DISTURBANCE IN LIPID METABOLISM IN RHEUMATOID ARTHRITIS AS A CARDIOVASCULAR RISK FACTOR

A Thesis to be presented by

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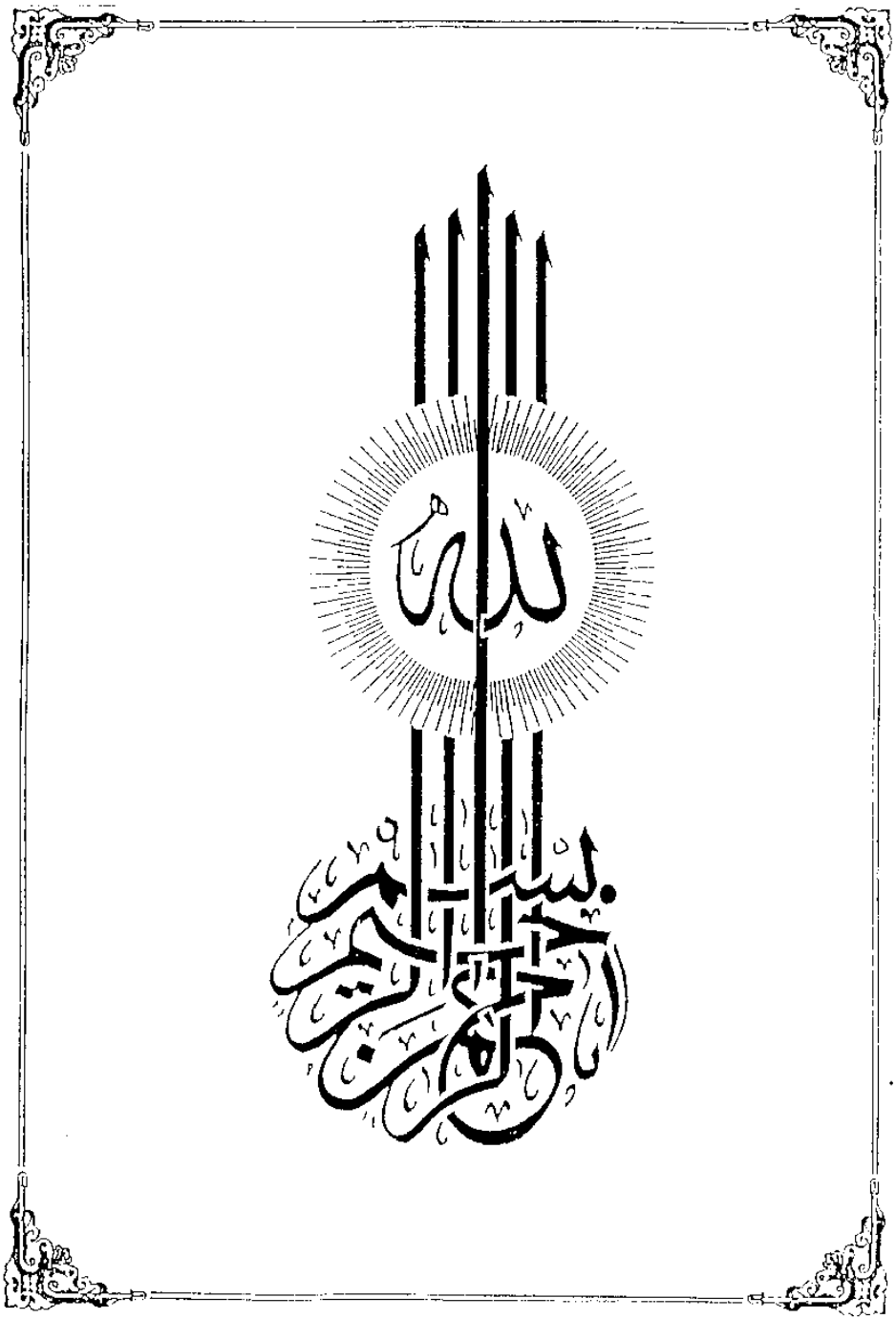

