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# SERUM LIPIDS AND LIPOPROTEINS IN PATIENTS WITH DOCUMENTED CORONARY ARTERY DISEASE

**SALAHUDDIN, MOHAMMAD ASLAM SIDDIQUI* AND S.I. AHMAD****
*Department of Biochemistry, *Department of Anatomy,*
*Hamdard College of Medicine and Dentistry, Hamdard University, Karachi*
***Dr. H.M.I. Institute, Hamdard University, Karachi*

**ABSTRACT**

Levels of various lipoprotein subclasses can provide useful information on coronary artery disease (CAD) risk status, even when traditional risk factors are known. Elevated serum level of lipids, lipoproteins and lipoprotein (a) have been identified as risk factor for atherosclerosis resulting in coronary artery disease, cerebrovascular disease, peripheral vascular disease and venous thromboembolism. The objective of this study is to evaluate the levels of serum lipids, lipoprotein and lipoprotein (a) in-patients suffering from documented coronary artery disease and normal healthy subjects. A case control study was conducted to evaluate the levels of lipid, lipoprotein and lipoprotein (a) in patients from our local population suffering from documented coronary artery disease. The present study was earned out in Dr. HMI Institute of Pharmacology & Herbal Sciences in collaboration with National Institute of Cardiovascular Diseases, Karachi from January 2001 to June 2001. One hundred and fifty persons were included in this case control study. Out of these one hundred were patients suffering from documented (coronary angiography done 4 month before the study) coronary artery disease (mean age 46.38 ± 1.38, 18 females and 82 males). 50 normal healthy subjects (mean age, 44.86 ± 1.15, 2 females and 48 males) had no history of IHD ever before. Their serum lipid, lipoprotein and lipoprotein (a) were estimated and compared.

## INTRODUCTION

Coronary artery disease (CAD) remains a common cause of morbidity and mortality throughout the world (Virk *et al.,* 1995) with the same high incidence in Pakistan as in the rest of the world (Haq and Kiyani, 1999). Many factors are involved in the development of CAD, including age, gender family history, hypertension, and diabetes: hyperlipidemia figures especially prominently as such a risk factor (Fanner and Gotto, 1997; Hennekens, 1998 and Blond, 1999).

The concept of risk factors and its relationship to the incidence of coronary artery disease has evolved from the prospective epidemiological studies in United States and Europe (Ross 1997). The risk of CAD multiplies when there is present more than one risk factor. People with a combination of risk factors (smoking, hypertension or diabetes), therefore, have the greatest risk of developing coronary heart disease (Edwards *et al.,* 1999).

*Dyslipidaemia* is the most important predictive factor for coronary artery disease. The strong, independent, continuous and graded positive association between total cholesterol level or LDL cholesterol level and risk of coronary artery disease events has been clearly demonstrated both in men and women in all age groups. In general, a 1% increase in the LDL cholesterol level may lead to a 2-3% increase in coronary artery disease risk (Gensini *et al.,* 1998). Lipids are transported through the plasma compartment in lipoproteins, a complex water-soluble molecule consisting of a core of cholesteryl ester and triglyceride covered by a surface monolayer of phospholipids, free cholesterol and apolipoprotein. The major plasma lipoproteins include chylomicrons, very low-

density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). They vary in their contribution to atherosclerotic risk. The triglyceride rich lipoproteins, chylomicrons and VLDL are not thought to be atherogenic but the remnants of their lipolysis, chylomicron remnants and IDL respectively are believed to be atherogenic. The atherogenicity of LDL, the metabolic end product of VLDL is established, as is the cardioprotective effect of HDL (Farmer and Gotto, 1997). In general population four types of abnormalities are frequent such as increased LDL-C level, decreased HDL-C levels, usually accompanied by increased triglyceride or VLDL levels; increased concentration of chylomicron remnants and IDL and the presence in plasma of increased concentration of an abnormal lipoprotein known as lipoprotein (a) (Breslow, 1993).

