STUDY OF APOLIPOPROTEINS A and B IN DIABETES MELLITUS

THESIS

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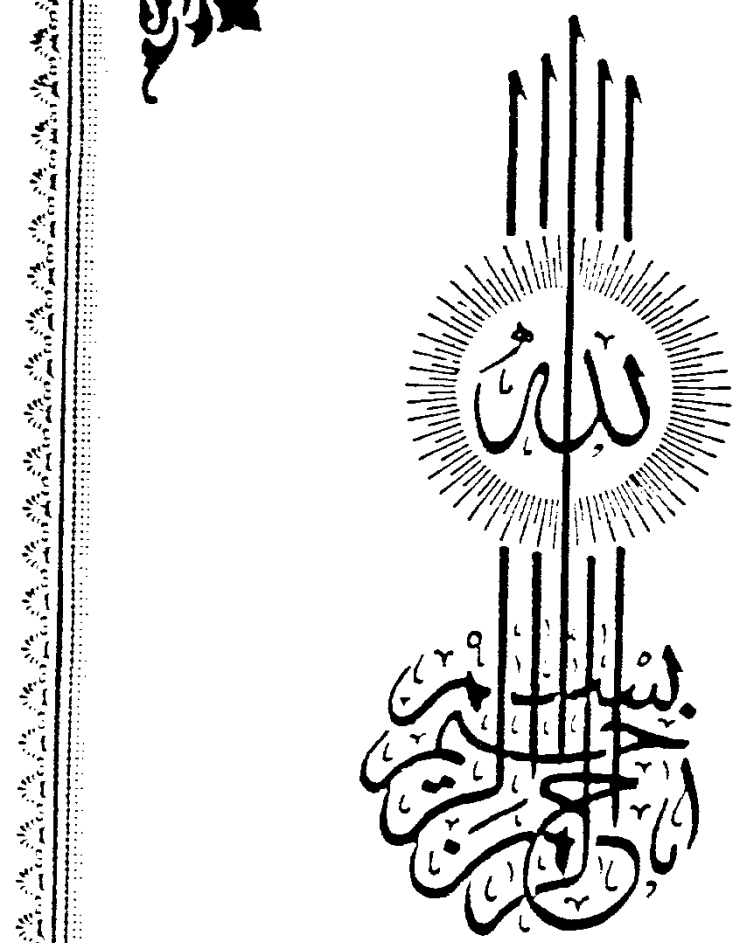

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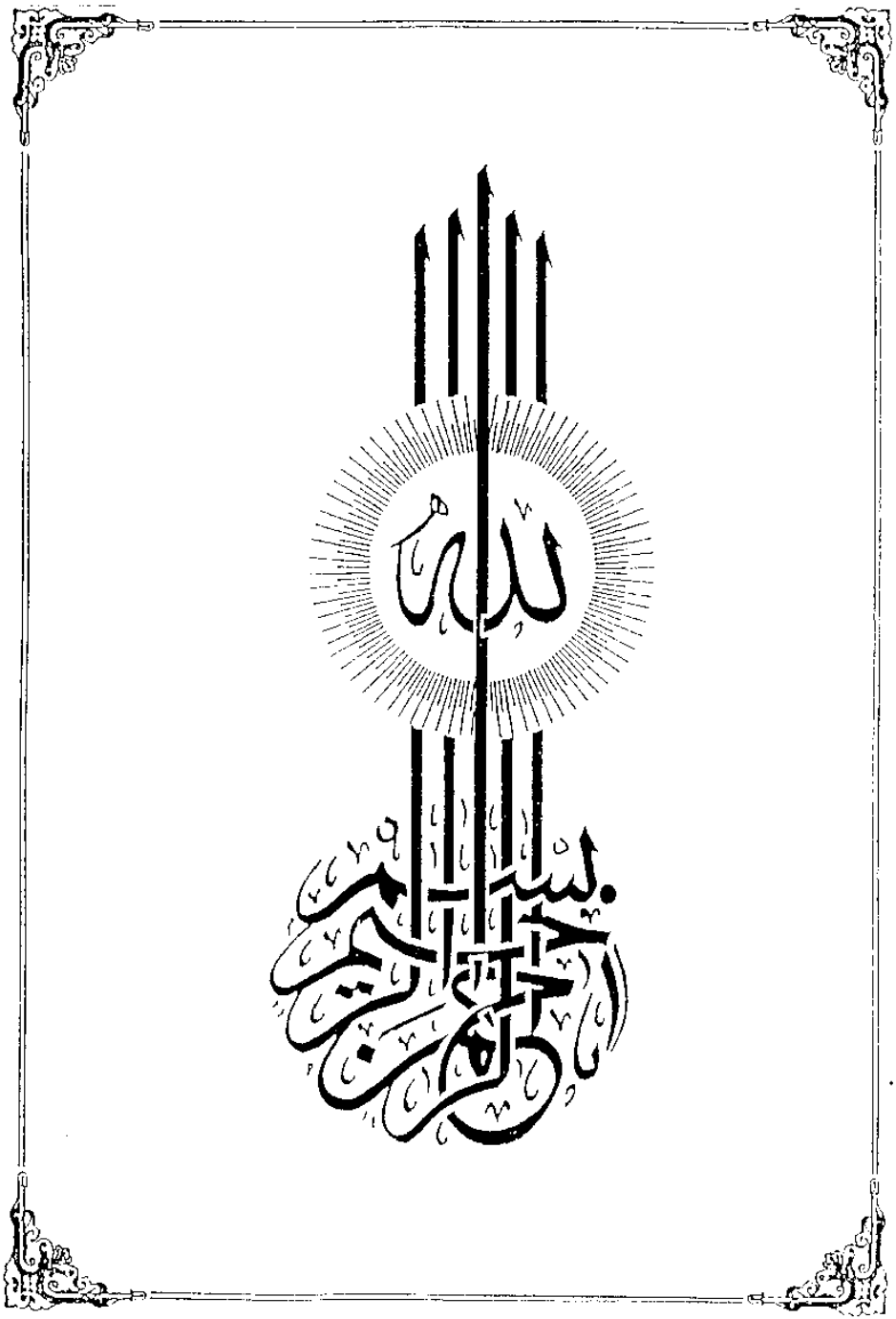

