

## STUDY OF LEVELS OF LIPOPROTEIN (A) IN CORONARY ARTERY DISEASE AND DIABETES MELLITUS

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### ABSTRACT

Coronary Artery Disease (CAD) leads to Angina and Myocardial Infarction (MI). Premature mortality on Coronary Heart Disease (CHD) is more common in diabetic atherosclerosis. In the present study serum level was Lipoprotein (a) estimated in patients of CAD with DM, CAD without DM, DM without CAD and CAD with DM and other risk factors compared to healthy normal subjects. The level of Lipoprotein (a) was significantly increased in all four groups of patients as compared to control group. **Conclusion** – Lp (a) acts as atherogenic protein by binding to LDL receptors, it also blocks plasminogen and competes for binding to fibrinogen, thus acting as a prothrombin agent. It inhibits clot lysis.

**KEYWORDS**-Coronary Artery Disease, Diabetes Mellitus,

Lipoprotein (a).

**INTRODUCTION**-Lipoprotein (a) was discovered in 1963 by Berg<sup>[1]</sup> and consists of two major components; an LDL particle containing the apoprotein B-100 molecule and an

apoprotein(a) (apo-a) molecule linked by a single disulfide bond.<sup>[2]</sup> Apo(a) is a large protein with an amino acid sequence similar to that of plasminogen. Both the apo(a) and plasminogen genes consist of specific coding sequences for loop structures stabilized by intrachain disulfide bonds, referred to as kringle domains. Five different Kringle domains (K1 to K5) are found in the plasminogen gene, and only K4 and K5 are present in apo(a) gene. The K4 sequence is repeated many fold in apo (a) gene.<sup>[2,3]</sup> The multiple copies are similar but not identical to each other.<sup>[4]</sup> This variation of apo(a) gene size leads to the heterogeneity of apo(a) protein size that also impacts on plasma Lp(a) level.<sup>[5,6]</sup> In general, it is widely believed that smaller apo (a) sizes leads to higher plasma Lp(a) levels, although the relationship is complex.<sup>[7,8]</sup>

Lp(a) is synthesized in the liver, and its molecular weight varies from 400 to 700 KDa. Although the plasma LDL concentration is primarily determined by the rate of removal, the Lp(a) level is controlled by the rate of synthesis at the level of the gene that encodes apo(a).<sup>[9]</sup>

Lipoprotein (a) is a cholesterol ester rich lipoprotein that is composed of low density lipoprotein (LDL) and a highly polymorph glycoprotein, apolipoprotein (a), which has a close homology with plasminogen. Due to its LDL like properties, it accumulates in the arterial wall leading to atherosclerosis. It has been shown to stimulate the secretion of plasminogen activator inhibitor and interfere with fibrinolysis. Lp(a) has both atherogenic as well as thrombogenic properties.<sup>[10]</sup>

When present at low levels, Lp(a) may serve a protective function by binding and possibly degrading oxidized phospholipids formed during normal homeostasis or in acutely stressful situations.<sup>[11]</sup> Lp(a) has also been shown to be involved in wound healing.<sup>[12]</sup> and elevated levels have been noted in centenarians.<sup>[13]</sup> When levels are chronically elevated, Lp(a) may be proatherogenic particularly because it has enhanced binding to the extracellular matrix of the artery wall.<sup>[14]</sup> The close homology between Lp(a) and plasminogen has raised the possibility that it may inhibit endogenous fibrinolysis by competing with plasminogen binding on the endothelium. Lp(a) may bind and inactivate tissue factor pathway inhibitor and may upregulate the expression of plasminogen activator inhibitor.<sup>[15,16]</sup>

Acute myocardial infarction is the most important consequence of coronary artery disease. Although traditional risk factors of MI are helpful in diagnosis, specific clinical markers would be valuable in identifying the persons who are at risk. In the past few decades, much

attention has been focused on serum Lp(a) and other lipids mainly because of their strong association with coronary artery disease.<sup>[17]</sup>

Most studies have been carried out in patients of all groups with concomitant risk factors. R.K.Khullar.<sup>[10]</sup> carried out a study to assess the Lp(a), lipid levels and coronary angiographic profile in young Indians (less than 40 years of age) with myocardial infarction (MI). Their results suggested a strong association of high Lp(a), HDL cholesterol, high TG with premature CAD in Indians.

Numerous studies carried out in several countries over the past 25 years have suggested that Lp(a) could be an independent risk factor for premature coronary artery disease (CAD). Six prospective studies concluded that Lp(a) is a risk factor for CAD but three other case – control studies did not arrive at this conclusion.<sup>[18]</sup>

Geethanjali et al noticed that the levels of Lp (a) have a wide scatter and a definite cut- off level could not be established. Hence they carried out study in a large number of patients and studied the relationship of serum Lp(a) levels with their phenotypes.<sup>[18]</sup>

## MATERIALS AND METHODS

The present study was carried out in the Department of Biochemistry, Dr.D.Y.Patil Education Society's Medical College and Hospital, Kolhapur. This study was approved by Institutional ethical committee.

In this study a total number of 200 subjects between age 40 yrs to 60 yrs matched with age and sex were included. They were distributed in controls and four groups.

