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"LIPOPROTEIN-A LEVEL AS A RISK FACTOR IN PATIENTS WITH ACUTE CORONARY SYNDROME" - A CASE SERIES

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Introduction

Lipoprotein(a) [Lp(a)] is an atherogenic particle that structurally resembles low density lipoprotein [LDL] but contains a molecule of apo-lipoprotein(a). Elevated plasma concentrations of Lp(a) have been shown to be one of the independent risk factors for atherosclerosis. Lp(a) levels have been found to be associated with stable CAD, ACS and with severity of ACS.

Lp(a) was first described in human plasma by Norwegian genetic scientist Karen Berg in 1963. By mid 1980s, it was recognised as an independent genetically determined risk factor for premature CAD. In earlier studies, it was highlighted as an independent risk factor for premature CAD in absence of other risk factors. Recent studies have highlighted the potent role of Lipoprotein (a) in accentuating positive risk associated with all conventional and emerging risk factors. Lp (a) excess increases risk of premature CAD, depending on the absence or presence of concomitant risk factors. [(1)]

Lp(a) levels in human samples are mainly measured using immunoassays with polyclonal antibodies against apoA. [(2)]

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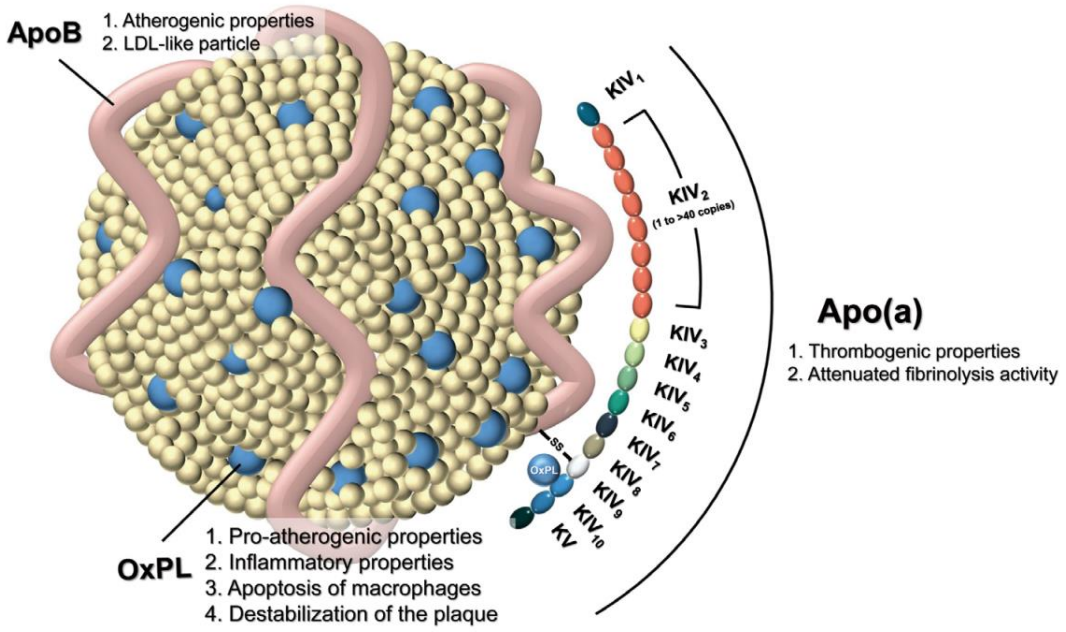

Figure. Schematic illustration of lipoprotein(a) (Lp(a)). Lp(a) consists of apolipoprotein (apo) B covalently bound to (apoA), which itself consists of a structure called kringle domains (K), which share structural homology with plasminogen. ApoA contains KIV and KV, with KIV having evolved 10 types of duplications, of which only KIV_2 has expanded copy numbers (ranging from 1 to > 40 copies, depending on the individual) Additional oxidized phospholipid (OxPL) is bound covalently to KIV_{10}, as well as in lipid phase of the low-density lipoprotein (LDL) particle.

