Apolipoprotein B and certain other lipid parameters in coronary atherosclerosis

Thesis

submitted for partial fulfilment of

the M.D. degree of Clinical Pathology

By

NADIA ALY ABDEL SATTAR

M.Sc. Clinical Pathology

Supervised by

Prof. SAMIR HANNA SADEK

Prof. of Clinical Pathology

Ain Shams University

Prof. MAHMOUD SABRY SALLAM

Prof. of Clinical Pathology

Ain Shams University

Prof. MOHAMED KHAIRY ABDEL DAYEM

Prof. of Cardiology

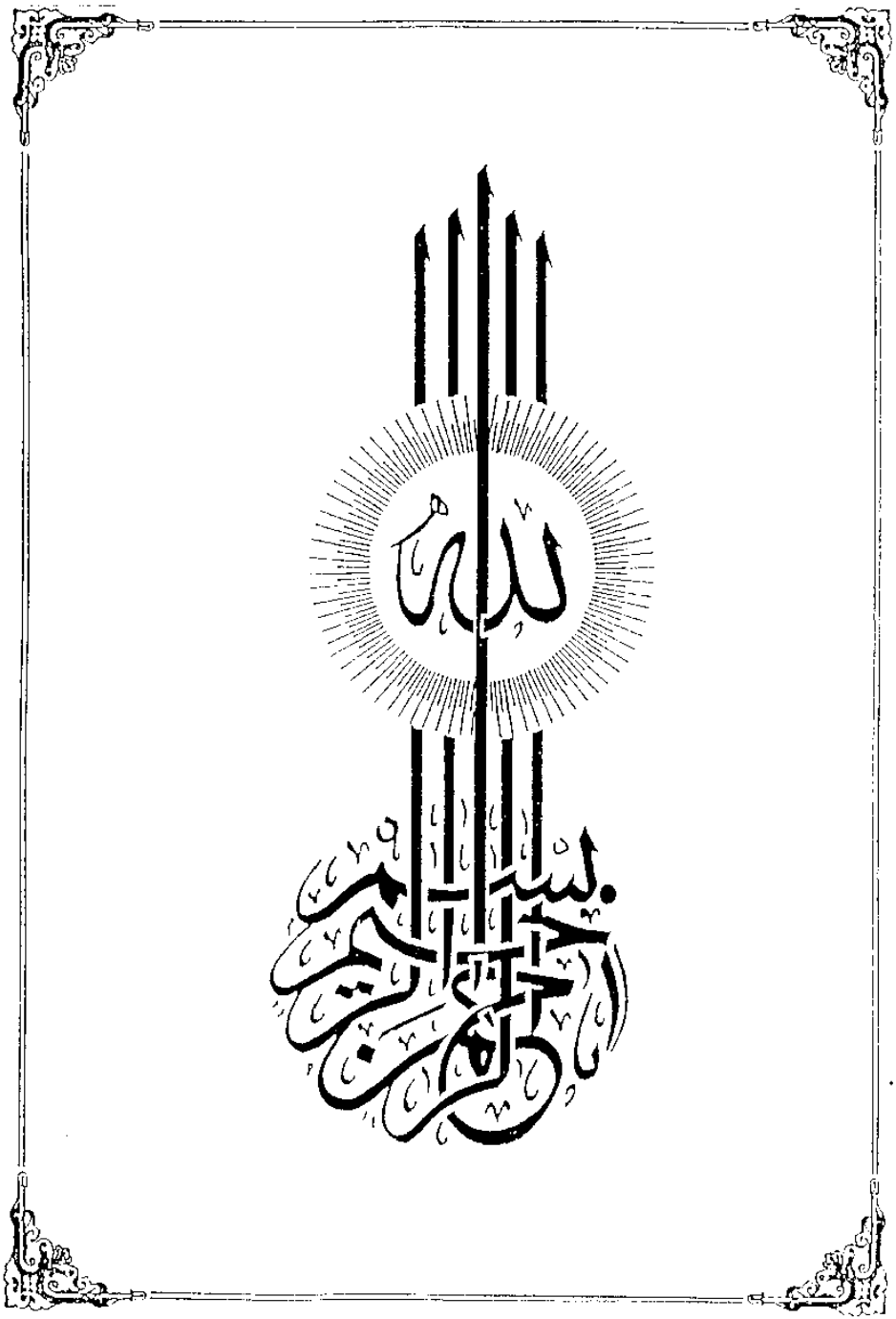
Ain Shams University

Faculty of Medicine

Ain Shams University

1986

بسم الله الرحمن الرحيم



ACKNOWLEDGEMENT

I wish to express my deepest gratitude to Prof. Samir Hanna Sadek. His valuable supervision and continuous advice made the completion of this work possible. He generously offered me with many materials which were necessary for my practical work. I will never forget his fruitful guidance and endless help.

