THE EFFECT OF ANTIHYPERTENSIVE DRUGS ON LIPID METABOLISM IN HEMODIALYSIS PATIENTS

THESIS

SUBMITTED FOR PARTIAL FULFELIMENT OF
MASTER DEGREE IN MEDICINE

BY

HANAN GABER EL-DISAWY
M.B. B.Ch.

SUPERVISED BY

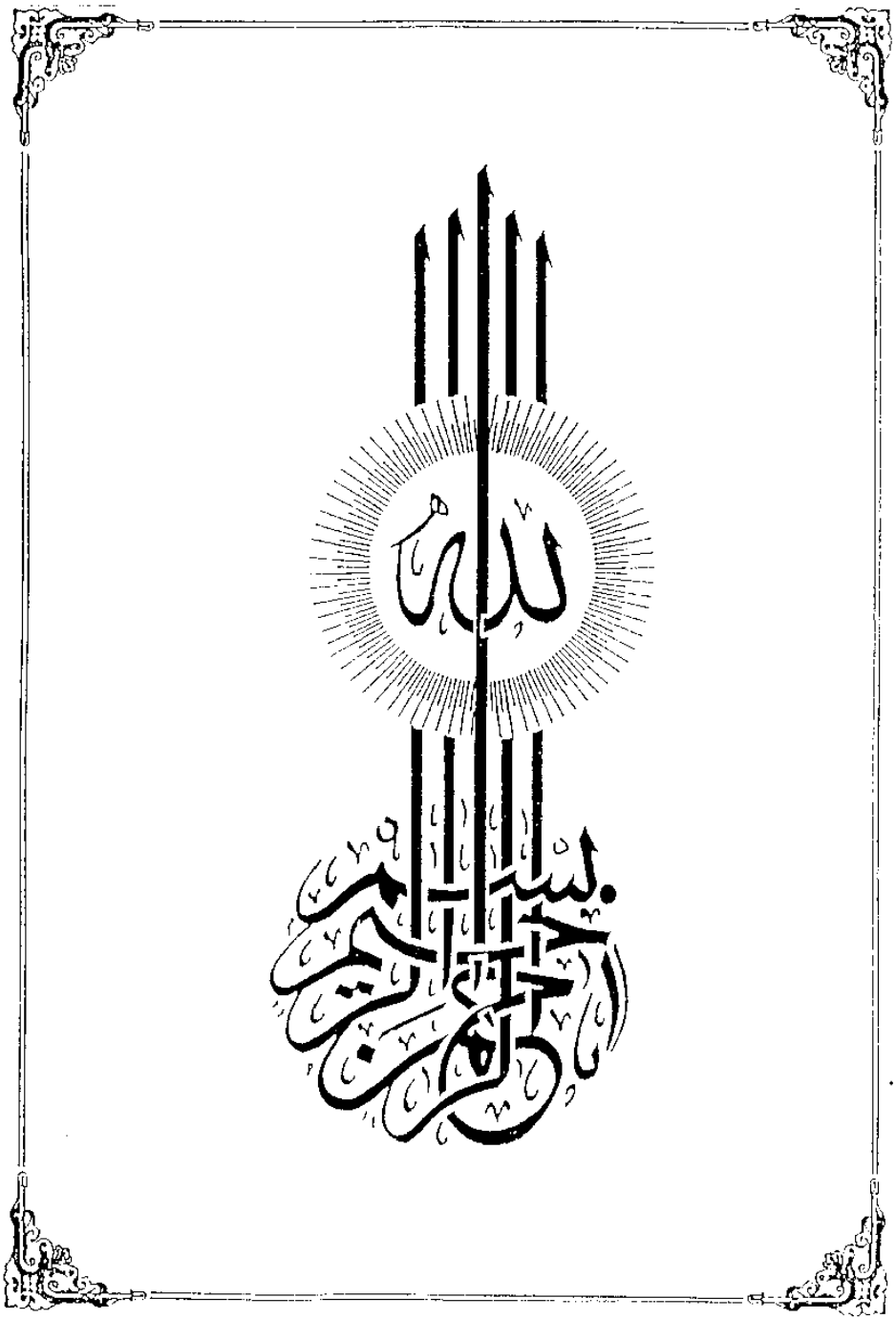
PROF. DR. ABOU EL MAATY NABIEH
PROFESSOR OF INTERNAL MEDICINE
FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

DR. MOHAMED FAHMY ABD EL AZIZ
ASS. PROFESSOR OF INTERNAL MEDICINE
FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

DR. HANY ALY REFAAT
ASS. PROFESSOP OF INTERNAL MEDICINE
FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

1993



ACKNOWLEDGEMENT

I'm deeply indebted to **Prof. Dr. Abou El Maaty Nabieh** Professor of Internal Medicine Faculty of Medicine Ain Shams University for his conscientious guidance, faithful, unfailing support, and for his precious time and effort he offered generously throughout this work.

Cordial thanks one owed to **Prof. Dr. Mohamed Fahmy Abd El** Aziz Ass. Professor of Internal Medicine Faculty of Medicine Ain Shams University for his unlimited help during this work.

