Scholars International Journal of Biochemistry
Abbreviated key title: Sch. Int. J. Biochem.
A Publication by "Scholars Middle East Publishers"
Dubai, United Arab Emirates

ISSN: 2616-8650 (Print)
ISSN: 2617-3476 (Online)

Applicability of Lipoprotein (a) as a Risk Predictor for Cerebrovascular Disease

Sanjay Bhatt[1*], V.S. singh[2], Sangeetasingh[2], S.R. Saxena[3], A. Joshi[4], Bindu Sati[5]
[1]Department of Biochemistry, SRMS IMS, Bareilly, UP, India
[2,5]Department of Biochemistry, UFHT Medical College Haldwani, Uttarakhand, India
[3, 4]Department of Medicine, UFHT Medical College, Haldwani, Uttarakhand, India

Original Research Article

***Corresponding author**
Sanjay Bhatt

Email:
sanjay_bhatt25@yahoo.com

Article History
Received: 24.05.2018
Accepted: 05.06.2018
Published: 30.06.2018

Abstract: Lipoprotein (a) is independently associated with Atherosclerotic Cardiovascular Disease (ASCVD) and is referred to as the most atherogenic lipoprotein. It is synergistic with the effects of low density lipoprotein cholesterol (LDL-C). Unlike other major classes of lipoproteins that have a normal distribution in the population, plasma levels of Lipoprotein (a) / Lp (a) have a skewed distribution towards the lower end with 85% population having concentration <30 mg/dL. The aim of present study is to estimate the level of serum Lp(a) in cerebrovascular diseases or Strokes. The study was conducted in the Department of Medicine, Department of Biochemistry, Sushila Tiwari Memorial Hospital, the teaching hospital of Uttaranchal Forest Hospital Trust (UFHT) Medical College, Haldwani (Nainital), Uttarakhand, on patients of cerebrovascular disease (CVD) which included estimation of Lp(a) and lipid profile (TC, TG, HDLc, LDLc, VLDLc) test. Out of the 17 women and 36 men in whom Lp (a) was measured, 2 women (mean age63.5 years) and 21 men (59years) had CVD (CVD(+), while 15 women (50.13 years) and 15 men (52.33 years) had no CVD [CVD(–)]. As shown in Table 1, there were no significant differences between women with or without CVD in age and concentration of total plasma cholesterol. The study was based on a small sized cohort of 23 cases suffering from (CVD) out of which 21 were males and 2 were females. Thirty (30) healthy subjects were taken as controls, who were not suffering from any disease, which may affect serum lipid levels and without any history of cerebrovascular disease. Total-C, LDLc, VLDLc, Triglyceride, HDLc, LDL/HDL, Cholesterol/HDL and Lp(a) were estimated in all the cases.

Keywords: Cerebrovascular disease (CVD), Lp(a) lipoprotein, chylomicron

INTRODUCTION

Lipoprotein(a) is found in lower concentrations than other lipoproteins, yet it carries a unique and significant risk for cerebrovascular disease. Because of its similarity to LDL, test methods often don't measure it separately, but include it within the LDL class. Testing specifically for this class may uncover why a person is not responding to standard cholesterol-lowering treatment. High lipoprotein(a) levels may not respond to treatment aimed at high LDL[1].

Lipoprotein (a) was discovered by chance by Berg in 1963; after twenty years of research, the chemical, physical and metabolic characteristics of Lp (a) are now known. This lipoprotein forms the missing link between the lipid metabolism and the coagulation-fibrinolysis process. The A. describe its similarity to plasminogen, its capacity to delay coagulum or embolus destruction and highlight its structural and functional similarity to lipid metabolism. Today, a total of 6 Lp (a) isoforms have been identified with different molecular weights: in addition, the inverse proportion between the isoforms' molecular weight and Lp(a) plasma concentration has been demonstrated. Lp(a) is not the product of the metabolism of other lipoproteins nor is it a catabolite of LDL; it is produced ex-novo and does not apparently exchange its proteic fraction with other lipoproteins. The paper also examines the question of whether Lp(a) is a plasma marker which increases during the formation of atherosclerotic plaqueor whether it should not be considered an atherogenetic factor[2]. To this end the possible mechanisms by which Lp(a) is deposited in plaque are examined. Lastly, the paper reviews all studies concerning the relationship between Lp(a) and cerebrovascular disease.