List of Abbreviations

ANA	Antinuclear antibody
APO	Apolipoproteins
C3	Third component of complement
Chylo	chylomicron.
CNS	Central nervous system
CRP	C- reactive protein
DIC	Disseminated intravascular coagulopathy
ESR	Erythrocyte sedimentation rate
HDL(HDLs)	High density lipoproteins
HDL-C	High density lipoprotein cholesterol
IDL(IDLs)	Intermediate density lipoproteins
Ig	Immunoglobulin
JRA	Juvenile rheumatoid arthritis
LCAT	Lecithin cholesteral acyl transferase
LDL(LDLs)	Low density lipoproteins
LDL-C	Low density lipoprotein cholesterol
LPL	Lipoprotein lipase

NSAID	Non steroidal anti-inflammatory drug
PCAT	Phosphatidyl choline cholesterol acyl transferase
RA	Rheumatoid arthratis
RF	Rheumatoid factor
VLDL (VDLs)	Very low density lipoproteins

CONTENTS

Introduction

INTRODUCTION

An increased mortality has been reported in hospital inpatients with rheumatoid arthritis compared with the general population. The most common cause of death in patients with rheumatoid arthritis as in the general population was cardiovascular disease (***Mutru et al., 1985***). Some studies found an even higher incidence of cardiovascular disease in patients with rheumatoid arthritis than in controls (***Prior et al., 1984***).

Increased concentrations of total cholesterol, low denistylipoprotein-cholesterol and total apolipoprotein B have been found to be associated with an increased risk for cardiovascular disease. Even low concentrations of high density lipoprotein-cholesterol and apolipoprotein AI have been found to be risk factors for cardiovascular disease (***Kottke et al., 1986***).

In patients with infalmmatory polyartheritis the serum concentration of high density lipoprotein-cholesterol and some subfractions of triglycerides have been found to be significantly lower than controls. A significant inverse correlation between infalmmatory activity and lipoprotein or lipid concentrations has previously been reported (***Svensson et al., 1987***).

The apolipoprotein AI / apolipoprotein B ratio has been found to be raised in rheumatoid arthritis (***Lorber et al., 1985; Rantapaa Dahlqvist et al., 1991***).

AIM OF THE WORK

Determination of changes in blood lipids in patients with rheumatoid arthritis in order to detect the possible relation between different blood lipids fractions, activity of disease and cardiovascular complications.

Plasma Lipoproteins

The lipoproteins are globular particles of high molecular weight that transport non polar lipids (primiraly triglycrides and cholesteryl esters) through the plasma. Each lipoprotein particle contains a non polar core, in which many molecules of hydrophobic lipid are packed to form an oil droplet. This hydrophobic core which accounts for most of the mass of the particle, consists of triglycerides and cholesteryl esters in varrying proportions. Surrounding the core is a polar surface coat of phospholipids that stabilize the lipoprotein particle so that it can remain in solution in the plasma. In addition to phospholipids, the polar coat contains small amounts of unesterfied cholesterol. Each lipoprotein particle also contains specific proteins (termed apoproteins) that are partly exposed at the surface. The apoprotein binds to specific enzymes or transport proteins on cell membranes, thus directing the lipoprotein to its sites of metabolism ***(Brown and Goldstein,1986)***.

The following table describes the charcterstics of the major clases of lipoproteins that normally circulate in human plasma. These lipoprotein classes differ in the composition of the nonpolar lipids in the core, the composition of the apoproteins, density, size and electrophoretic mobility.

Lipoprotein class	Major core lipids	Major apoprotin	Density g/ml	Diameter A	Electroph retic mobility
Chylomicrons	Dietary triglycerides	AI,AII,B,CI,CII,CII	<1.006	800-5000	Remains at origin
VLDL	Endogenous triglycerides	B,CI,CII,CIII,E	<1.006	300-800	Pre-B
Remnants	Colesterol esters, triglycerid	B,CIII,E	<1.019	250-350	Slow pre-B
LDL	Cholesteryl esters	B	1.019-1.063	180-280	B
HDL	Cholesteryl esters	AI,AII	1.063-1.210	50-120	Alpha

Table showing charcteristics of the major classes of lipoprotein

in human plasma(Brown and gldstein, 1982)

