AIN SHAMS UNIVERSITY

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EFFECTS OF VARIOUS DIURETICS ON LIPOPROTEINS PATTERN IN ISCHEMIC AND NON ISCHEMIC PATIENTS

THESIS

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the Master Degree in Cardiology

By

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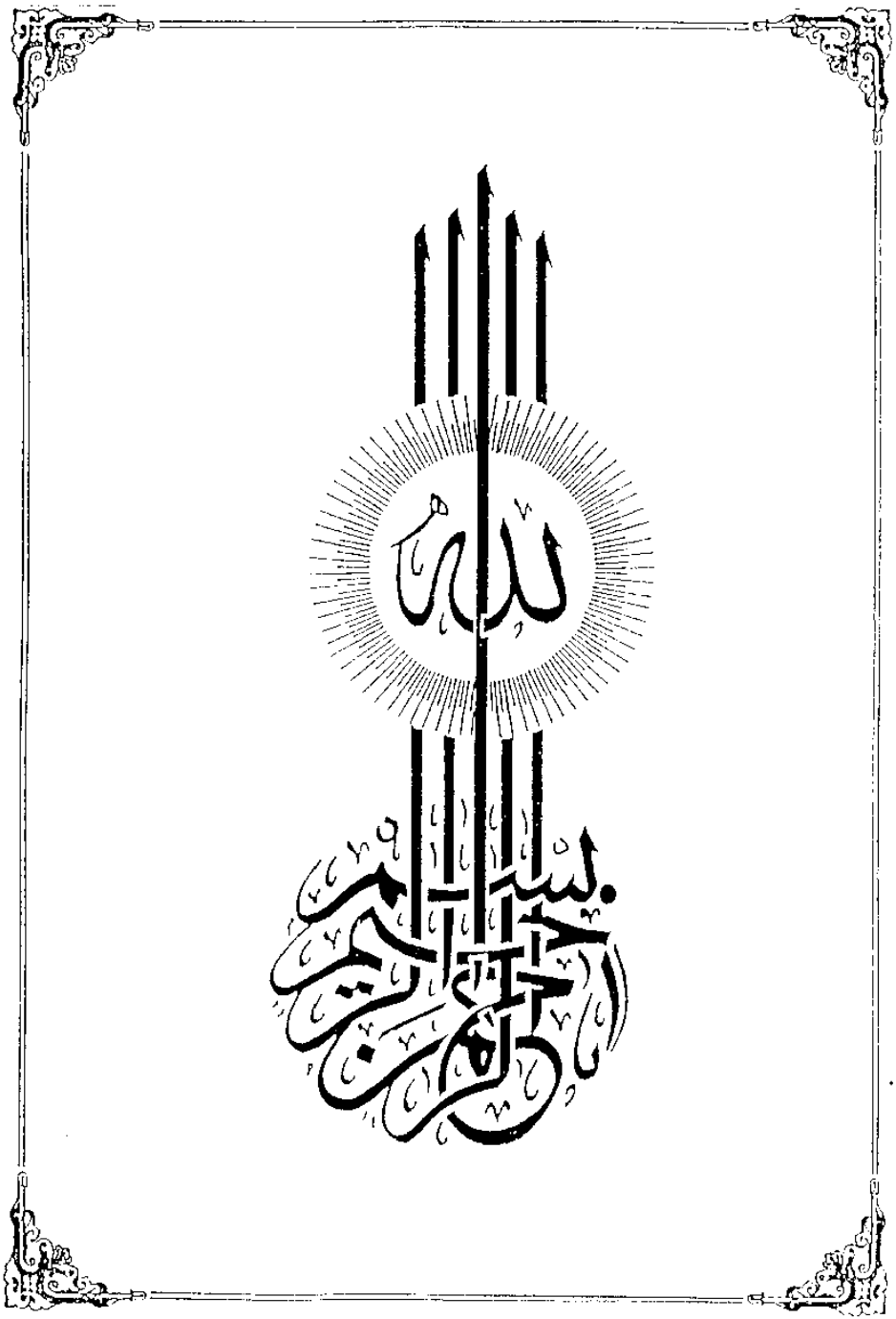

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Introduction

INTRODUCTION

Hypertension is one of the major risk factors for coronary heart disease (CHD) according to epidemiologic studies (Gordon & Kannel 1971; Rosenman et al., 1976). It is perhaps the most readily treatable risk factor for CHD, either by hygienic measures or, when these are not enough, by drug therapy (Culter 1983).

Based on favorable ratio between blood pressure lowering efficacy and known relative side effects,diuretics are established as the major drugs in the treatment of hypertension (Dustan et al., 1974). Lately, the use of diuretics has been recommended also for the treatment of the mildest forms of hypertension, with a view to avoiding the complications that may develop later in the course of the disease (Culter 1983). Yet a number of large intervention trials have failed to show any substantial benefit of blood pressure lowering on CHD mortality. In fact, according to the recent Multiple Risk Factor Intervention Trial (MRFIT), CHD mortality did not decrease after stepped-care treatment of hypertension, counseling for cigarette smoking and dietary advice for lowering blood cholesterol levels as compared with a similar population who received only their usual sources of health care in the community. This is in marked contrast

to the significant improvements in stroke, heart failure and renal failure that have been reported as a result of controlling high blood pressure (MRFIT 1982). Because CHD is rsponsible for the largest number of deaths among patients with cardiovascular diseases, its lack of response in hypertension to conventional therapy based mainly on diuretic drugs constitute a major problem in cardiovascular care (Ames 1983).

The lack of impact of blood pressure lowering on CHD mortality has raised the question of whether the antihypertensive agents commonly used may be offsetting the potential benifit of such a reduction. The effect of diuretics on blood lipids and lipoproteins have been cited as a probable cause.