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ABBREVIATIONS

ACTH	*: Adrenocorticotropic hormone.*
Apo	*: Apolipoprotein*
CHD	*: Coronary heart disease*
HDL	*: High-density lipoproteins*
LCAT	*: Lecithin-cholesterol acyltransferase*
LDL	*: Low-density lipoproteins*
LPL	*: Lipoprotein lipase*
VLDL	*: Very-low density lipoproteins*
FFA	*: Free fatty acid*
UEFA	*: Unesterified fatty acid*
IDDM	*: Insulin-dependent diabetes mellitus*
NIDDM	*: Non insulin dependent diabetes mellitus.*
HMG-CoA	*: Hydroxy, methyl glutaryl Co A.*

CONTENTS

INTRODUCTION AND AIM OF THE WORK

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Apolipoproteins are the protein moieties of lipoproteins, they stabilize the lipids in the aqueous plasma. They are synthesized only in two parenchymal cells, the liver and mucosal cells of small intestine (Kreisberg, 1983).

Diabetes mellitus is a biochemico-clinical syndrome characterized by hyperglycemia, glycosuria, and disordered lipid and protein metabolism (Keen, 1981). In a large percentage of cases, diabetes mellitus leads to hyperlipidemia. In addition to the diabetes related secondary hyperlipidemias all types of primary disturbances of lipid metabolism can also be observed in diabetics (Dammann et al., 1990).

As apolipoprotein A and apolipoprotein B represent high density lipoproteins and low density lipoproteins respectively, the aim of this work is to study changes of apolipoprotein A and apolipoprotein B in diabetic patients to see wheather these changes are related etiologically to diabetic hyperlipidemia or not.

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetes mellitus is the most common endocrine disease. The true frequency is difficult to ascertain because of differing standards of diagnosis but probably is between 1 and 2 percent. (Foster, 1991).

The disease is characterized by metabolic abnormalities, by long term complications involving the eyes, kidneys, nerves, and blood vessels, and by a lesion of the basement membranes demonestrable by the electron microscopy. Patients fulfilling these criteria are not homogeneous, and several distinct diabetic syndromes have been delineated (Foster, 1991).

Diabetes mellitus is a disease or syndrome manifested by an increase in blood sugar due to a relative or absolute insulin deficiency. It is a fairly common disease occuring in about 3% of the population. About 5% of the cases have their onset in childhood, most cases have the onset between the ages of 30-70 years (Fajans, 1979).