Other conditions in which elevated levels of LP (a) are seen [(3)]:

• Chronic Kidney disease

• Estrogen depletion

• Familial Hypercholesterolemia

• Severe Hypothyroidism

• Stroke

• Uncontrolled DM

Low levels are seen in [(3)]

• Alcoholism

• Chronic liver disease

• Malnutrition

Acute Coronary Syndrome is when occlusion of one or more of the coronary arteries occurs, usually following plaque rupture, resulting in decreased oxygen supply to the heart muscle. The spectrum of clinical conditions ranging from:

- Unstable angina
- Non-Q wave MI (NSTEMI)

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- Q-wave MI (STEMI) [4]

Lp(a) excess is now recognised as the foremost genetic risk factor forpremature CAD in diverse populations. Lp(a) excess (30 mg/dl) is an independent risk factor for the development of premature CAD [5]

Although Lp(a) is an independent risk factor in itself, its synergistic adverse effects with other risk factors is even more impressive [6]

→ High Cholesterol and LDL: Lp(a) levels is an important determinant of CAD among pts with familial and non familial hypercholesterolemia. The pathogenicity of Lp(a) increases with high LDL and vice versa.

→ Low HDL: Low HDL markedly increases the risk from high Lp(a). WhereasLp(a) levels appear to play an important role in the early asymptomatic stages of coronary atherosclerosis. Low LDL plays a crucial role in later stages of coronary artery disease.

→ High Triglycerides: The combination of high TG with high Lp(a) is dangerous.

→ Diabetes: DM increases the CAD risk asso with Lp (a) excess by > 3 fold.

→ High Lp(a) levels are associated with almost all complications of DM including Retinopathy, Micro/Macroalbuminuria, Nephropathy and Renal failure. Lp(a) levels are not increased or influenced by DM.

→ Hypertension: Lp(a) levels are a potent predictor of the presence and severity of target organ damage in pts with hypertension.

→ Homocysteine: Pts with elevation of both Homocysteine and Lp(a) have a 32 fold high risk of CAD compared with only 3 fold risk when Lp(a) is low.[6]

→ The desirable and optimal test result range of Lp(a) is <14mg/dL. The highest risk range is >50 mg/dl. Patients with an Lp(a) of 14-30mg/dl are considered to be at borderline risk, and those within the range of 31-50md/dl are at high risk. Lp(a) levels directly contribute to serum LDL levels [7]

Aims and Objectives

1. To study plasma Lp(a) levels in patients admitted to the hospital with CAD above 18 years of age.
2. To assess the role of Lp(a) and its relation to other known risk factors for CAD.
3. To see its relationship with severity, progression and mortality associated with CAD.

Materials and methods

This study was conducted in the Department of General Medicine, SMS Multispeciality Hospital, Dr. MK Shah Medical College and Research Centre, Ahmedabad, India during February 2023 to March 2023.

Inclusion criteria

- Subjects who are 18 years or older
- Patients with acute coronary syndrome

Exclusion criteria: Patients with the following comorbidities:

- Chronic Kidney disease

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- Estrogen depletion
- Familial Hypercholesterolemia
- Severe Hypothyroidism
- Stroke
- Uncontrolled DM
- Alcoholism
- Chronic liver disease

The above mentioned are taken as exclusion criteria as they are confounding factors for levels of lipoprotein (a)

After establishing a diagnosis of Acute coronary syndrome via Electrocardiographic findings, cardiac biomarkers and angiographic findings, demographical data (identity, history of certain disease) was obtained via thorough history taking and data from laboratory findings (complete blood count, liver function tests, lipid profile, Random blood sugar, C reactive protein, Homocysteine levels, protein c,protein s levels, haemostasis function tests) was obtained.

Observation and results

A total of 50 patients of ACS are included in this study. They include 35 males and 15 females with age group varying from 25 to 75 years. Patients with confirmed diagnosis of ACS and satisfying the inclusion and exclusion criteria are included in the study group.

