TOTAL CHOLESTEROL/HDL RATIO AS A PREDICTOR OF CORONARY ARTERY DISEASE

Thesis

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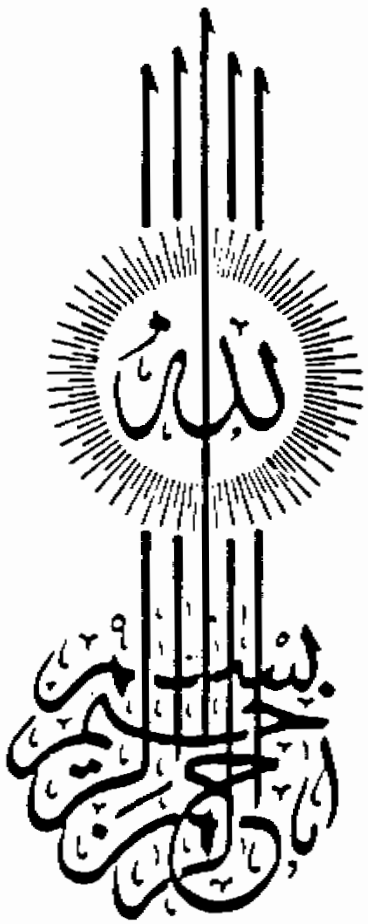

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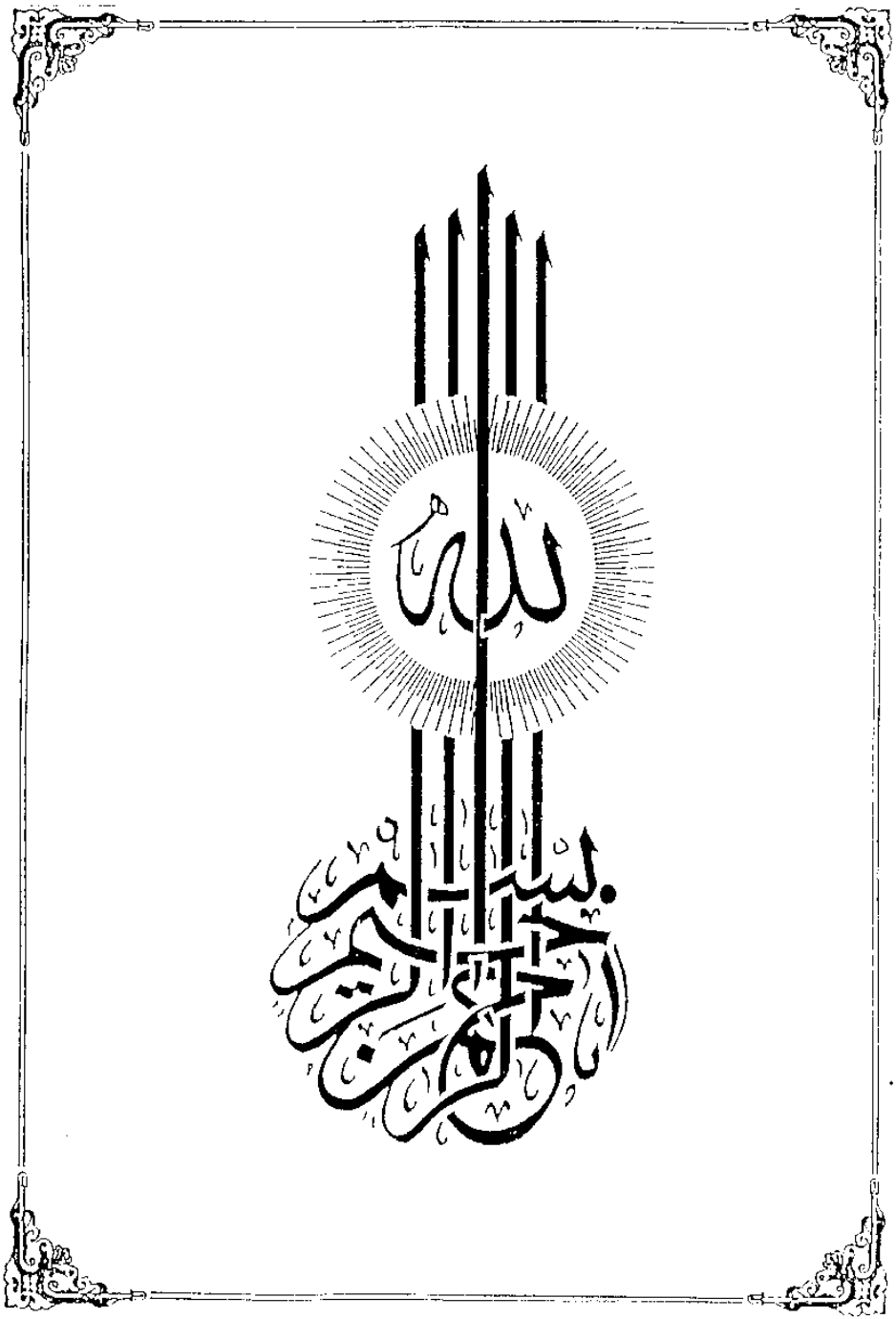