Controls	Normal Healthy controls- 100 cases
Group- I	Patients with CAD and DM- 25 cases
Group- II	Patients with CAD – 25 cases
Group- III	Patients with DM – 25 cases
Group- IV	Patients with CAD and DM + Other risk factors- 25 cases

All controls were from the same age groups as patients, not showing any clinical signs and symptoms suggestive of CAD. They were having normal blood pressure (BP), ECG, blood sugar level and apparently no other cardiac risk factors. Group-I contained patients diagnosed to have CAD(based on angiography )with confirmed DM and were receiving treatment for the same Group- II contained patients with CAD but no DM Group-III contained Type II DM patients receiving treatment for DM, and were not showing any complications of DM,

and had normal ECG and BP. Group- IV contained patients with CAD and DM along with other risk factors.

(such as smoking, hypertension, family history of CAD, obesity etc.)

**Sample collection-** 4 ml of venous blood was collected in plain bulb and was allowed to clot. Serum was separated by taking necessary precautions to avoid haemolysis. This serum was used for the estimation of Lipoprotein (a)

**Inclusion Criteria:** A) Control group: 100 age matched healthy subjects were included in the control group. The subjects were selected after screening for any prior history of cardiovascular disease or any other disease. B) CAD Patients: Angiographically proven patients by the cardiologists with relevant coronary artery disease showing greater than 50% stenoses in at least one major coronary artery at the time of diagnostic catheterization were enrolled in this study. Each subject was screened by a complete history, physical examination and laboratory analysis. C) Diabetic Patients with CAD: Clinically diagnosed patients whose fasting blood glucose level was above 125 mg/dl.

**Exclusion Criteria:-**The patients with hemodynamically significant valvular heart disease undergoing catheterization, surgery or trauma, known cardiomyopathy, known cancer, abnormal hepatic and renal function, past or concurrent history of any disease and taking any medication that could influence the oxidant and antioxidant status and endothelial functions were excluded from the study group.

## RESULT

**Table Showing the levels of Lipoprotein (a) in (mg/dl) in control subjects and different study groups**

Groups	Lipoprotein(a) (mg/dl)
Control	19.3 ± 6.8
Group I (CAD with DM )	42.7 ± 18.5 *
Group II (CAD with out DM )	46.7 ± 32.2 *
Group III (DM with out CAD )	39.0 ± 32.1 #
Group IV (CAD with DM and other risk factors )	44.6 ± 23.2 *

Values are expressed as mean ± SD

\* P< 0.001 Group I, II, IV as compared to control.

# P< 0.05 Group III as compared to control.

In the present study significant increase was seen in the level of lipoprotein (a) in groups I, II, III and IV compared with control subjects.

## DISCUSSION

Lipoprotein (a) is a cholesterol ester-rich lipoprotein composed of an LDL particle and a large hydrophilic glycoprotein, apolipoprotein (a). Lp (a) has recently been categorized as an emerging lipid risk factor for CAD.<sup>[19]</sup> Several control and prospective studies have identified elevated levels of plasma Lp(a) as risk factor for CAD.<sup>[2,3]</sup>

In the present study significant increase was seen in the level of lipoprotein (a) in groups I, II, III and IV compared with control subjects.

Studies in Indian population have shown that Lp(a) levels are significantly higher among coronary artery disease patients as compared to controls.<sup>[20]</sup> Our results are in accordance with these studies.

Lp (a) is considered to be an independent level risk factor for premature<sup>[21]</sup> and multi- vessel CAD.<sup>[22]</sup> Lipoprotein (a) consists of two different components, Apolipoprotein B-100, which binds to LDL receptors and acts as an atherogenic protein, and Apolipoprotein A, which resembles plasminogen ( a zymogen of the coagulation and fibrinolytic system) and competes with the latter for binding to fibrinogen and fibrin monomers, thus acting as prothrombotic agent. Thus, lipoprotein(a) functions as a dual pathogen which is highly atherogenic and is also prothrombotic. Lipoprotein (a) is thus an important molecule in the processes of atherosclerosis as well as thrombosis.<sup>[23,24]</sup> Thrombosis in situ is considered as one of the pathogenic mechanisms in CAD.<sup>[25]</sup> A thrombus may result from injury to the endothelium, abnormal fibrinolysis, enhanced procoagulant activity and / or platelet abnormalities. There are in vivo and in vitro studies which support the theory that lipoprotein (a) has a thrombogenic effect.<sup>[26]</sup>

The accumulation of Lp (a) has been well documented in the arterial wall at the site of atherosclerotic lesions<sup>[27]</sup> Due to its LDL like properties, it accumulates in the arterial wall leading to atherosclerosis.

Lp (a) may induce atherosclerosis in the following manner. The apo(B)-100 which is a component of Lp(a) binds to LDL receptors and acts as atherogenic protein. It also mimicks

or blocks plasminogen and competes for binding to fibrinogen, thus acting as a prothrombin agent. Lp(a) inhibits clot lysis.<sup>[27]</sup>

The accumulation of Lp(a) has been well documented in the arterial wall at the site of atherosclerotic lesion. Within intima, Lp(a) can interact with various tissue matrix components including fibrinogen, fibrin and fibronectin. It has also been shown to upregulate the secretion of plasminogen activator inhibitor-1 (PAI-1) and inhibit fibrinolysis. All these effects may be potentiated by concomitant dyslipidemias.<sup>[28]</sup>

Lipoprotein (a) is ten times more atherogenic than LDL. It has dual mechanism of action.

- i) Due to its LDL like action it is atherogenic.
- ii) Due to its plasminogen like properties, it is thrombogenic.

As mentioned earlier hypertriglyceridemia was observed in our study and hypertriglyceridemia is a thrombogenic factor the thrombotic effect of lipoprotein (a) is mimicked by hypertriglyceridemia leading to CAD.

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