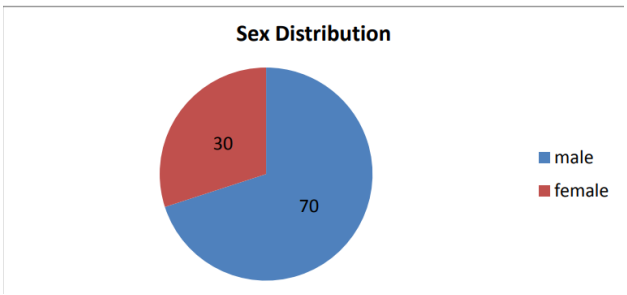
The diagnosis of ACS is based on typical chest pain, characteristic ECG evolution, raised cardiac enzyme levels and 2D-echo findings and coronary angiography.

Following investigations were done in all patients in study group:

Random Blood Sugar [RBS] / S.Creatinine / S. Creatine Phosphokinase MB (CPKMB) / Troponine-I / Lipidprofile / S.Lp (a) / S.Uric Acid / ECG / Chest X- ray / 2D Echo / Coronary Angiography. The result of the study are discussed in following tables.

1. Sex distribution of ACS

In this study ACS prevalence in males is 70% while females is 30%. This suggests that ACS prevalence is more common in males compared to females.



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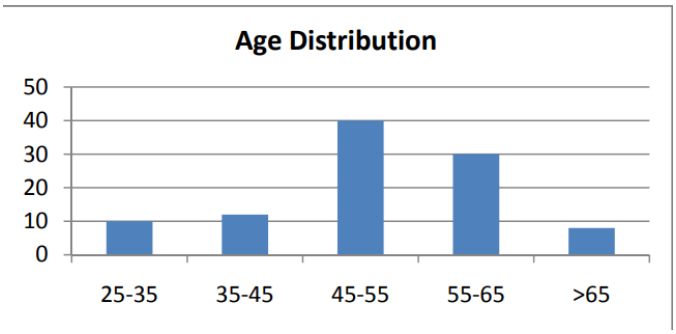
2. Age distribution of ACS

Chances of developing ACS is more above 45 yrs of age but now a days, the average age for ACS is decreasing showing a predilection towards younger age.



3.Type of ACS

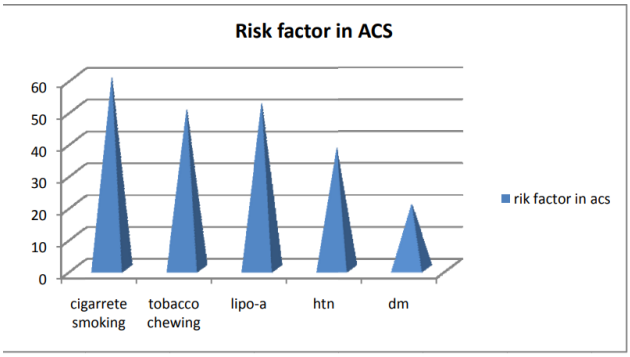
STEMI	80%
NSTEMI	14%
UA	6%

4. Risk factors for ACS

Cigarette smoking – commonest (60%)

Tobacco chewing – 50%

Lipoprotein A levels were higher than normal in more than 60% subjects



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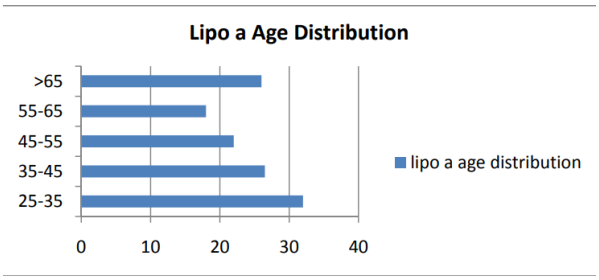
5. Lipoprotein (a) Age distribution



6.Lp(a) and Hypertension

No significant variation in Lp(a) values were seen among Hypertensives and Non-hypertensives in our study.

7. Lp(a) and Diabetes

Lp(a) levels has been found to be elevated in Diabetics than non-diabetics in our study.