Content

INTRODUCTION AND AIM OF THE WORK

Introduction:

Lipids play a central role in atherogenesis and coronary artery disease (CAD) ***(Ross 1986)***.

In the past, determination of total cholesterol and triglycerides were used to assess the degree to which dyslipoproteinaemia plays a role as a risk factor for developing CAD. Many studies have shown that these parameters were not sensitive or specific enough to identify high risk patients unequivocally ***(Stamler, 1973)***.

Determination of HDL-cholesterol and LDL-cholesterol then took the upper hand. They showed widely differing behaviours with respect to atherogenecity. While LDL is atherogenic, HDL is considered to be protective against atherogenesis ***(Miller and Miller, 1977; Castelli et al., 1977)***.

Different studies were done correlating ratios such as total/HDL cholesterol and LDL/HDL cholesterol with CAD trying to find a better lipid predictor as a risk factor for coronary atherosclerosis than the correlation of each lipid parameter alone ***(Kannel, 1983; Holmes et al., 1984; Schmidt et al., 1985)***.

Recent studies revealed that the ratio of total cholesterol to HDL cholesterol was the best predictor of CAD ***(Nikkila et al., 1990; Luria et al., 1991)*** and was significantly correlated with extent and severity of CAD ***(Hong et al., 1991a)***.

Aim of the Work:

The aim of the present study is to determine whether total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, total cholesterol/HDL-cholesterol ratio and LDL-cholesterol/HDL-cholesterol ratio are predictors of coronary artery disease (CAD). In addition, we attempt to find out whether lipid parameters are related to both extent and severity of CAD.

REVIEW OF LITERATURE

PLASMA LIPIDS AND LIPOPROTEINS

The major classes of plasma lipids are cholesterol, cholesterol ester, and phospholipid. They are insoluble in water and do not circulate in a free form in blood stream. To reach those tissues, lipids must be transported in the blood stream by complex, water-soluble molecules called lipoproteins. Structurally, lipoproteins consist of a core of nonpolar cholesteryl ester and triglyceride covered by a polar surface monolayer made up of phospholipids, free cholesterol and the protein or polypeptide moieties called apoprotein. The major lipoprotein classes are chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), and high density lipoproteins (HDL) ***(Farmer and Gotto, 1992)***.

The four most frequent used systems for classification of lipoproteins are based on: Analytical ultracentrifugation, electrophoresis and precipitation techniques ***(Kaplan and Presce, 1984)***.

The five principle lipoprotein classes are defined according to their density on ultracentrifugation and by their mobility on agarose gel electrophoresis. The composition and properties of human plasma lipoproteins are as follows (Table 1):

Table (1): *The composition and properties of human plasma lipoproteins:*

PROPERTIES	*Chylomicrons*	*VLDL*	*IDL*	*LDL*	*HDL*
Density (mg/dl)	0.95	0.95-1.006	1.006-1.019	1.019-1.063	1.061-1.210
Electrophoretic mobility	Origin	Pre-Beta	Beta	Beta	Alpha
Major lipid constituents	Triglyceride (exogenous)	Triglyceride (endogenous) phospholipid	Esterified cholesterol phospholipid	Triglyceride esterified cholesterol	Phospholipid, cholesterol
Apoprotein constituents	Apo A-I Apo II Apo IV Apo B-48	Apo B-100 Apo C-I Apo C-II Apo C-III Apo E	Apo B-100 Apo E	Apo B-100	Apo A-I Apo A-II Apo C-II Apo E

VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

(Farmer and Gotto, 1992)

Apoproteins:

Apoproteins are key lipoprotein components that serve both as enzymatic cofactors and as recognition elements that bind to specific receptors on peripheral tissues, including the vascular endothelial cells. The apoproteins are distinguished alphabetically and numerically as Apo-I through Apo-E.