High Lp(a) concentration is associated with a higher incidence of ischemic stroke in blacks and white women, but not in white men.

Stroke, is the death of brain tissue that occurs when the brain does not receive enough blood flow and oxygen.The term stroke is applied to a sudden focal neurologic syndrome, specifically the type due to cerebrovascular disease[3]. The term cerebrovascular disease designates any abnormality of the brain resulting from a pathologic process of the blood vessels. Pathologic process is given an inclusive meaning namely, occlusion of the lumen by embolus or thrombus, rupture of a vessel, an altered permeability of the vessel wall, or increased viscosity or other change in the quality of the blood flowing through the cerebral vessels[4]. The vascular pathologic process may be considered not only in its grosser aspects-embolism, thrombosis, or rupture of a vessel-but also in terms of the more basic or primary disorder, i.e. atherosclerosis, hypertensive, arteriosclerotic change, arteritis etc. Disorders of the cerebral circulation include any disease of the vascular system that causes ischemia or infarction of the brain or spontaneous hemorrhage into the brain or subarachnoid space.

Lipoproteins: Lipoproteins are the "packages" in which cholesterol and triglycerides travel throughout the body. Measuring the amount of cholesterol carried by each type of lipoprotein helps determine a person's risk for cerebrovascular disease (disease that affects the brain and blood vessels, also called CVD).

Clinically important lipids are Cholesterol and triglycerides . Cholesterol is used to build cell membranes and hormones[5]. The body makes cholesterol and gets it from food. Triglycerides provide a major source of energy to the body tissues. Both cholesterol and triglycerides are vital to body function, but an excess of either one, especially cholesterol, puts a person at risk of cardiovascular disease.

Because cholesterol and triglycerides can't dissolve in watery liquid, they must be transported by something that can dissolve them in blood serum. Lipoproteins contain cholesterol and triglycerides at the core and an outer layer of protein, called apolipoprotein.

There are four major classes of lipoproteins: chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). There also are less commonly measured classes such as lipoprotein(a) and subtypes of the main classes.

Each lipoprotein has characteristics that make the cholesterol it carries a greater or lesser risk. Measuring each type of lipoprotein helps determine a person's risk for cerebrovascular disease (CVD) more accurately than cholesterol measurement alone. When a person is discovered to be at risk, treatment by diet or medication can be started and his or her response to treatment monitored by repeated testing[6].

Aims and objective: To estimate the level of serum Lp(a) in cerebrovascular diseases or Strokes.

MATERIALS & METHODS

Study design: An observational analytical study.

Ethical approval: This study was approved by Institutional Ethical committee (IEC) of UFHT Medical College and Sushila Tiwari Hospital, Haldwani, along with informed consent.

Study setting: The present study was carried out on patients of CVD **attending "**Department of Medicine", Sushila Tiwari Memorial Hospital, the teaching hospital of Uttranchal Forest Hospital Trust Medical College, Haldwani (Nainital),UK. All the patients were asked for history of vascular disease, family history and presence of major risk factors for CVD.

Study duration: Duration of this study was **Jan 2005 to July 2007.**

Sample size: Dample size was n= 30 taken as controls and n=53 taken as CVD patients.

Inclusion criteria: Men/Women 18-70 years of age and clinically stabilized CVD patients. In this study fifty three clinically, pathologically proven fresh cases of CVD (age: 21-45 years), only minimal and moderately advanced patients of CVD were included. For comparison 30 clinically healthy volunteers of either sex (age: 17-40 years) were included as control group.

Exclusion criteria: CAD patients, Psychiatric patients, pregnant, lactating womenand patients with Diabetes and hypertension.

Grouping: Group 1: Control n= 30, **Group 2:** CVD n=53

Sample collection: Six milliliters of blood was collected from each subject in plain and sterile vials containing heparin as anticoagulant.