I would like to express my deep sincere gratitude to **Prof. Dr. Hany Aly Reffaat** Ass. Professor of Internal Medicine Faculty of Medicine Ain Shams University for his kind supervision, Continuous encouragement and wise directions

No Words can express my gratitude to **Dr. Mohamed Amr** Ayad, Head of Unit of Nephrology and Transplantation Mataria Hospital for his encouragement, continual advice and helpful suggestions.

CONTENTS

LIST OF ABBREVIATION

1	AHT	: Antihypertensive.
2	ANP	: Atrial natriuretic peptide.
3	AVP	: Arginine vasopressin.
4	CHD	: Coronary heart disease
5	CO	: Cardiac output.
6	CRF	: Chronic renal failure.
7	ESRD	: End stage renal disease.
8	GFR	: Glomerular filtration rate.
9	HDL	: High-density lipoprotein.
10	IDL	: Intermediate-density lipoprotein.
11	LDL	: Low - density lipoprotein
12	LPL	: Lipoprotein lipase.
13	MI	: Myocardial infarction.
14	PRA	: Plasma renin activity.
15	Tg	: Triglycerides
16	TPR	: Total peripheral resistance.
17	VLDL	: Very low-density lipoprotein.

INTRODUCTION AND AIM OF THE WORK

INTRODUCTION
AND
AIM OF THE WORK

Renal replacement therapy by regular hemodialysis is nowadays a frequent modality of therapy maintaining thousands of human beings on life despite their serious affection. Hypertension is frequently a major problem in these patients. Unfortunately, many of the antihypertensive drugs currently used, have a deliterious effect on lipid metabolism, which is already altered in uremic patients on regular hemodialysis. The additive effect of the antihypertensive therapy on this altered lipid metabolism will add to the importance of this risk factors (Day, et al., 1982). These patients experience an explained acceleration of atherosclerosis, and develop in a few years vascular lesions which evolve in the non-uremic population over a period of many decades (Bagdade et al., 1976).

Hence the choice of different antihypertensive molecules will affect either negatively or positively the lipidemic profile of the patients.

AIM OF THE WORK:-

Is to study and evaluate the effect of different antihypertensive drugs (one calcium-channel blocker, one beta-blocker, one angiotensin converting enzyme inhibitor and one vasodilator) on lipid metabolism in uremic patients on regular hemodialysis therapy.

REVIEW OF LITERATURE

HYPERLIPIDEMIA AND ATHEROSCLEROSIS IN CHRONIC RENAL FAILURE

Introduction:-

The association between hyperlipidemia and kidney disease was first noted in 1827 By Bright who described lactescent serum in patients with nephrotic syndrome. The advent of dialysis and renal transplantation has allowed more detailed study of lipoprotein metabolism in C.R.F and accumulating evidence of accelerated atherosclerosis in these patients has renewed interest in uremic hyperlipidemia. Many studies have demonstrated that lipid abnormalities occur in patients with C.R.F before and after institution of dialysis therapy (Chan et al., 1981). The most common lipid abnormality observed is hypertriglyceridemia.

The reported incidence of this abnormality in dialysis patients have varied between 28 and 100% (Ponticelli, et al., 1978).

Comparison of peritoneal and hemodialysis patients shows a similar frequency in both groups (Chan, et al., 1982).

There is now considerable evidence that patients on renal replacement therapy experience an increased risk of death from ischemic heart disease. Hyperlipidemia is likely to be an important risk factor in the development of premature atherosclerosis in such patients, but the serum triglyceride levels observed do not adequately explain the increased incidence of myocardial infarction and it is possable that subtle changes in lipoprotein particles may increase their atherogenicity (Somer et al., 1979).

In renal transplantation, it is important to appreciate that hyperlipidemia continues to affect many renal allograft recipients even when graft function is normal. Following transplantation, cholesterol levels tend to rise and HDL -cholesterol may return to normal. Transplant patients continue to experience an increased incidence of death from ischemic heart disease when compared with the normal population (Brunner et al., 1979) and lipid abnormalities like wise constitute an important risk factor in these patients. (Wheeler et al., 1989).

* Normal lipoprotein metabolism:-

The major serum lipids in human are cholesterol, triglycerides, phospholipids and fatty acids (Levy and Rifkind, 1980).

Cholesterol and triglycerides are virtually insoluble in water and circulate in the blood stream associated with proteins in lipoprotein particles. The particles are composed of a core containing cholesterol esters and triglyceride surrounded by an outer coating of phospholipids, unesterified cholesterol and apoproteins.

Differences in protein and lipid composition allow classification of particles into five major groups which can be roughly separated by ultracentrifugation. The properties of these five groups, chylomicrons (CM), very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL) and high density- lipoproteins (HDL) are outlined in table 1. (Tatami et al., 1981).

The genetically determined apoprotein component is vitally important in maintain the conformation of the particle, in influencing enzymatic degradation and in acting

as a ligand for cellular uptake of particles by specific receptors. At least eight major classes of apoprotein (opo AI, AII, B 48, B-100, CI, CII, CIII and E (table 2), have been identified and the primary sequences of all have been determined.