Table (2): Summary of Apoproteins:

NAME	LIPOPROTEIN	APOPROTEINS MOLECULAR WEIGHT	FUNCTION
Apo A-I	HDL, chylomicrons	28.000	Structural Activator of LCAT enzyme
Apo A-II	HDL, chylomicrons	16.000	Structural
Apo A-IV	HDL, chylomicrons, VLDL	46.000	Unknown
Apo B-100	LDL VLDL	550.000	Structural Synthesis and secretion of VLDL Binds to LDL receptor
Apo B-48	Chylomicrons,	250.000	Structural Synthesis and secretion from intestine
Apo C-I	HDL, chylomicrons, VLDL	6.000	Activator of LCAT
Apo C-II	HDL, chylomicrons, VLDL	7.000	Activator of lipoprotein lipase
Apo C-III	HDL, chylomicrons, VLDL	7.000	Stabilizes surface Provides negative charge
Apo D	HDL, chylomicrons	21.000	Cholesteryl ester exchange
Apo E	HDL,VLDL, chylomicrons	34.000	Binds to receptor on cell membrane of liver and macrophage

HDL = high-density lipoprotein ; LDL = low-density lipoprotein ; LCAT = lecithin: cholesterol acyltransferase ; VLDL = very low-density lipoprotein
(Farmer and Gotto, 1992).

Lipoprotein metabolism:

Two organs-the liver and the gut-produce lipoproteins. After a fat-containing meal, the dietary triglycerides undergo digestion in the intestine to fatty acids and

monoglycerides. These are absorbed by the intestinal mucosa, recombined into triglycerides and incorporated into lipoproteins called chylomicrons (fig. 1). The chylomicrons are secreted into the chyle, enter the systemic circulation through the thoracic duct and pass into the peripheral circulation. Here they come into contact with an enzyme named lipoprotein lipase; this enzyme hydrolyzes the triglycerides to free fatty acids and glycerol. When lipolysis is almost complete, a residual particle, called chylomicron remnant, is released in the circulation and is cleared by the liver ***(Grundy, 1984)***.

The liver, like the gut, produces a triglyceride-rich lipoprotein, very low density lipoprotein (VLDL) (fig. 2). The metabolism of VLDL is similar to that of chylomicrons. The triglycerides of VLDL also undergo lipolysis by lipoprotein lipase and VLDL remnants are released into the circulation. A major portion of VLDL remnants are contained in intermediate-density lipoprotein (IDL). VLDL remnants can have two fates, about half of these lipoprotein are removed by the liver and the remainder are converted to a smaller lipoprotein, low-density lipoprotein (LDL).

LDL is the major cholesterol-carrying lipoprotein of plasma, and it also can have 2 fates. Normally, about 70% to 75% of LDL is cleared by cell surface receptors for this lipoprotein. The liver is probably the major site of LDL clearance, but peripheral tissues also may remove a portion of circulating LDL. The remaining plasma LDL (25% to 30%) is removed by nonreceptor mechanisms (for example, nonspecific pinocytosis) in a variety of tissues ***(Goldstein and Brown, 1977)***.

Another class of lipoproteins are the high-density lipoproteins (HDL) (fig. 3). lipoprotein precursors are secreted by the liver and gut as cholesterol-poor particles called nascent HDL . The latter apparently take up cholesterol in peripheral tissues for transport to the liver; this process have been called "reverse cholesterol transport". The exact mechanisms by which HDL returns cholesterol ester to the liver have not been resolved. The liver may remove HDL directly, or HDL may transfer its cholesterol to VLDL where the cholesterol can later be removed by the liver in association with IDL or LDL ***(Grundy, 1984)***.

