Serum Lipoprotein (a) as an independent marker of cardiovascular risk in patients with Essential Hypertension

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Abstract
Aim: Aims of the study was to find out the level of serum lipoprotein (a) in healthy and hypertensive subjects and role of serum lipoprotein (a) as an independent marker of cardiovascular risk in patients with essential hypertension.

Material and Method: Hundred patients with essential hypertension and 50 apparently healthy subjects were included in the study. Sera were collected from them and measure serum Lipoprotein(a) [Lp(a)] with Latex turbidimetric method on automated chemistry analyzer. Unpaired t-test was used to assess the significant difference in the means of the studied variables in the different groups.

Results: The mean level of serum lipoprotein(a) is higher in patients with essential hypertension comparing with the control group (21.6 ± 11.9 and 30.3 ± 13.6,p <0.001).

Conclusion: The findings clearly project that plasma concentration of Lp(a) albeit within the normal range could be an independent risk factor for atherosclerosis and could contribute towards increasing the risk of cardiovascular diseases (CVD) in persons with essential hypertension.

Keywords: Essential Hypertension, Serum Lipoprotein (a).

1. Introduction
Hypertension (HT) is a major health burden and the leading cause of death in the world. Although it is common in economically developed countries, than in developing countries, it is a greater population burden on the latter because of the much larger population1. The Asia Pacific Cohort studies collaboration clearly demonstrated the log linear relationship of blood pressure with ischemic & hemorrhagic stroke, ischemic heart disease, congestive cardiac failure, renal insufficiency, obstructive sleep apnoea and cardiovascular death1. The role of Lp(a) [lipoprotein(a)] as an independent biomarker of vascular risk has been investigated for more than 20 years, but recently the European Atherosclerosis Society (EAS) has issued a new consensus statement endorsing routine measurement of Lp(a) among patients with moderate to high risk of cardiovascular disease2. Many prospective epidemiological studies have reported positive associations of baseline Lp(a) concentration with coronary heart disease (CHD) risk3, but very limited case-control studies studied the association between elevated Lipoprotein (a) and essential hypertension that frequently occurs in conjunction with metabolic disturbances and in particular with atherogenic dyslipidemia4. The Lp (a) was described for the first time in 1963 by Berg5. It consists of a set of lipoproteins with different molecular weights (from 350 to 900 KD)6, in which particles of Low density lipoprotein (LDL) are bonded to apoprotein(a) (apo(a)), which has a Cringle structure with a high level of homology to plasminogen5. The physiological function of this lipoprotein is still unknown but the importance attributed to it has increased considerably in the light of the evidence that high plasma concentrations of Lp(a) are not only associated with an increased risk of vascular diseases such as CHD and the re-stenosis of coronary bypass but are also considered an independent risk factor
for these pathologies. Lipoprotein (a) [Lp (a)] is considered as a risk factor for vascular diseases, especially those associated with renal failure. Adequate studies have not been conducted on the lipoprotein (a) in essential hypertensive patients. There is a controversy about the mechanisms by which Lp (a) is associated with essential hypertension. It is unclear whether Lp (a) contributes to atherogenesis or to thrombogenesis or both. Recent studies suggest that Lp(a) can act as a marker for determining vascular or tissue injury. Reports on Indian population indicate elevated levels of Lp (a), together with other serum lipoproteins emphasizing an important role in coronary Heart Disease (CHD) and peripheral atherosclerosis.