Lp(a) was first discovered in human plasma by Berg (Tahir *et al.,* 1995). Lipoprotein(a) is synthesized by the liver (Cobbaert *et al.,* 1997b), it consists of an LDL particle covalently attached to apolipoprotein(a) (apo(a)), and it can also contain apo AI and apo E (Marcovina *et al.,* 1995, Igarashi, 1998). Apo (a) is highly homologous to plasminogen, and the size variation of apo (a) is due to the number of cysteine-rich kringle, followed by an inactive protease domain present in the molecule (Wong, 1999). Plasma level of Lp(a) vary a 1000-fold range from 0.1 to over 100 mg/dl (Saku *et al.,*1999). The catabolism of Lp(a) is less well known. Lp(a) can be degraded by the LDL receptor, but the affinity of Lp(a) for the receptor is low (Uttermann, l987). High plasma levels of lipoprotein (a) have been positively associated with atherosclerosis (Dahlén *et al.,* 1994 and Tahir *et al.,* 1995), myocardial infarction and stroke (Miyata *et al.,* 1996) in numerous cross-sectional studies. The atherogenicity of Lp(a) is at least partly associated with an elevated concentration of LDL cholesterol and a reduction of LDL cholesterol without a change in the Lp (a) concentration associates with slowing down of CAD progression (Maher *et al.,* 1995). Diet has no effect on the serum concentrations of Lp(a), and so far, neomycin and nicotinic acid are the only hypocholesterolemic drugs with an Lp(a) lowering effect (Tahir *et al.,*1995).

## MATERIAL AND METHOD

The present study was carried out in Dr. HMI Institute of Pharmacology & Herbal Sciences in collaboration with National Institute of Cardiovascular Diseases, Karachi. Subjects were divided into two groups, Group A and Group B.

***Group A:***

Included fifty subjects with no history of CAD and served as control.

***Group B:***

Included one hundred patients having documented (coronary angiography done 4 month before the study) coronary artery disease.

The controls were free of overt disease. There was no clinical or ECG evidence of coronary artery disease in any of these individuals.

The data collection for various groups was standardized through the use of similar methodology, protocol and procedure using a standard questionnaire.

The questionnaire provided information about type of work, smoking habit, medical history of cardiovascular disease, hypertension and family history of coronary heart disease. Smoking habits of subjects were grouped into current smokers and nonsmokers, weight was measured on a

balance scale while participants were without shoes and heavy outer garments, height was measured in the standing position following weight measurement. Blood pressure of subject was measured twice in the right arm with a 5-minute interval of rest, using a standard mercury sphygmomanometer. Values from the second measurement were used in this study. Angiographically diagnosed cases of coronary artery disease were selected from National Institute of Cardiovascular Disease, Karachi. The subjects were asked to fast for 10-12 hours and 6 ml of blood was collected from the antecubital vein (after all aseptic measures), while the subjects were sitting up right. Sampling was done between 0700 and 0900 hours.

Samples were analyzed in one run at the end of the study (to omit analytical variations between run) except serum glucose that was analyzed within four hours of sample collection. Serum total cholesterol, HDL-C, triglyceride and glucose were analyzed enzymatically, using the kits supplied by SPINREACT, Spain. LDL-C was calculated by the Friedwald formula (Friedwald, 1972). Lp (a) was measured on HUMALYSER 2000 (spectrophotometer), Cat. No.18-3000, manufactured by Human Diagnostics, Germany, using the kit code: 1107020 supplied by Spinreact Spain.

## RESULTS

Table-1 shows the comparison of mean values of demographic characteristics such as age, weight, height, body mass index and smoker status, in control (group A) and case (group B) subjects.

No significant difference of age, weight, height and BMI was observed. As far as the smoking habit is concerned none of the subjects was smoker in control group, while in group B, 27 {42.0%} patients were smokers which is significantly high (P<0.00l) as compared to control group.

Table-2 shows comparison of mean values of systolic blood pressure, diastolic blood pressure, heart rate, family history of ischemic heart disease and history of hypertension in control group A and patient group B.

No significant differences were seen in values of systolic blood pressure, diastolic blood pressure and heart rate between group B and group A individuals.

When history of hypertension and family history of IHD was compared between control and group B, control subjects did not have a hypertension history while 4 people (8%) had family history of IHD but in group B, 28 {28.0%} patients had a history of hypertension and were on antihypertensive therapy and 23(23%) had family history of IHD. The difference was significantly high as compared to control group.

Table-3 shows comparison of serum glucose, triglyceride, total cholesterol, Lipoprotein (a), {Lp(a))}, HDL-C and LDL-C levels in control and group B subjects. The difference in the values of serum glucose, triglyceride and total cholesterol of group B patients with those of control group A subject was non-significant.

Serum Lp(a) level of group B was significantly high (P<0.005) as compared to control subjects. The value of high-density lipoprotein cholesterol of group B was significantly low (P<0.001) as compared to control subjects and the value of low-density lipoprotein cholesterol of group B was significantly high (P<0.01) as compared to control subjects.