METHODOLOGY

- Lipoprotein (a): Measurement of Lipoprotein (a) by Lp(a)-Turbilatex method
- Photometric determination of serum total Cholesterol: CHOD-PAP method.
- Photometric Estimation of Triglycerides: Enzymatic method.
- Enzymatic determination of HDL-Cholesterol In serum or plasma: HDL-Direct Method.

- LDLc estimation without the need of any centrifugation steps: Calculated method.

Statistical analysis:

Statistical analysis of data was done by using the statistical package for social sciences (SPSS 12) for windows software, Microso excel 2007 and Scientific Calculator. Result were expressed as Mean±S.D.

RESULTS

Of the 17 women and 36 men in whom Lp(a) was measured, 2 women (mean age63.5 years) and 21 men (59years) had CVD (CVD(+), while 15 women (50.13 years) and 15 men (52.33 years) had no CVD [CVD(–)], there were no significant differences between women with or without CVD in age and concentration of total plasma cholesterol. Women with CVD(+) had slightly higher triglycerides, LDL-cholesterol and lower HDL-cholesterol levels compared to CVD(–), while the two groups of men differed in age only. There were several significant differences between men and women. Women were older than men in both CVD groups; plasma cholesterol, HDL- and LDL-cholesterol were higher in women compared to men with CVD(+), while in those with aCVD(–) the only difference was in higher concentration of HDL-C in women.

Table-1: CVD(+) vs CVD(-) men

	MEN			**Women**		
	CVD(+)	CVD(-)	p value	CVD(+)	CVD(-)	
Age (years)	59±12	52.33±7.02	0.1407 **(NS)**	63.5±1.5	50.13±6.81	0.4559 **(NS)**
HDL-C (mg/dl)	38.9±10.7	41.33±4.92	0.1232 **(NS)**	35±2	41.13±4.77	0.0735 **(NS)**
Total-C(mg/dl)	168±36.4	161.66±8.85	0.8718 **(NS)**	159.5±24.5	119.73±12.10	0.9706 **(NS)**
LDL-C(mg/dl)	105±26.9	119±14.44	0.5829 **(NS)**	104.5±25.5	119.73±12.10	0.9265 **(NS)**
VLDL-C(mg/dl)	30±31	17.73±4.50	0.1811 **(NS)**	20±1	19.4±3.97	0.8971 **(NS)**
Triglyceride(mg/dl)	124±62.89	106.13±34.94	0.675 **(NS)**	10.5±5.5	107.33±32.33	0.9706 **(NS)**
LDL/HDL	3.04±1.17	2.94± 0.58	0.9059 **(NS)**	3±0.9	2.96±0.53	0.8088 **(NS)**
Cholesterol/HDL	4.69±1.61	3.94±0.34	0.0952 **(NS)**	4.6±1	3.99±0.33	0.8088 **(NS)**
Lp(a) (mg/dl)	29.2±1.96	13.4±2.24	< 0.0001	41±1	14.05±2.59	0.0147

DISCUSSION AND CONCLUSION

The study was based on a small sized cohort of 23 cases suffering from Cerebrovascular disease(CVD) out of which 21 were males and 2 were females.

Thirty (30) healthy subjects were taken as controls, who were not suffering from any disease, which may affect serum lipid levels and without any history of Cerebrovascular disease. Total-C, LDLc, VLDLc, Triglyceride, HDLc, LDL/HDL , Cholesterol/HDL and Lp(a) were estimated in all the cases. After careful analysis of the results following conclusions were drawn-

Abnormal level of Total-C (>200 mg/dL) was seen in 21.74% cases of the CVD this proves a poor correlation between serum cholesterol level and Cerebrovascular disease.

Level of HDLc below 35 mg/dL (<35 mg/dL) has been taken as abnormal, was seen in 30.43% cases of CVD this degree of abnormality is again the same as that of serum cholesterol therefore there is no use of measuring serum HDLc alone over Total-C to predict the risk of CVD.