2. Materials and Methods

2.1 Exclusion Criteria:

The following patients were excluded from the study:

1. Patients with accelerated / malignant hypertension
   Systolic blood pressure > 180 mmHg
   Diastolic blood pressure >110 mmHg
2. Patients with secondary hypertension.
3. Patients with either of the following associated disease
2.2 Conditions:

a. CHF/Grade III retinopathy.
b. History of stroke.
c. History of MI within 6 months.
d. History of angina within 2 years.
e. Diabetes mellitus (FBS >140 mg/dl).
f. History of chronic infections, TB, Leprosy.
g. Familial hyperlipidemia.
h. History of hypersensitivity.
i. Abnormal kidney function.
j. Endocrine disease.
k. Pregnancy and lactation.
l. Gout.
m. History of alcohol abuse.
n. Pre-eclampsic toxemia.
o. Patients on drugs known to cause hyperuricemia, e.g. thiazide diuretics.
p. Patients on lipid lowering drugs.
q. Obese patients.
r. Smoking

2.3 Classification of Essential Hypertension:

Hypertension was defined according to the JNC VII classification of hypertension as those with SBP of < 120 mm Hg and DBP of < 80 mm Hg as normal, those with SBP of 120-139 mm Hg or DBP of 80-89 mm Hg were labelled pre-hypertensive were not taken up for the study, those with SBP 140-159 mm Hg or DBP of 90-99 mm Hg were labelled as stage I were labelled as having stage 1 hypertension, and those with SBP ≥ 160 mmHg or DBP ≥ 100 mmHg were labelled as Stage 2 hypertension.

2.4 Study Design:

Informed consent of subjects included in the study was obtained for involvement in study groups and for venipuncture. After that a detailed history including personal data, present complaints and complication, treatment history, past history, family history and personal history was taken followed by a thorough physical examination. For each control/patient, overnight fasting blood sample was collected in fluoride vacutainer for FBS (Fasting Blood Glucose), EDTA vacutainer for hemoglobin and in plain vacutainer for other biochemical parameters. Urine sample was collected in a universal container for albumin and sugar.

The study was undertaken at the Shree Sayajirao General Hospital and Medical College, Vadodara. The study parameters were analyzed at the Clinical Chemistry Laboratory of Biochemistry Department of Medical College and S.S.G
Hospital, Baroda. The subjects selected for the study were grouped as follows:

**Group I – Control group (n=50):** This group consisted of age and sex matched non-hypertensive subjects. They were free from any major ailment which could affect the parameters under study (No clinical history or investigative result showing involvement of any organ). They were taken from medical or paramedical staff, attendants of patients, indoor patients with status unrelated to hypertension (e.g. hernia, fractures etc.), persons coming to hospital for fitness purpose and outdoor patients of minor illness (e.g. common cold). Patients who come for health check-up were also included after taking proper history.

**Group II – Essential hypertension patients (n=100)**

**Inclusion criteria:**

1. Healthy normotensive subjects and hypertensive subjects who were on anti-hypertensive therapy.
2. Age group 20 to 60 years and gender for an appropriate match to avoid bias.
3. All biochemical and haematological investigations should be in normal limit.
4. Hypertension was diagnosed when on at least 3 separate occasions:
   - Systolic Blood Pressure ≥ 140 mmHg.
   - Diastolic Blood Pressure ≥ 90 mmHg.

**2.5 ESTIMATION OF SERUM LIPOPROTEIN (a) [Lp (a)]**

**Method:** Latex Turbidimetric Method

**Principle:** Latex particles coated with antibodies anti-Lp(a) are agglutinated when mixed with samples containing Lp(a). The agglutination causes an absorbance change, dependent upon the Lp(a) contents of the sample that can be quantified by comparing from the calibrator of known Lp(a) concentration.

**3. Results and analysis**

| Table 1. Comparison of study groups: |
|--------------------------------------|
|                                      |
| Control                              |
|                                      |
| Cases                                |
|                                      |
| Number of patients                   | 50 | 100 |
| Sex (M/F) %                          | 26/24 | 51/49 |
| Average age (years)                  | 41 | 7 | 47 | 8 |
| Average duration of HT (in year)     | - | - | 5 | 3 |
| Average SBP                          | 120 | 9 | 151 | 9 |
| Average DBP                          | 81 | 5 | 97 | 3 |