**Table-1**
Comparison of age, weight, height, BMI and smokers status of Group A (Control) and Group B (patients with documented coronary artery disease) subjects

| Groups | Male/female | Age (Years) | Weight (Kg) | Height (m) | BMI ($Kg/m^2$) | Smokers |
|---|---|---|---|---|---|---|
| Group-A (Control) (50) | 48/2 | 44.86±1.15 | 71.0±1.17 | 1.71±0.02 | 24.53±0.64 | 0 |
| Group-B (Patients) (100) | 82/18 | 46.38±1.38 | 67.71±1.96 | 1.69±0.02 | 23.73±0.59 | 43* (43.0%) |

The values are expressed as mean ± SEM. The Number of observation and units are given in parentheses
BMI: Body mass index
*P<0.001 significant as compared to control group

**Table-2**
Comparison of hypertension, systolic blood pressure, diastolic blood pressure, heart rate among Group-A (Control) and Group B (patients with documented coronary artery disease) subjects

| Group | Hypertension % | SBP (mm/Hg) | DBP (nm/Hg) | Heart Rate (b/min) | FH of IHD % |
|---|---|---|---|---|---|
| Group A Control (50) | 0 | 118.57±5.57 | 76.67±2.70 | 71.90±3.36 | 4 (8.0%) |
| Group B Patients (100) | ** 28 (28.0%) | 127.14±1.71 | 80.48±0.76 | 78.29±0.97 | * 23 (23.0%) |

The values are expressed as mean + SEM. The number of observation and units are given in parentheses

*P< 0.05 **P< 0.00 1, significant as compared to control
SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure
FH of IHD: Family History of Ischemic Heart Disease

**Table-3**
Comparison of fasting serum glucose, triglyceride, total cholesterol high density lipoprotein cholesterol, low-density lipoprotein cholesterol and lipoprotein (a) [Lp(a)] among Group-A (Control) and Group-B (patients with documented coronary artery disease) subjects

| Groups | Glucose (mg/dl) | Total Cholesterol (mg/dl) | Triglyceride (mg/dl) | HDL-C (mg/dl) | LDL-C (mg/dl) | LP(a) (mg/dl) |
|---|---|---|---|---|---|---|
| Group-A Control (50) | 74.57 ± 0.31 | 166.14 ± 11.89 | 140.52 ± 9.01 | 44.95 ± 1.75 | 93.08 ± 11.43 | 20.31 ±2.07 |
| Group-B | | * | | | *** | ** |
| Patients (100) | 84.38 ±0.23 | 195.95 ±6.23 | 146.09 ±11.92 | 25.17 ±1.77 | 141.57 ±5.60 | 34.30 ±4.40 |

The values are expressed as mean ± SEM. The number of observation and units are given in parentheses

*P<0.05, **P<0.005, ***P<0.001 significant as compared to control group
HDL-C High density lipoprotein cholesterol
LDL-C Low-density lipoprotein cholesterol

## DISCUSSION

Coronary artery disease (CAD) is a condition of diverse etiology all having in common disturbance between oxygen supply and demand. The disease remains a common cause of morbidity and mortality throughout the world. Hyperlipidaemias are the important risk factor for coronary artery disease. Blood lipids due to their insolubility in water are carried in lipoproteins. Lipoproteins are divided into several classes depending upon their apoproteine composition and their distinct densities. Plasma lipids and other cardiac risk factors interact adversely with endothelial cell and result in endothelial dysfbnction (Selwyn *et al.,* 1992). Atherosclerosis is the result of a complex interaction between blood elements, disturbed flow and vessel wall abnormality (Flak *et al.,* 1995). The dyslipidemia most clearly associated with increased risk for CAD is Hypercholesterolemia, particularly elevated plasma levels of cholesterol carried in LDL. The association between elevated blood cholesterol and CAD has been established in observational and interventional epidemiological studies (Farmer and Gotto, 1997). Stamler *et al.* (1986) has demonstrated a continuous and graded positive relation between total cholesterol level and CAD mortality. Ridker *et al.* (1998), have demonstrated in their study that total cholesterol was significantly high in the patients having myocardial infarction (MI) than in controls, similarly HDL cholesterol was significantly low in patients than in controls. Pancharuniti *et al*. (1994), has shown a case-control comparison between patients with myocardial infraction and controls without disease and demonstrated a nonsignificant difference between patients and controls for total cholesterol and BMI. In Prospective Cardiovascular Munster Heart Study (PROCAM), 39% of subjects with myocardial infarction or CAD death compared with 21% of surviving subjects without myocardial infarction or stroke had a significantly higher triglyceride levels (Assmann *et al*., 1996). HDL-C is believed to be secreted by the liver and intestine as a discoidal precursor particle of phospholipid, cholesterol and apolipoproteins. Through the activity of lecithin: cholesterol acyltransferase (LCAT), a core of cholesteryl ester is generated from the phospholipid