8. Lp(a) and S.LDL

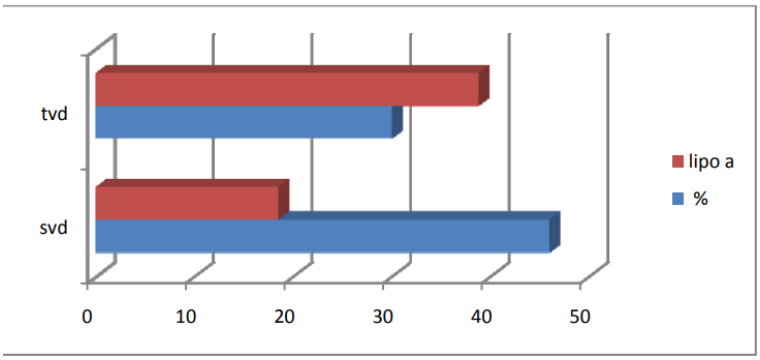
No statistically significant observation made with LDL levels and Lp(a) values in our study.

9.Lp(a) and HDL

Lp(a) levels has inverse correlation with HDL levels in our study.

10. Lp(a) and Angiographic overview of Vessel Involvement

In 46% of patients with SVD, average Lp(a) level is 18.43. but as Lp(a) levels increase, more than one vessel involvement is seen. Highest levels of mean Lp(a) value are seen in TVD, which are 38.77. so, we can say that raised levels of Lp(a) are associated with increased number of disease vessels as well as severe and critical vessel occlusions.



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Discussion

1) In men Lp (a) remained constant at approx.. 5 mg/dl across all age groups.

2) In general,20mg/dL is the level of Lp(a) above which cardiovascular risk is thought to be increased.

3) Both increased level of LDL cholesterol and Lp(a) are associated with increased risk of MI. They also indicated that Lp(a) doesn't increase risk at LDL cholesterol below 130mg/dL. This may suggest that in individuals with raised Lp(a), LDL cholesterol should be lowered to below 130 mg/dl.

4) Lp(a) levels in women also increased across all age groups.

5) Lp(a) increases with age in women and also with BMI. In men,by contrast no such relationship was established.

The structural combination of apoB-containing LDL-C and apoA confers the superior athero-thrombogenicity of Lp(a) over apoB-only LDL-C. The lysine-binding site of the kringle domains within an apoA molecule predisposes Lp(a) molecules to bind to the endothelial receptors, thereby contributing to atherogenicity. The structural homology of apoA to the plasminogen molecule also confers thrombogenicity of Lp(a). Therefore, an excess concentration of Lp(a) abrogates the function of plasmin activators, decreases plasmin levels, and eventually leads to attenuated fibrinolysis activity. [(8)]

A meta-analysis regarding the effect of statins on Lp(a) levels and subsequent CV outcomes has been published. Statins showed benefits on conventional CV risk factors, although a modest increase was noted in Lp(a) levels. [(9)]

Extended-release niacin in addition to statin therapy was studied in the AIM-HIGH trial.48 However, in that trial the modest decrease in Lp(a) of 19% in the niacin plus statin combined therapy group compared with the placebo group did not result in a reduction in CV events. [(10)]

The Lp(a)-lowering effect of PCSK9 mAbs is well established, as demonstrated in the FOURIER trial. Evolocumab reduced Lp(a) by 26.9% independent of baseline LDL-C concentrations. Interestingly, patients with Lp(a) concentrations above the median (>37nmol/L) had a greater rate of absolute risk reduction and number needed to treat compared with the placebo control group by 1.41% and 71, respectively. [(11)]

Recently, however, promising results were published for 2 clinical trials that used ASO technology to directly inhibit the synthesis of apoA.[(12)(13)]. These trials are the first to target lowering Lp(a). The ASO technology used in these trials is also in its infancy, although the GalNAc conjugated to the ASO has enabled the drug to effectively lower Lp(a) by up to 99% at a tolerable dose. Previously developed drugs were only able to reduce Lp(a) up to 40%

Conclusion

It has been shown that high Lp(a) is associated with CVD. In general,20mg/dL is the level of Lp(a) above which cardiovascular risk is thought to be increased.

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Although conventional pharmacological therapies, including statins, are not able to mitigate the CV risk elevated by Lp(a), emerging therapeutic strategies using ASO technology have shown promising results in effectively lowering Lp(a).

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