I would like also to express my sincere thanks and appreciation to Prof. Mahmoud Sabry Sallam for his close supervision and faithful review of this work. His helpful guidance was attending every part of this thesis. Without his help this work would have never come to end.

I am greatly indebted to Prof. Mohamed Khairy Abdel Dayem. He offered me a great help in obtaining a large number of cases and interpreting their results. I am thankful for giving me a lot of his time and attention.

My sincere gratitude should be expressed to Prof. Ismail Sallam, professor of cardiosurgery, Ain Shams University, for providing me with a good number of cases of this thesis.

My deep thanks are to all the Staff of Clinical Pathology Department, all the Staff of cardiac catheterisatien, Cardiology Department, my colleagues and all the patients who co-operated with me during this work.

Last but not least, I would like to record a debt of gratitude to my family for the continuous support and help which I recieved throughout the course of my work.

CONTENTS

INTRODUCTION
AND
AIM OF THE WORK

"INTRODUCTION"

I GENERAL INTRODUCTION AND AIM OF WORK:

Coronary atherosclerosis is a common cardio-vascular disease which develops over several decades. It starts to manifest itself clinically as angina pectoris, myocardial infarction or sudden cardiac death after many years of silent development of atherosclerotic vascular stenosis. Since this disease is a common and serious one, it is apparent that preventive medicine on both the economical and medical levels, is mandatory. As laboratory investigations play a major role in preventive medicine, it is essential to study the risk factors related to coronary atherosclerosis so as to help in the prevention or prediction of such a serious disease.

The principal risk factors and atherosclerotic lesions have been studied by different epidemiologic surveys. Hyper lipoproteinemia is considered to be a major risk factor in the development of coronary atherosclerosis. Lipoproteins circulate in plasma as particles , each composed of several lipids and a variable number of proteins called apolipoproteins. Recently, some workers are claiming that the addition of apolipoprotein B to other lipid parameters is a valuable datum in the prediction of patients with coronary atherosclerosis.

One of the best investigations to study the coronary arteries is coronary angiography. Using this procedure, atherosclerotic lesions can be defined with considerable accuracy as regards the site of the lesion, the degree of atherosclerosis, and the number of affected vessels. Therefore correlating the angiographic findings with apolipoprotein B and other lipid parameters may extend our understanding of the atherosclerotic process and in turn may help in better prediction of patients at risk. The aim of this work is to do a correlative study between the level of apolipoprotein B, triglycerides, cholesterol, LDL-cholesterol and HDL- cholesterol with angiographic findings in Egyptian patients to find the relation of these parameters with coronary atherosclerosis. This may also help to search for the most non invasive predictive parameter of coronary artery disease.

REVIEW OF LITERATURE





II REVIEW OF LITERATURE:

(A) APOLIPOPROTEINS

1- Definition:

Lipids are transproted in plasma in the form of lipoproteins. Every lipoprotein molecule has two basic chemical components, one of them is lipid and the other is protein. The protein component of the lipoprotein molecule is called apolipoprotein.

2-Apolipoprotein Nomenclature and Types:

It is now widely agreed that there is a heterogenous group of apolipoproteins which differ in their primary, secondary and tertiary structure as well as their functions and distribution throughout the whole lipoprotein spectrum. Five of these apolipoproteins have already been sequenced and numerous reports have appeared detailing the unique characteristics that allow these proteins to bind lipid (Schaefer et al., 1978a).

Unfourtunately, overlapping systems of nomenclature for apolipoproteins have led to some confusion. The A,B,C system of Alaupovic (1971) is coming into increasingly wider use and will be used throughout this review. According to this system the different apolipoproteins are called apo A,B,C,D,E,F. Apo A is further subdivided into Apo AI,A-II,A-IV. and apoC into

C-I,C-II,C-III. Another nomenclature is based on the terminal amino acids. Thus apo A-I. is "Asp-apolipoprotein- Gln" indicating that Aspartate is at the N.terminus while Glutamine at the C.terminus (Varley et al., 1980).