The apoprotein composition of each lipoproteins subclass is well defined although several apoproteins can exchange between particles. The identification of abnormalities of apoproteins, their genes and receptor has improved our understanding of many disorders of lipoprotein metabolism (Rees, 1987).

Table (1) Physiochemical properties of human lipoproteins.

Class	Density g/ml	Electrom-obility agorose-gel.	Trigly-ceride %weight	Esterif. cholest-erol % weight	Major apoproteins
CM	>0.95	Origin	80-95	2-4	AI, AII, B48, CI, CII, E
VLDL	0.95-1.006	Pre-β	45-65	16-22	B 100,CI,CII, CIII, E
IDL	1.006-1.019	β	35	25	B-100, E
LDL	1.019-1.063	β	4-8	45-50	B-100
HDL	1.063-1.210	alpha	2-7	15-20	AI,AII,CI, CII, E

Table (2) Molecular mass and functions of human apoproteins:-

Class	Molecular mass Daltons	Functions
AI	28,000	Activation LCAT
AII	17,000	-
B-48	264,000	-
B-100	249,000	Ligand for LDL receptor
CI	6,500	Activation LCAT
CII	8.800	Activation lipoprotein lipase
CIII	8.750	Inhibition lipoprotein lipase
E	36,000	Ligand for LDL receptor

Chylomicrons (CM), the largest lipoproteins, are synthesized in the intestine from dietary triglycerides and cholesterol. These particles passes apo B 48, AI and All, but acquire apo CI, CII, CIII and apo E from HDL in the lymphatic system (Tietz, 1987).

VLDL particles synthesized and secreted by the liver, are rich in triglycerides and possess the larger apo B 100, apo CI, CII, CIII and apo E. (Tietez, 1987).

Both CM and VLDL are hydrolyzed in the plasma compartment by the endothelial enzyme lipoprotein lipase. Apo CII on the surface of the lipoprotein particle increases the activity of this enzyme, whilst apo CIII inhibits it.

Fatty acids released by hydrolysis provide energy for muscle contraction and re-esterified in adipocytes to form triglyceride stores. Hepatic uptake of intermediate particles is inhibited by the presence of apo CIII, but this is removal along with apo A and incorporated into new HDL particles. The end products of CM and VLDL metabolism are the CM remnant and LDL respectively.

The CM remnant posses apo B 48 and apo E and is avidly taken up by the liver via a receptor which appears to be specific for apo E. The cholesterol-rich LDL particles each have a single molecule of apo B which is recognized by the apo B/E receptor of the liver and extra hepatic tissues (Levy and Refkind, 1980). Binding to this cell surface receptor is followed by internalization of the receptor /lipoprotein complex, recycling of the receptor and degradation of the lipoprotein by lysosomal enzymes thus delivering triglyceride and cholesterol to the cell. (Kesaniemi et al., 1987).

To maintain cholesterol homeostasis, internalization of LDL regulates three cellular processes. Firstly cholesterol synthesis by the cell itself is slowed by suppression of the rate-limiting enzyme 3- hydroxy-3- methyl glutaryl co-enzyme A reductase (HMG-CoA reductase). Secondly, the cholesterol-esterifying enzyme, Acyl CoA cholesterol acyl transferase (ACAT) is activated to allow storage of incoming cholesterol in the cell. Finally, synthesis of the apo B/E receptor itself is inhibited when the intracellular cholesterol content rises. Alternative pathways of LDL uptake

exist and may be particularly important when the apo B/E receptor is absent or defective (e.g. familial hypercholesterolemia (Tolleshaug et al., 1983), or when the apoprotein ligands are abnormal as may occur in uremia. The macrophage has an important role in scavenging cholesterol and can ingest LDL by an alternative receptor mechanism with a particularly high affinity for the acetylated form of the lipoprotein (Broun and Goldstein 1983). Macrophages that have taken up large amounts of cholesterol becoming laden with cholesterol ester droplets (foam cells) are found in atheromatous plaques and this back - up pathway of cholesterol metabolism may contribute to lipid deposition in the atheromatous plaque.

High-density lipoproteins, a group of small heterogeneous particles, are synthesized by the liver and intestine and secreted as discoid precursors possessing apo AI, AII and C (Anderson, et al., 1978). These precursors are converted to mature spherical particles by the enzyme lecithin-cholesterol acyl-transferase (LCAT) which catalyses the esterification of cholesterol. During maturation, HDL accepts lipid from the triglyceride - rich lipoproteins and from cell membranes. Cholesterol laden cells bind HDL, possibly via a receptor, promoting efflux of lipid stores (Fidge and Nestel, 1985). This process, termed reverse cholesterol transport, may explain the negative correlation between HDL-cholesterol and accelerated vascular disease. During maturation the apoprotein content of HDL is also modified. Apo E originating from VLDL and CM displaces apo AI to become predominant, apo AI circulating back to newly formed HDL particles. The fate of mature HDL remains uncertain. It may be taken up by peripheral tissues in the same way as LDL via the apo B/E receptor but hepatic uptake is important if excess cholesterol