Serum LDLc was abnormally high (that is >130 mg/dL) in 26.09% cases of CVD again there is no use of measuring serum HDLc alone over Total-C to predict the risk of CVD.

Levels above 30 mg/dL which was the abnormal level of serum VLDLc was seen in 30.43% cases of CVD this was too low a value to predict the risk of CVD.

Hypertriglyceridemia (>170 mg/dL) was seen in 30.43% cases of the CVD this again was too low a value to predict risk of CVD.

Cholesterol /HDL ratio was abnormal in 73.91% cases of CVD the correlation of this ratio with CVD was seemed to be more related to CVD then Total-C, HDLc, LDLc, triglyceride and VLDLc.

LDL/HDL ratio was abnormal in 86.96% cases of CVD, the correlation of this ratio with CVD was statistically more significant as compared with the above individual levels.

There were no significant differences between CVD(+) and CVD(-) women in age, Total-C, HDLc, VLDLc, Triglycerides and Cholesterol/HDL.

When the values were analyzed with each other, in the two groups of men, CVD(+) and CVD(-), no significant difference was seen in Triglyceride, LDL/HDL and Cholesterol/HDL.

No significant difference was seen while analyzing CVD(+) Men vs. CVD(+) Women in Age, LDLc, VLDLc, Triglyceride, LDL/HDL and Cholesterol/HDL.

When the values were analyzed with each other in CVD (-) men & CVD (-) women,no significant difference was seen in Age, Total-C, LDLc, VLDLc, Triglyceride, HDLc, LDL/HDL , Cholesterol/HDL and Lp(a).

Most pronounced differences between CVD (+) and CVD (–) patients were found in plasma concentration of Lp(a).There was significantly higher plasma Lp(a) level in both women (median 41 mg/dl) and men (29.17 mg/dl) with CVD (+) compared to those with CVD (–) (14.05 and 13.40 mg/dl, respectively). Lp(a) levels were significantly higher in women compared to men with CVD (+) ($p<0.0001$). There was no significant difference in Lp(a) levels between men and women without evidence of CVD.

The purpose of this study was to determine whether a routine assessment of Lp(a) in patients at risk of CVD further adds to their risk assessment.The objective correlated with the plasma concentration of Lp(a) and routine lipids. In our small sized cohort of patients the routine lipid profile had fairly low predictive value for positive CVD. The multivariate analysis has confirmed that plasma Lp(a) besides LDL/HDL was a significant independent predictor of positive findings of CVD.

Our findings suggest that Lp(a) measurement is of value in investigation of patients at risk for CVD and that it is a particularly useful predictor of risk in women and men.