Kostner and Alaupovic in 1972 have postulated that the plasma lipoprotein system consists of a mixture of individual lipoprotein families each of which is characterized by the presence of a single apolipoprotein or its constituent polypeptides. In contrast to the operational concept based on five major density classes their chemical concept currently recognizes, as a first approximation, three lipoprotein families: lipoprotein family LP-A characterized by apo A, lipoprotein family LP-B by apo-B, and lipoprotein family LP-C by apo-C. Although this classification system recognizes that varying concentrations of each lipoprotein family may exist in most, if not all, segments of density spectrum. It establishes apo-fractions to be the sole determinants of lipoprotein as definable chemical entities. They were able to isolate and separate LP-A, LP-B, LP-C families from normal high density lipoprotein (HDL) and provided the first experimental evidence for the postulated existance of lipoprotein families. According to this chemical concept an apolipoprotein is defined as a protein which binds neutral lipids and phospholipids to form soluble polydisperse lipoprotein family.

3- Position of The Apolipoprotein in Relation to The Lipoprotein Molecule:

The lipoprotein molecules especially those of the high density lipoprotein (HDL) and low density lipoprotein (LDL) have a certain spatial configuration. The hydrophilic molecules are present on the surface (polar coat) while the hydrophobic molecules lie in the center (apolar core) of the lipoprotein molecule. Three types of components are present at the surface:

- Apolipoproteins which are in part highly hydrophilic.
- Non-esterified cholesterol which is slightly hydrophilic due to its free secondary alcoholic group.
- Most of the phospholipids.

Phospholipids have the double property of being hydrophilic (ionized phosphoryl choline or ionized phosphoryl ethanol amine groups) and hydrophobic (the aliphatic side-chains of the two fatty acid molecules esterifying glycerol). The hydrophilic groups face the outer coat while the hydrophobic groups face the inner apolar core of the macromolecule.

There are three extreme possibilities for the location of the protein in the outer surface shell: -

(a) Interdigitating completely between the surface lipids.

(b) Occupying a monolayer completely covering the outer polar phospholipid.

(c) Occupying autonomous domains in the matrix of polar lipid.

Various combinations of these extreme cases are also possible (Morrisett et al., 1975).

4- Structure and Physical Properties:

a-Apolipoprotein A:

It is further subdivided into A-I, A-II and A-IV.

i- Apo A-I:

Apo A-I is the major apolipoprotein of HDL. Two different amino acid sequences have been reported for human apo A-I. The one reported by Baker et al., (1974) consists of 245 amino acid residues and a molecular mass of 28. 331 daltons. A later study reported apo A-I to consist of 243 amino acid residues, at least 23 of which were different from those reported by Baker et al (Brewer et al., 1978). Glutamine is the carboxy terminal amino acid and aspartic acid is the amino terminal (Shaefer et al., 1978 a). It contains three residues of methionine and four of tryptophan, but no cysteine, cystine or isoleucine (Morrisett et al., 1975).

Three strutural variants of apo A-I are reported. One of them was discovered in an italian family. It was designated A-I Milano apoprotein and denoted A-I cys. It contained two amino acid residues, cysteine and leucine which were not present in the amino acid sequence of normal human apo A-I. This variant has a familial tendency as it was found in a patient and his children (Weisgraber et al., 1980). Two other variants of apo A-I were demonstrated by Uterman et al., (1982). One was identified in a patient with hypertriglyceridemia and low HDL-cholesterol. It was called apo A-I Marburg. The genetic character of apo A-I Marburg has been established by an extensive study of the proband's family in which 14 individuals with apo A-I mutant were detecded in four generations of the Kindred. Affected family members, including the proband, were heterozygous having normal and variant apo A-I. Normal apo A-I focuses as one major band (apo $A\text{-}I)_1$ and one minor band (apo $A\text{-}I)_2$ by isoelectric focusing technique. In the heterozygotes for the Marburg variant, a second set of apo A-I proteins occurs in a more acidic position. The other variant of apo A-I was observed in a healthy blood donor. This individual exhibited an additional more alkaline apoprotein with an apparent pI of 5.67. This variant was designated apo A-I Giessen.

ii- Apo A-II:

Apo A-II is also a structural protein of HDL. It is composed of two identical protein chains of 77 amino acids