

LIPOPROTEIN (a) IN CHRONIC KIDNEY DISEASEBarathiraja P¹, Raja Mahendran P²¹Assistant Professor, Department of General Medicine, KAPV Medical College, The Tamilnadu Dr. M.G.R. Medical University, Trichy, Tamil Nadu.²Assistant Professor, Department of General Medicine, KAPV Medical College, The Tamilnadu Dr. M.G.R. Medical University, Trichy, Tamil Nadu.**ABSTRACT****BACKGROUND**

In Chronic Kidney Disease (CKD) patients, comprehensive care of patients involves not only the management of renal disease, but also the appropriate management of its complications. The study of Lipoprotein (a) levels (LP(a)) in CKD patients becomes important as it expresses the link between Chronic Renal Failure (CRF) and cardiovascular complications. In our study, Lipoprotein(a) is analysed in relation to various criteria in CRF to evaluate the risk group for complications.

MATERIALS AND METHODS

This study was done for a period of 1 year from April 2017 to March 2018 at Medicine OPD, ward, Nephrology OP and wards, Government KAPV medical college hospital, Trichy. During this period, 50 patients admitted with chronic renal failure of both sexes, irrespective of age were selected and enrolled for the study.

RESULTS

37 out of 50 patients had elevated LP(a) levels. Age and sex were not found to be significant factors affecting LP(a). Increased LP(a) levels were seen in patients with severe anaemia, elevated serum creatinine levels, increased diastolic BP and ECG changes.

CONCLUSION

Elevated serum LP(a) level is very much useful in assessing the risk in CRF as accelerated atherosclerosis, uncontrolled hypertension, coronary artery disease and end stage renal disease.

KEYWORDS

Chronic Renal Failure, Chronic Kidney Disease, Lipoprotein (a), Anaemia, Serum Creatinine.

HOW TO CITE THIS ARTICLE: Barathiraja P, Raja Mahendran P. Lipoprotein [a] in chronic kidney disease. J. Evid. Based Med. Healthc. 2019; 6(10), 780-783. DOI: 10.18410/jebmh/2019/161

BACKGROUND

Chronic kidney disease is defined as the irreversible, substantial and usually longstanding loss of renal function causing ill health usually referred as uremia.¹ The clinical course of CKD usually passes from a long asymptomatic period of compensation to a more accelerated terminal phase.

Despite chronic injury which leads to destruction of more than fifty percent of nephrons, plasma elevation of urea and creatinine may still lie within normal limits for these substances.

The further loss of nephrons and reduction of renal function leads to continued accumulation of solutes which results in abnormally elevated plasma concentration. The accumulation of products of protein, amino acids and glucose metabolism results in uremia. The occurrence of

cardiovascular disease is substantially higher in uremic patients than in general population. The study of estimating LP(a) levels in CRF patients becomes important as it expresses the link between CRF and cardiovascular complications.²

In our study LP(a) is analysed in relation to various criteria in CRF to evaluate the risk groups for complications.

Aims and Objectives

1. To determine the incidence of elevated LP(a) in CKD.
2. To determine the importance of LP(a) in managing CKD.
3. To assess the risk in relation to LP(a).

MATERIALS AND METHODS

This study was done for a period of 1 year from April 2017 to March 2018 at Medicine OP, ward, Nephrology OP and wards, Government KAPV medical college hospital, Trichy. During this period, 50 patients admitted with CRF of both sexes and irrespective of age were selected and enrolled for the study.

All patients were evaluated with full clinical history and detailed physical examination. They were followed up regularly from the time of admission till discharge. The clinical features evaluated were vital signs, anaemia, hydration status, jugular venous pulse, pedal edema,

Financial or Other, Competing Interest: None.
Submission 27-02-2019, Peer Review 02-03-2019,
Acceptance 09-03-2019, Published 11-03-2019.

Corresponding Author:

Dr. Raja Mahendran P,
Plot No. 10, Rani Annadurai Street,
K. K. Nagar, Trichy- 620021,
Tamil Nadu.

E-mail: rajmahend@gmail.com

DOI: 10.18410/jebmh/2019/161



sensorium, gastrointestinal symptoms, basal crackles, ascites, pericardial rub etc.

Investigations like routine urine and blood examination, blood sugar, urea, serum creatinine, 24 hr urinary protein, ultrasonogram abdomen, and ECG were done. LP(a) is estimated by Turbidimetric method. LP(a) level > 30 mg was taken as positive.

Inclusion Criteria

All patients admitted with CRF
Age - all ages
Sex - both males and females

Exclusion Criteria

Diabetes mellitus
Acute renal failure
Chronic liver disease
Hyperthyroidism
Nephrotic syndrome
Patients on hormone replacement therapy
Patients with septic focus or septicaemia
Bacterial infection like pneumonia
On treatment with lipid lowering drugs

RESULTS

37 out of 50 patients with CKD had elevated levels of serum LP(a). Age and sex were not found to be significant factor affecting LP(a). There was a significant correlation between serum creatinine and LP(a) level. LP(a) is significantly elevated in severe anaemic patients. ECG changes and increased diastolic BP are associated with elevated level of serum LP(a).