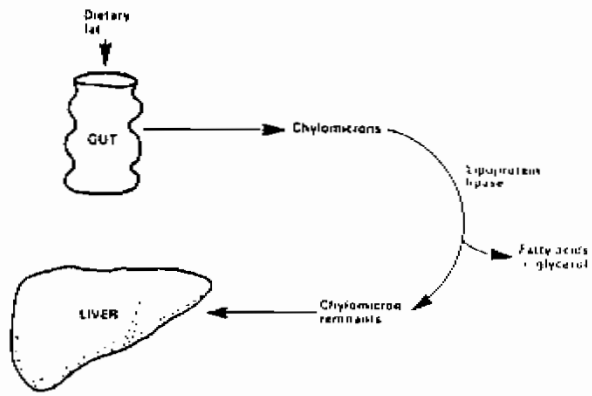

Fig. (1): Metabolism of chylomicrons

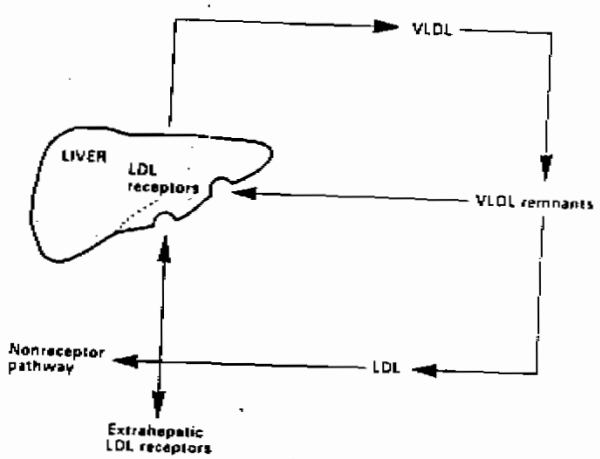

Fig. (2): Metabolism of lipoproteins containing apolipoprotein B-100. VLDL=very low density lipoprotein, LDL=low density lipoprotein

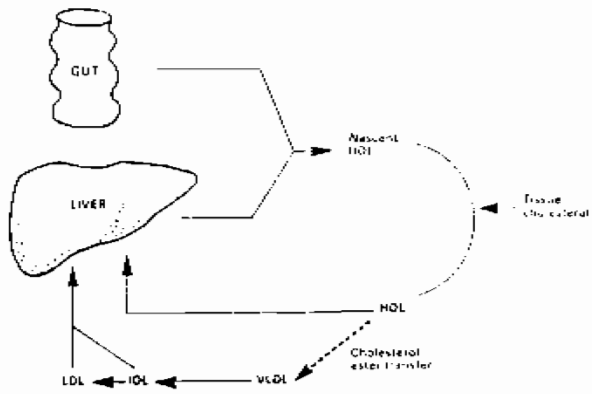

Fig. (3): Metabolism of high-density lipoprotein (HDL). LDL=low density lipoprotein. IDL=intermediate-density lipoprotein. VLDL=very low density lipoprotein

Some of the major advances in the lipoprotein field have been the elucidation of the structure and function of the proteins, or apolipoproteins, of the lipoprotein complexes. Each apoprotein appears to have a specific function. The major "structural" lipoprotein associated with chylomicrons is apo B-48 (small apo B), whereas that with hepatic VLDL is apo-100 (larg apo B). Both chylomicrons and VLDL contain 2 other apo-proteins, apo C and apoE. The apo C class appears to be required for the activation of lipoprotein lipase. Apo E play an important role in uptake of remnants of chylomicrons and VLDL by the liver. APO B-100 is necessary for the structural integrity of VLDL and LDL, and it directs VLDL remnants and LDL to LDL receptors for removal ***(Brewer et al., 1983)***.

VLDL remnants are cleared more rapidly by the liver because of the presence of apo E on the surface coat; apo E enhances receptor-mediated clearance of apo B-containing lipoproteins. Apo A-I and apo A-II are the major apoproteins of HDL, and they are probably important in extraction of cholesterol from peripheral tissues and in reverse cholesterol transport ***(Grundy, 1984)***.

The different categories of lipoproteins seemingly differ in their atherogenic potential. Chylomicrons are probably not atherogenic. They are large particles and apparently do not filter well into the arterial wall; they also contain mainly triglycerides that contribute little to the atherosclerotic plaque.

VLDL may be mildly atherogenic, and because VLDL is a heterogenous fraction, the various forms of VLDL may differ in their atherogenicity; small VLDL contains the most cholesterol and seemingly filters better into the arterial wall than large VLDL. IDL seems to be moderately atherogenic, and LDL is markedly so. These cholesterol-rich lipoproteins are small and readily penetrate the arterial wall. Their atherogenicity is enhanced by the presence of apo B, because this apoprotein can interact with interstitial materials of the subintimal region, leading to precipitation and sequestration of LDL cholesterol. The importance of apo B in atherogenesis is illustrated by the fact that another small cholesterol-rich lipoprotein-HDL-is not atherogenic ***(Grundy, 1984)***.