In the childhood onset cases there is usually a more severe deficiency of insulin whereas the older patients usually exhibits only mild to moderate degrees of insulin deficiency. The disorder is, for the most part, primary and thought to be a genetic disorder which results in some way in a deficiency of insulin. A relatively minor portion of

cases are due to presence of insulin antagonists like excessive growth hormone in acromegaly, excessive catecholamines in pheochromocytoma or excessive hydrocortisone in Cushing's syndrome (Olefsky et al., 1976).

A relatively minor portion of cases may be due to the destruction of the islets of langerhans by chronic relapsing pancreatitis, homocromatosis and possibly occasionally by invasion by certain viruses. thus the bulk of the disorders are of unknown etiology and are genetically transmitted in some obscure manner. The most recent opinions seem to be that it is a polygenic disorder rather than a single locus gene such as autosomal dominant or recessive (Gepts et al., 1981).

It is considered that four general areas are affected in the complete clinical syndrome and that these should be considered in making a clinical diagnosis.

1. Hyperglycemia: There is an abnormality of carbohydrate metabolism resulting in hyperglycemia and often associated with accelerated fat and protein catabolism. This abnormality probably contributes to the other features but seems unlikely to be their sole cause.

2. Large vessel disease : There is accelerated atherosclerosis and medial calcification.

3. Microvascular disease. There is an abnormality of capillary basement membranes characterized by thickness and abnormal function.

These capillary-related lesions are often termed the microvascular concomitants of diabetes.

4. Neuropathy: There are peripheral sensory and motor defects, autonomic nervous system dysfunction, segmental demyelenation and abnormalities of Schwan Cells.

None of these findings is specific for diabetes, as such is also found in other diseases and syndromes. It is likely that more than one mechanism can produce each of these four abnormal findings. (Porte and Holter, 1981).

Since the primary defect in diabetes is unknown, a patient with any one or all of these abnormalities must be considered a possible diabetic. The final decision is based on clinical and laboratory observations and depends largely on the particular frame of reference and concept of the term 'diabetes mellitus' for each clinician (Porte and Holter, 1981).

Clinical classification of diabetes mellitus:

1. Juvenile-onset type Diabetes (Type I):

Insulin deficiency is the most characteristic finding of this type of diabetes mellitus. It is the classic type that we have known for over 2000 years, with sudden onset, severe hyperglycemia and rapid progression to ketoacidosis and death unless treated with insulin (Olefsky and Reavan, 1978).

Patients with type I diabetes are usually of lean body type and prone to episodes of ketoacidosis when they are under stress or experiencing insulin deficiency. The onset of their disease, which may be abrupt, can be heralded by weight loss and hyperglycemic symptoms.

This type of diabetes is usually diagnosed before the age of 30.

It is characterized by selective autoimmune destruction of the beta cells of the pancreatic islets. The delta and alpha cells remain intact.

Unfortunately, as the autoimmune process continues, total insulin deficiency ensues. (Hofeldt, 1991).

About 50% of patients of juvenile diabetes are diagnosed before the age of 21 years with a peak incidence near puberty.

Those patients don't respond to oral hypoglycemic drugs and at autopsy have gross B-cell failure. There is some evidence that this form of the disease is due to certain viral infections that trigger an autoimmune response in genetically susceptible individuals which leads to destruction of the beta cells. This selective immune destruction of beta cells occurs in persons who have certain homologous leukocytic antibodies (HLA). (Chen et al., 1985).

2. Maturity onset diabetes:

Type II diabetes:

Type II diabetes accounts for more than 90% of all cases. In these patients, the postprandial insulin levels are usually elevated, although they may be normal or even decreased when metabolic control is poor.

While type II patients are characteristically not prone to ketoacidosis, some may exhibit ketoacidosis when they are under severe stress (e.g., myocardial infarction or pancreatitis).

The onset of type II diabetes usually occurs after age 40, it is the most common form of diabetes among the elderly. 80% of type II diabetics are obese. Patients with type II diabetes often have a positive family history. The disease occurs as an autosomal - dominant inheritance with varying degrees of penetration (Hofeldt, 1991).

This disease usually has a slow onset and in the begining is often asymptomatic, making it difficult to date the onset of the metabolic abnormality. There is a higher incidence of non insulin dependent diabetes in family members of patients who have this disease than of those with juvenile onset type diabetes (DeFronzo et al., 1983).

This type of diabetes is associated with retinopathy, nephropathy, microvascular disease, neuropathy and