REFERENCES

1. Albers, J. J., & Hazzard, W. R. (1974). Immunochemical quantification of human plasma Lp (a) lipoprotein. *Lipids*, *9*(1), 15-26.
2. Andrew, M. (1995). Developmental hemostasis: relevance to thromboembolic complications in pediatric patients. *Thrombosis and haemostasis*, *74*(1), 415.
3. Andrew, M., Paes, B., & Johnston, M. (1990). Development of the hemostatic system in the neonate and young infant. *The American journal of pediatric hematology/oncology*, *12*(1), 95-104.
4. Andrew, M., Vegh, P., Johnston, M., Bowker, J., Ofosu, F., & Mitchell, L. (1992). Maturation of the hemostatic system during childhood. *Blood*, *80*(8), 1998-2005.
5. Berg, K. (1963). A new serum type system in man—the Lp system. *Acta Pathologica Microbiologica Scandinavica*, *59*(3), 369-382.
6. Berg, K., Dahlén, G., & Frick, M. H. (1974). Lp (a) lipoprotein and pre-β1-lipoprotein in patients with coronary heart disease. *Clinical genetics*, *6*(3), 230-235.
7. Cambillau, M., Simon, A., Amar, J., Giral, P. H., Atger, V., Segond, P., ... & Plainfosse, M. C. (1992). Serum Lp (a) as a discriminant marker of early atherosclerotic plaque at three extracoronary sites in hypercholesterolemic men. The PCVMETRA Group. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *12*(11), 1346-1352.
8. Gerique, J. G., Porres, A., Martinez, D. L., Sala, L. Á., Blazquez, E., Montoya, M. T., & Oya, M. D. (1996). Levels of lipoprotein (a) and plasma lipids in Spanish children aged from 4 to 18 years. *Acta Pædiatrica*, *85*(1), 38-42.
9. Hoff, H. F., Beck, G. J., Skibinski, C. I., Jürgens, G., O'neil, J., Kramer, J., & Lytle, B. (1988). Serum Lp (a) level as a predictor of vein graft stenosis after coronary artery bypass surgery in patients. *Circulation*, *77*(6), 1238-1244.
10. Jürgens, G., & Költringer, P. (1994). Cerebrovascular disease and Lp (a): its role in atherosclerotic plaque formation and vessel wall elasticity of the carotid arteries. *Chemistry and physics of lipids*, *67*, 429-434.
11. Kohlhase, B., Vielhaber, H., Kehl, H. G., Kececioglu, D., Koch, H. G., & Nowak-Göttl, U. (1996). Thromboembolism and resistance to activated protein C in children with underlying cardiac disease. *The Journal of pediatrics*, *129*(5), 677-679.
12. Margaglione, M., DiMinno, G., Grandone, E., Celentano, E., Vecchione, G., Cappucci, G., ... & Mancini, M. (1996). Plasma lipoprotein (a) levels in subjects attending a metabolic ward: discrimination between individuals with and without a history of ischemic stroke. *Arteriosclerosis, thrombosis, and vascular biology*, *16*(1), 120-128.
13. McLean, J. W., Tomlinson, J. E., Kuang, W. J., Eaton, D. L., Chen, E. Y., Fless, G. M., ... & Lawn, R. M. (1987). cDNA sequence of human apolipoprotein (a) is homologous to plasminogen. *Nature*, *330*(6144), 132.

14. Miles, L. A., Fless, G. M., Levin, E. G., Scanu, A. M., & Plow, E. F. (1989). A potential basis for the thrombotic risks associated with lipoprotein (a). *Nature*, *339*(6222), 301.
15. Murai, A., Miyahara, T., Fujimoto, N., Matsuda, M., & Kameyama, M. (1986). Lp (a) lipoprotein as a risk factor for coronary heart disease and cerebral infarction. *Atherosclerosis*, *59*(2), 199-204.
16. Nagayama, M., Shinohara, Y., & Nagayama, T. (1994). Lipoprotein (a) and ischemic cerebrovascular disease in young adults. *Stroke*, *25*(1), 74-78.
17. Nowak-Göttl, U., Dübbers, A., Kececioglu, D., Koch, H. G., Kotthoff, S., Runde, J., & Vielhaber, H. (1997). Factor V Leiden, protein C, and lipoprotein (a) in catheter-related thrombosis in childhood: a prospective study. *The Journal of pediatrics*, *131*(4), 608-612.
18. Nowak-Göttl, U., Funk, M., Mosch, G., Wegerich, B., Kornhuber, B., & Breddin, H. K. (1994). Univariate tolerance regions for fibrinogen, antithrombin III, protein C, protein S, plasminogen and α2-antiplasmin in children using the new automated coagulation laboratory (ACL) method. *Klinische Pädiatrie*, *206*(06), 437-439.
19. Nowak-Göttl, U., Koch, H. G., Aschka, I., Kohlhase, B., Vielhaber, H., Kurlemann, G., ... & Schneppenheim, R. (1996). Resistance to activated protein C (APCR) in children with venous or arterial thromboembolism. *British journal of haematology*, *92*(4), 992-998.
20. Nowak-Göttl, U., von Kries, R., & Göbel, U. (1997). Neonatal symptomatic thromboembolism in Germany: two year survey. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, *76*(3), F163-F167.
21. Rath, M., Niendorf, A., Reblin, T., Dietel, M., Krebber, H. J., & Beisiegel, U. (1989). Detection and quantification of lipoprotein (a) in the arterial wall of 107 coronary bypass patients. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *9*(5), 579-592.