Haemoglobin	No. of Cases	Mean LP(a)	SD LP(a)
Hb >8 gm	24	35.88	28.82
Hb <8 gm	26	71.93	32.24

Table 1. Hb and LP (a)

Here the P value is <0.05. Lipoprotein(a) level is significantly elevated in patients with severe anaemia.

P < 0.001 significant.

Creatinine	No. of Cases	Mean LP(a)	SD LP(a)
Less Than 5 mg	8	13.96	4.8
5 to 10 mg	35	59.71	31.01
More Than 5 mg	7	75.7	43.21

Table 2. Creatinine vs. LP(a)

Mean creatinine for 50 cases = 7.636

SD = 2.117

P < 0.001 significant.

DISCUSSION

The etiology of CKD is multiple resulting in inevitable loss of number and function of nephrons leading to end stage renal

disease.³ Untreated acute and chronic renal failure can lead to uremia which results in dysfunction of all organ systems. In CRF patients the comprehensive care of the patients involves not only the management of renal disease but also the appropriate management of complications it produce.

This study deals with the association of serum LP(a) with the possible risks that occur in the course of CKD. The pathogenic effects of LP(a) are atherogenesis and thrombosis leading to increased risk of coronary artery disease.

Pathophysiological Mechanism

The accumulation of LP(a) molecule have been demonstrated in arterial walls of human coronary and cerebral blood vessels. This occurs due to the tendency of apo(a) to bind to connective tissue elements such as proteoglycans, glycosaminoglycans especially fibronectin. This binding process is promoted by lipoprotein lipase or sphingomyelinase.⁴

The lipoprotein(a) particles are susceptible to oxidative modification and scavenger receptor uptake leading to intracellular cholesterol accumulation and foam cells formation which contribute further to atherogenesis.⁵

The raised sialic acid content of LP(a) is thought to contribute to oxidative resistance of native particle.

Thrombosis results when LP(a) competes with plasminogen for its receptors on endothelial cells leading to diminished plasmin formation thereby delaying clot lysis. The high affinity of LP(a) for fibrin results in the inhibition of plasminogen binding to these substrates. The high affinity of lipoprotein(a) for fibrin explains their frequent localisation in atherosclerosis plaques.

LP(a) displaces plasminogen from the surface of macrophages in atherosclerotic plaques and reduces the activation of TGF-beta cytokines which induces smooth muscle cell proliferation and transformation of these cells to a more atherogenic cellular phenotype.⁶

LP(a) and Atherogenesis

LP(a) binds to fibrin and provides a carrier system for low density lipoprotein cholesterol (LDL-C) leading to enhanced lipid accumulation at site of vascular injury. Oxidized LDL-C and LP(a) accumulate in excessive amounts in macrophages transforming them into foam cells accelerating the formation of fatty streak.⁷ Intact LP(a) is deposited in atherosclerotic lesions and it correlates with serum levels. Accumulation of LP(a) has been demonstrated in arterial walls and venous grafts. Oxidized LP(a) dysregulates endothelium dependent vasodilatation as well.

Evidence from previous research reveal that endothelial function disturbance, infiltration of intimal endothelial surface of the arterial wall with naive LDL particles, their oxidative modification, migration and proliferation of smooth muscle cells, extracellular matrix reorganization and growing fibro lipid plate, were the main mechanisms of atherogenesis.

In CRF patients, the hypertriglyceridemia present, brings about modification of HDL and LDL particle structure

resulting in the occurrence of small dense LDL with increased capacity of binding to the arterial wall and a special tendency to oxidative modification. The decreased concentrations and proactive abilities of modified HDL particles impose an additional factor in the contribution of premature atherosclerosis development in CRF.

LP(a) and Thrombosis

The homology of plasminogen to LP(a) enables to interfere with thrombosis and thrombolysis. LP(a) competitively inhibits the binding of plasminogen to high affinity binding sites in endothelial cells, fibrinogen, fibrin and platelets. Also, LP(a) is an important regulator of synthesis of plasminogen activator inhibitor-1 by the endothelium, which leads to thrombotic state.⁸

LP(a) is also implicated in enhanced oxidation and foam cell formation. Now, it has been proposed that in settings of enhanced oxidative stress and increased LP(a) concentrations, a proinflammatory milieu may predominate, that contribute to the clinical expression of cardiovascular disease.

Thus, available evidence suggests that LP(a) plays an important role in atherogenesis and thrombus formation, leading to rapid evolution of atheroma and myocardial infarction.⁹

LP(a) and Risk of Coronary Artery Disease

LP(a) is considered to be ten times more atherogenic than LDC-C. Higher LP(a) levels were noted in patients with coronary artery disease when compared to controls. Relative risk in coronary artery disease is increased threefold in males if LP(a) level is above 30 mg/dl. Adverse effects of LP(a) on atherogenesis are enhanced by high levels of LDC-C and low levels of HDL-C. Hence LP(a) should be included in coronary artery disease risk assessment wherever facility for its estimation is available.