| Table 2: Results of the control group and patients with essential hypertension |
|--------------------------------------------------------------------------------|
| Control (Mean ± SD) | Cases (Mean ± SD) | t value | P value |
|---------------------|-------------------|---------|---------|
| Systolic BP (mmHg)  | 120 ± 9           | 151 ± 9 | 42.186  | <0.0001 |
| Diastolic BP (mmHg) | 81 ± 5            | 97 ± 3  | 69.402  | <0.0001 |
| Lipoprotein(a)      | 21.6 ± 11.9       | 30.3 ± 13.6 | 7.835 | <0.0001 |

| Table 3: Distribution of controls and cases according to serum Lp(a) levels |
|----------------------------------------------------------------------------|
| Lp(a) mg/dl                    | Controls (n=50) | Cases (n=100) |
|                                 |                 |               |
| ≥ 30 mg/dl (High)              | 7 (14%)         | 32 (32%)      |
| < 30 mg/dl (Normal)            | 43 (86%)        | 68 (68%)      |

**Inference:** Percentage of patients with Lp(a) of >30.0 mg/dl is significantly larger in cases when compared to controls (32% vs. 14% with P < 0.001)

Interpretation was done according to p-value as follows:

- p<0.05—significant
- p<0.001—highly significant
- p<0.01—very significant
- p>0.05 — not significant
4. Discussion

The study was undertaken to assess the level of serum lipoprotein (a) [Lp(a)], lipid profile and serum uric acid in patients of essential hypertension. It was carried out in Shree Sayajirao General Hospital and Medical College, Vadodara. The cross sectional study consists of 150 subjects; out of them 100 were patients of essential hypertension and the rest 50 were age and sex matched non-hypertensive subjects. It is evident from the mean Lp(a) values across groups that the patients having essential hypertension have raised concentration of Lp(a) compared to the controls (Mean of cases was 30.3 and of controls it was 21.6). These values also showed large inter-individual variations (SD of Lp(a) in cases was 13.6 and in controls it was 11.9 ). Substantial controversy surrounds the role of elevated levels of Lp(a) as a risk factor for vascular disease. Prospective and retrospective studies have suggested an independent association between high levels of Lp(a) (>1.07 µmol/L [>30mg/dL]) and presence and extent of coronary artery disease, premature coronary artery disease, myocardial infarction, cerebrovascular disease, saphenous vein bypass graft disease. Up to 20% of patients with premature coronary artery disease have elevated Lp(a) levels, making Lp(a) excess the most common inherited lipoprotein disorder in these patients. In the present study, it was found that the hypertensive patients had higher plasma concentrations of Lp (a) than in the controls. In a similar study, Catalano et al reported significantly elevated levels of plasma Lp(a) in 123 Caucasian essential arterial hypertensive patients (47 men and 76 women). The pathogenicity and atherogenic role of Lp (a) is greatly influenced by the concentration of other serum lipids and lipoproteins. Several investigators reported correlation between Lp(a) and other lipid variables. In the present study a significant correlation was observed between TC and LDLc levels and Lp (a). Mechanism of pathogenicity of Lp(a) excess includes destabilization of plaque, increased smooth muscle cell proliferation and migration, inhibition of transforming growth factor β, formation of occlusive thrombus, impaired formation of collateral vessels, enhanced oxidation uptake and retention of LDLc and upregulation of expression of the plasminogen activator inhibitor-1 (PAI-I). The striking homology of apo(a) with plasminogen causes impaired fibrinolysis by competing with plasminogen and enhances thrombogenesis. So Lp(a) modulates thrombosis and fibrinolysis. In our study higher mean Lp(a) levels were observed in cases than controls and the difference was statistically significant (p<0.001). Percentage of essential hypertension patients with Lp(a) ≥30.0 mg/dL is significantly larger in cases when compared to controls (32% vs. 7% with p<0.001) in our study.

5. Conclusion

The findings clearly project that plasma concentration of Lp(a) albeit within the normal range could be an independent risk factor for atherosclerosis and could contribute towards increasing the risk for cardiovascular diseases in persons with essential hypertension.

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