Schoenfield and Goldberger (1964) reported that serum cholesterol increased in five of six cardiac patients treated with the thiazide diuretic bendroflumenthiazide and decreased when the drug was withdrawn. This report was not widely acknowleged or confirmed untill 1976 when Ames and Hill have reported increases in serum cholesterol of 11 mg/dl and serum triglycerides increases of 34 mg/dl in patients treated with chlorthalidone. During the following 10 years, several workers studied the effects of diuretics on blood lipids and lipoproteins. Although their

results were not identical, yet the majority of these workers reported an increase in total cholesterol, total triglycerides, low density lipoprotein-cholesterol; together with a slight decrease in high density lipoprotein-cholesterol. These observations are of interest since epidemiological studies indicate that total cholesterol and low density lipoprotein-cholesterol concentrations are positvely correlated with CHD risk; whereas, high density lipoprotein-cholesterol is negatively correlated with CHD risk (Gofman et al. 1966, Slack 1969, Kannel et al. 1971, Carlson & Bottiger 1972, Stone et al. 1974, Miller & Miller 1975, Castelli et al. 1977, and Gordon et al. 1977). There has been a growing use of indices or ratios as indicatives of CHD risk, these are: total cholesterol / high density lipoprotein-cholesterol and low density lipoprotein-cholesterol / high density lipoprotein-cholesterol ratios (Castelli et al. 1977, Gordon et al. 1977).

AIM OF WORK

AIM OF THE WORK

The aim of the present study is to: **(1)** delineate the short-term effect of the 3 commonly used diuretics (hydrochlorothiazide, furosemide and spironolactone) on the blood lipids and lipoproteins; **(2)** evaluate the CHD risk status of the patients (in the form of risk ratios) before and after therapy with these diuretics; **(3)** compare the response of both sexes towards each diuretic; **(4)** compare the response of both ischemic and non ischemic patients towards each diuretic.

Plan of the work :

1- Choice of 60 mild hypertensive patients which include both sexes and both ischemics and non-ischemics.

2- Classification of patients randomly into 3 equal groups each receiving one of the 3 mentioned diuretics

3- Determination of the lipid profile of each patient before and after therapy with the diuretic.

Review of Literature

REVIEW OF LITERATURE

1) A brief account on metabolism of lipoproteins

Classification of lipoproteins :

A lipoprotein can be simply visualized as a globular structure with an outer solubilizing coat of protein and phospholipid and an inner hydrophobic neutral core of triglyceride and cholesterol. The protein and phospholipid import solubility to the otherwise insoluble lipids. The protein moiety of a lipoprotein is called "apoprotein".

Most systems of classification are based on the physiochemical properties of the lipoprotein complex.

The four most frequent used systems are based on: analytical ultracentrifugation, ultracentrifugation, electrophoresis and precipition tehcniques.

Electrophoretic pattern shows that chylomicrons remain at the origin; pre-betalipoproteins migrate in the beta one globulin area; betalipoproteins migrate in the beta two globulin area and alphalipoproteins migrate in the alpha one globulin area.

Using the ultracentrifuge, one can separate the lipoproteins into: (1) The chylomicrons; the lightest

lipoproteins of a density less than the plasma; **(2)** "VLDL": separated at density less than 1.006 gm/ml; **(3)** "LDL": separated at density between 1.006 and 1.063 gm/ml; **(4)** "HDL": separated at density between 1.063 and 1.210 mg/ml

These lipoprotein classes correlate with electrophoretic pattern: pre-betalipoproteins with "VLDL"; betalipoproteins with "LDL" and alphalipoproteins with "HDL" (Kaplan & Pesce 1984).

INDIVIDUAL LIPOPROTEINS METABOLISM

A- Chylomicrons

After intestinal absorption, fatty acids and cholesterol are reesterified in the mucosal cells to form triglycerides and cholesterol esters. These are packaged together with intestinal apoproteins (A and B) and polar lipids (phospholipids and cholesterol) and are secreted as nascent chylomicrons. These latters acquire additional apoproteins (mainly E & C) from HDL in the blood and lymph (Havel 1982).

The modified chylomicrons then interact with lipoprotein lipase enzyme (LPL) in peripheral tissue resulting in rapid hydrolysis of most of the triglycerides in their core. At the same time, much of the surface lipid and apo C, together with all of apo A, are transfered to HDL. Loss of apo C_2, the essential co-factor of LPL, reducesthe affinity of the particles for LPL.

The chylomicron remnants are taken up by the liver where they ae degraded by hepatic lysozymes. Apo E of the chylomicron remnants is essential for this step since it is recognized by an "apoprotein E receptor" on the surface of the hepatic parenchymal cells. This hydrolysis

leads to release of cholesterol; which, in turn, is excreted in the bile or incorporated into hepatogenous lipoproteins (Kaplan & Pesce 1984).

B- Very low density lipoprotein (VLDL)

VLDL contains 52% triglycerides, 18% phospholipids, 22% cholesterol, and about 8% proteins. Apo B accounts for 30-35%, with apo C comprising over 50% of the apoprotein content in VLDL.

The major stimulus for VLDL synthesis is the demand for triglycerides transport. In the intestine, this demand is created by dietary fat influx, but in the liver the stimulus is the availability of precursors for endogenous triglycerides synthesis, of which fatty acids are the principal stimuli. When dietary cholesterol is sufficient, the liver uses that source (derived from the receptor mediated uptake of chylomicron remnants) for VLDL synthesis. When dietary cholesterol is insufficient, the liver synthesizes its own cholesterol (Eisenberg 1975).

After acquisition of more apo C from HDL in the circulation, the VLDL interact with LPL enzyme and remnant particles are formed, as with chylomicrons. During further