HLD=Hight density lipoprotein

LDL= Low Density Lipoprotein

VLDL=Very Low Density Lipoprotein

Lipid transport: the exogenous pathway

The largest amounts of lipoproteins are involved in the transport of dietry fat, which amounts to more than 100 gm triglyceride and about 1 gm cholesterol per day. Within intestinal epithelial cells, dietary triglycerides and cholesterol are incorporated into large lipoprotein particles called chylomicrons. The chylomicrons are secreted into the intestinal lymph and pass into the general circulation to be transported to the capillaries of the adipose tissue and skeletal muscles, where they adhere to binding sites on the capillary walls. While bound to these endothelial surfaces, the chylomicrones are exposed to the enzyme lipoprotein lipase, which hydrolyze the triglycerides of chylomicrons releasing free fatty acids and monoglycerides. The fatty acids pass through the endothelial cells and enter the underlying adipocytes or muscle cells, where they are either oxidized or reesterified to triglycerides. After the core triglycerides have been removed, the remainder of the chylomicrons dissociates from the capilliary endothelium and reenters the circulation. It has now been transformed into a particle that is relatively poor in triglycerides and enriched as regards cholesteryl esters. It has also undergone an exchange of apoproteins with other plasma lipoproteins. The net result is the conversion of the chylomicron to a remnant particle, rich in cholesteryl esters and apoprotein B, CIII and E. This remnant travels to the liver, where it is taken up with great efficiency. The overall result of the chylomicron transport process is the

delivery of dietry triglycerides to adipose tissues and cholesterol to the liver (***Kannel et al.,1971***).

Some of the cholesterol that reaches the liver is converted to bile acids, which are excreted into the intestine to act as detergents and facilitates the absorption of dietry fat. In addition, some cholesterol is excreted into the bile without being metabolized to bile acids. The liver also distributes cholesterol to other tissues (***Havel,1986***).

Lipid transport: the endogenous pathway

Triglyceride synthesis in the liver is enhanced when the diet contains excess carbohydrates. The liver converts carbohydrates to fatty acids, esterifies the fatty acids with glycerol to form triglycerides, and secretes the triglycerides into the blood stream in the core of very low density lipoproteins (VLDL). The VLDL particles are relatively large, carry five to ten times more triglycerides than cholesteryl esters and contain apoproteins that are similar to those of chylomicrons (***Mattson,1972***).

The VLDL particles are transported to tissue capillaries, where they interact with the same lipoprotein lipase enzyme that catabolizes chylomicrons. The core triglycerides of the VLDL are hydrolyzed, and the fatty acids are used for triglyceride synthesis within adipose tissues. The remnants generated from

the action of lipoprotein lipase on VLDL are similar to those formed from chylomicrons. However in contrast to chylomicon remnants, most of the VLDL remnants are not catabolized by the liver in humans. Rather, the VLDL remnants undergo a further transformation, in which nearly all the residual triglycerides are removed and replaced with cholesteryl esters. During this conversion, all the apoproteins are removed from the particle, with the exception of apoprotein B. The result is the transformation of the VLDL remnant particle into the cholesterol-rich low density lipoprotein. The core of low density lipoprotein (LDL) is composed almost entirely of cholestryl esters, and the surface coat contains only one apoprotein, apoprotein B. About three-fourths of the total cholesterol in normal human plasma is contained within LDL particles (***Mahley et al., 1980***). The function of LDL is to supply cholesterol to a variety of extrahepatic parenchymal cells, such as adrenal cortical cells, lymphocytes, muscle cells and renal cells. These cells have LDL receptors localized on the cell surface. LDL, that binds to this receptor is taken up and digested by lysosomes within the cells. The cholesteryl esters of LDL are hydrolyzed by a lysosomal cholesteryl esterase (acid lipase), and the liberated cholesterol is used both for membrane synthesis and as a precursor for steroid hormone synthesis. This LDL receptor pathway serves as the major route for degradation of LDL (***Jung et al., 1980***). In addition to its degradation by the LDL pathway in extrahepatic parenchymal cells, some of the LDL is degraded by a