Factors Affecting LP(a)

LP(a) levels do not vary with age or sex of the patient.

LP(a) levels are increased as a part of acute phase response in diabetes, CRF, nephritic syndrome, cancer and menopause.

LP(a) levels are decreased in liver failure and hyperthyroidism. LP(a) levels can be reduced by diet rich in saturated and n-3 poly unsaturated fatty acids. Strict vegetarian diet may also help to reduce LP(a).¹⁰

Nicotinic acid has favourable though inconsistent effect on LP(a) concentration. However, this drug is difficult to tolerate in the high doses required.¹¹

Statins¹² do not reduce LP(a) concentration. It supports the concept that LDL receptors does not play an important role in the catabolism of LP(a).

Fibric acid derivatives exert a favourable effect on high density lipoprotein and triglyceride concentration as on LDL quantity and quality. These drugs also reduce fibrinogen and possibly LP(a) values.¹³

Anti-hypertensive agents can affect plasma fibrinogen and LP(a) concentration.¹⁴ Optimising body weight and strict

glycemic control may beneficially influence LP(a) values in patients with type 1 and 2 diabetes mellitus.

According to the results of the study, the recommendations suggested are:

Serum LP(a) levels have to be included among the list of modifiable cardiovascular risk factors in CRF

Supplemented vegetarian diet helps to bring down LP(a) values in CRF

Those individuals with elevated LP(a) values have to be treated with folic acid, niacin and cyanocobalamin.

Further Therapeutic Directions

The post translational modifications of LP(a) after its entry into arterial wall (oxidation and proteolysis) would become the potential targets for therapeutic interventions.

CONCLUSION

This study shows a definite association between serum LP(a) and CRF. Elevation of serum LP(a) is independent of age and sex. Elevated LP(a) values correlates with severe anaemia, increased diastolic BP, ECG changes and increased level of serum creatinine. Thus, elevation of serum LP(a) is very much useful in assessing the risk in chronic renal failure as accelerated atherosclerosis, uncontrolled hypertension, coronary artery disease and end stage renal disease.

REFERENCES

- [1] Cumming AD, Swainson CP, Davison AM. Diseases of the kidney and genito-urinary system. In: Edwards CRW, Bouchier AD, Haslett C, et al, eds. *Davidsons principles and practice of medicine*. 17th edn. New York: Churchill Livingstone 1995:631-636.
- [2] Brenner BM, Lazarus JM. Chronic renal failure. In: Isselbacher KJ, Braunwald E, Wilson JD, et al, eds. *Harrisons principle of internal medicine*. 13th edn. New York: McGraw-Hill 1994:1274-1281.
- [3] Burton C, Harris KP. The role of proteinuria in the progression of chronic renal failure. In: Braunwald E, Fauci AS, Kasper DL, et al, eds. *Harrisons principle of internal medicine*. 15th edn. New York: McGraw-Hill 2001:1551-1552.
- [4] Collins AJ, Li S, Gilbertson DT, et al. Chronic kidney disease and cardiovascular disease in the Medicare population. *Kidney Int Suppl* 2003;87:S24-S31.
- [5] Pauling L, Rath M. A Unified Theory of Human Cardiovascular Disease Leading the Way to the Abolition of This Disease as a Cause for Human Mortality. *Journal of Orthomolecular Medicine* 1992;7(1):5-12.
- [6] Muntner P, He J, Astor BC, Folsom AR, et al. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. *J Am Soc Nephrol* 2005;16(2):529-538.
- [7] Longenecker JC, Coresh J, Klag MJ, et al. Lipoprotein (a) level as a predictor of cardiovascular disease and small apolipoprotein(a) isoforms in dialysis patients:

- Assay-related differences are important. *Clin Chim Acta* 2008;397(1-2):36-41.
- [8] Deighan CJ, Caslake MJ, McConnell M, et al. Atherogenic lipoprotein phenotype in end stage renal failure: origin and extent of small dense low-density lipoprotein formation. *Am J Kidney Dis* 2000;35(5):852-862.
- [9] Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;32(5 Suppl 3):S112-S119.
- [10] Hunsicker LG, Adler S, Caggiula A, et al. Predictors of the progression of renal disease in the modification of diet in Renal Disease Study. *Kidney Int* 1997;51(6):1908-1919.
- [11] Owada A, Suda S, Hata T. Antiproteinuric effect of niceritol, a nicotinic acid derivative, in chronic renal disease with hyperlipidemia: a randomized trial. *Am J Med* 2003;114(5):347-353.
- [12] Tonelli M, Moye L, Sacks FM, et al. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. *J Am Soc Nephrol* 2003;14(6):1605-1613.
- [13] Throp ML, Eastman L, Smith DH, et al. Managing the burden of chronic kidney disease. *Dis Manag* 2006;9(2):115-121.
- [14] Grundy SM. Management of hyperlipidemia of kidney disease. *Kidney Int* 1990;37(3):847-853.