial.[Cahill,1982].

[2] HISTORICAL APPROACH

Descriptions of the disease were made 3000 years ago in EGYPT . About 400 B.C.,Charak and Susrut in India noted not only the sweetness of the urine but also the correlation between obesity and diabetes , the tendency of the disease to be passed from one generation to another and even two types of disease,one associated with emaciation , denydration , polyuria and lassitude and the other characterized by stout built,gluttony , obesity and sleepiness.Near the begining of the Christian era,the Romans Aretaeus and Celsus described the disease and gave it the name diabetes (=siphon) mellitus (MELLI=honey or sweet). Its correlation with gangreen was mentioned by the Arab Avicenna,1000 A.D. In 1775,Dodson demonstrated that the sweetness was due to sugar and suggested it was not formed de novo by the kidney,but rather that the kidney removed it from the body,a fact scientifically confirmed by a great French physiologist , Claude Bernard in mid 1800's. In 1889,Von Mering and Minckowski first produced experimental diabetes by removing the dog's pancreas. Subsequently Opie (1901) noted changes in the islets of cells in the pancreas (the islets having been described by Langerhans in 1869),in humans dying with the disease.This led to attempts by many to prepare pancreatic extracts which could correct the deficiency. Active fractions were obtained by some,but not until 1921 did Banting and Best in Toronto achieve continuous success,and their discovery was rapidly applied to clinical therapy within 6 months of their first report. Until then, only a careful semistarvation diet with elimination of excess carbonydrates was even partially effective in prolonging life in the more insulin-dependent juvenile form of the disease , or in amelurating the symptoms in many patients with the milder maturity-onset or non-insulin dependent variety.

The Banting-Best era changed the outlook of the juvenile diabetic from certain death within 2-3 years to a nearly normal , albeit shortened life expectancy.In 1936,the use of long acting insulin was introduced,simplifying the management of the insulin requiring diabetic.It became apparant at that time,however,that although insulin therapy prevented many of the acute metabolic problems such as ketoacidosis or those closely correlated with the hyperglycaemia,eg..pruritis vulvae or furunculosis , other sequelae such as retinitis,neuropathy or renal glomerulosclerosis appeared in most patients with the insulin-dependent form of the disease for two or more decades in spite of insulin therapy.These complications had been noted prior to the advent of insulin but were relatively unusual,because death from ketoacid-osis or infection shortened the life of the patient before these could become manifest.Thus,insulin,although a tremendous step forward did not provide the total solution for the diabetic and his problem.Another develop-ment,clearly less significant than that of insulin,stemmed from the German observation during World War II that certain sulphonamide derivatives lowered blood glucose,and subsequent controlled trials in France which established their clinical efficacy.In 1955,oral sulphonylureas began to be generally used as hypoglycaemic therapy in diabetics with the milder non-insulin-dependent type of the disease.....(Canii,1982).

[3] CLASSIFICATION & PATHOGENESIS

The age-old terms of"juvenile onset" and "maturity onset"diabetes have outlived their usefulness.Two main classifications have appeared in the past few years . The first refers to Type-I and Type-II diabetes , with sub-categorisation of types Ia & Ib.The second refers to insulin-dependent(IDDM) &non-insulin-dependent(NIDDM). [Alberti and hockaday,1983].

(1)Type Ia:

Other names used are insulin-dependent,juvenile onset or ketosis-prone diabetes.it is less familial than Type-II and possibly more influenced by environment,exactly the reverse of other inherited diseases in which the more severe form appears to be more transmissible through heredity.It has been suggested that it may be due to viral destruction of B-cells,and British studies have shown it to occur in clusters associated with certain common viral epidemics (e.g.,group B coxackie virus) . It also correlates strongly with inheritance of genetic factors on chromosome 6 . There are significant correlations with certain alleles on the B,C and D loci of the major histocompatibility complex,in particular B8/D3 and B15/D4.Most new cases of this type demonstrate both cell-mediated and antibody-related autoimmunity.[Cahill,1982].

The developement of IDDM correlates with the presence of biologic markers pointing to the involvement of the immune system in the disease process.In addition to clinical observations of association of IDDM with other autoimmune disease and morphologic evidence of a mononuclear cell infilteration of the islets of Langerhans at the onset of the disease , anti-

islet cell antibodies are detected in the serum of IDDM patients.Moreover,a strong genetic association with HLA DR3 and DR4 identifies a genetic background compatible with autoimmune phenomena . Whether autoimmune phenomena are primary or secondary to an initial damage of the islets by infectious agents or other environmental factors is unknown.Whether or not the autoimmune response participates in the selective destruction of insulin secreting cells has been a major issue in the past few years . The presence of T-lymphocytes and anti-islet cell antibodies,which selectively inhibit or lyse insulin secreting cells in vitro,strongly suggests that it may be the case.[Bottazzo et al.,1986].

The findings of lymphocytotoxic antibodies in healthy relatives of Type I diabetics,irrespective of consanguinity,suggests that an environmental agent such as a virus is at least partially responsible for this lymphocytotoxic effect.[Charlesworth et al.,1982].

A considerable interest has been shown in the possibility that the environmental factor might be viral.Coxsackie virus B4 in Europe and mumps virus in India have been incriminated as a result of raising antibody titers of Coxsackie virus B4 has been isolated from the pancreas of a diabetic baby who died following an episode of diabetic ketoacidosis.The isolate from his pancreas caused hyperglycaemia when injected into susceptible mice.[Foster,1980].

Many children who die of Coxsackie virus B4 infection are found to have islet lesions at post-mortem.Congenital rubella is associated with an increased incidence of diabetes in later life , especially in patients with