and cholesterol, and the disk is transformed into mature, spherical HDL3. HDL3 acquires additional phospholipid and cholesterol, from cell membrane and form TG rich lipoproteins through continued LCAT activity, HDL3 is converted to HDL2, which is larger and more cholesterol rich than HDL3. The mechanism by which HDL confers decreased risk for CAD is complex and poorly understood. One proposed mechanism is that, it acts as the possible vehicle of reverse cholesterol transport, the process by which cholesterol is returned from peripheral cell to the liver for excretion in to the bile acid pool or for reconstitution in to cell membranes or VLDL (Farmer and Gotto, 1997). Genest *et al*. (1991) demonstrated in their study that low HDL-C is a strong and independent risk factor for the development of atherosclerosis.

LDL-C is a heterogeneous group of lipoproteins differing in some physico-chemical characteristics such as size, density, electric charge and composition (Quesada *et al.,* 1999). Oxidized LDL attracts circulating monocytes, which then adhere to the arterial wall and precipitates their activation as macrophages, which are then prevented from leaving the arterial wall (Schwartz *et al.,* 1993). Scavenger receptors on macrophages recognize and bind oxidized LDL and become lipid-laden foam cells, the component of fatty streak, which is the precursor of atherosclerotic lesion (Farmer and Gotto, 1997). In our study we have found a significant difference between the total cholesterol levels of cases (patients with CAD) and control subjects. The values of triglyceride were found to be nonsignificant in two groups. Similarly we report lower mean levels of HDL-C, with a significant difference ($P<0.001$) in group B subjects as compared to control which is in agreement with Ridker *et al.,* 1998 and Genest *et al*., 1991. We have also observed that, the patients with CAD have significantly ($P<0.05$) high levels of LDL-C as compared to control which is in agreement with Schwartz *et al.,* 1993 and Farmer and Gotto, 1997.

High plasma levels of lipoprotein (a) have been positively associated with atherosclerosis myocardial infarction and stroke in numerous cross-sectional studies (Dahlén *et al.,* 1994). Lipoprotein (a) is the only major risk factor, which remains remarkably constant in an individual, in addition lipoprotein(a) shows a strong heritability (Rallidas *et al.,* l998). In a recent prospective case control study reported by Rosengren *et al.* (1990), Lp(a) was also found to be an independent risk factor for subsequent MI or death CAD (Brizzi *et al.,* 1999). Lp(a) concentration greater than 30 mg/dl are reported to be associated with a two fold increased risk of the developing CAD (Wong *et al.,* 1999). Moreover, a serum Lp(a) concentration greater than or equal to 30 mg/dl is a risk factor restenosis following percutaneous transluminal coronary angioplasty (Yaniamoto *et al.,* 1995 and Miyata *et al.,* 1996), that is why serum Lp(a) concentrations are closely related to the progression of CAD (Dangas *et al.,* 1999). In our study we have found a significant difference between the Lp(a) levels of cases (patients with CAD) and control subjects and this in agreement with the above mentioned studies.

As far as the other parameters we have evaluated in our study are concerned the percentage of smokers and family history of IHD was significantly high ($P<0.001$), ($P<0.05$) in patients with CAD as compared to control subjects. This is in agreement with Akosh *et al.,* 2000 and Nygard *et al.,* 1995 who have reported that history of smoking is independently associated with premature coronary heart disease. We found a significantly high ($P<0.001$) percentage of history of hypertension in patients with CAD as compared to control subjects. This is in agreement with Brochier *et al.,* 1998 who reported that elevated blood pressure (Hypertension) was a significant, strong and independent risk factor for coronary artery disease, both in men and women. In our study we could not find any significant difference of serum glucose between controls and patients with coronary artery disease (CAD) and this could be because the sampling was done in fasting state or it could be attributed to a good glycemic control.

The present study has demonstrated that hypertension, smoking, deranged lipid levels i.e. increased LDL cholesterol, decrease HDL cholesterol, as well as a raised serum lipoprotein (a) levels are strongly associated with coronary artery disease. More large-scale studies are required to explore the role of lipoprotein (a) in the development of CAD.

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