

Original Research Article

Study of Lipoprotein (a) in Patients of Type 2 Diabetes Mellitus with Nephropathy

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ABSTRACT

Introduction: Diabetes mellitus is a major health concern because of its increasing prevalence rate globally. Presence and progression of microalbuminuria in patients with diabetes is not only a marker of nephropathy but also of cardiovascular risk. Lipoprotein (a) [Lp (a)], a subtype of low-density-lipoprotein, has been associated with risk of cardiovascular disease (CVD),^[6] but its role in type 2 diabetes is unclear. Aim of this study was to assess the possible relationship between the serum concentrations of Lp (a) and the level of albuminuria in a cohort of type 2 diabetes patients with nephropathy.

Materials and Methods: This cross-sectional hospital based study was conducted at a medical college hospital of North India. We included 246 patients of type 2 diabetes and assessed for albuminuria, glycemic status, vascular complications and Lipoprotein (a) measurement.

Results: Amongst 246 patients, 92 patients had normal albuminuria while 90 patients had micro and 64 had macroalbuminuria. We found that 42% patients had retinopathy, 60% neuropathy and 36% had macrovascular complications. Mean lipoprotein (a) levels were significantly high in patients with micro or macroalbuminuria than those who had normal albuminuria. It was also observed that levels of lipoprotein (a) had significant positive correlation with level of albuminuria.

Conclusion: We observed high Lp (a) levels in patients of diabetes who had micro or macro albuminuria than normal albuminuria. Lp (a) level might be an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria but more evidence is needed to establish this fact in our population.

Key words: Type 2 diabetes, albuminuria, nephropathy, Lipoprotein (a).

INTRODUCTION

The adoption of western lifestyles, mostly in urban areas, contributes to increase the prevalence of hypertension and diabetes mellitus in this setting.^[1] Diabetes mellitus is a major health concern because of its increasing prevalence rate globally that has led to consequent increase in the incidence of related microvascular as well as macrovascular complications, including kidney disease.^[2] Diabetic nephropathy affects approximately one-third of individuals with diabetes mellitus and

constitutes an important cause of chronic kidney disease (CKD). CKD is an independent risk factor for cardiovascular (CV) disease and CV mortality.^[3] Among other derangements, the circulating lipid profile seen in CKD includes elevated levels of lipoprotein (a).^[4]

Presence and progression of microalbuminuria in patients with diabetes is not only a marker of nephropathy but also of cardiovascular risk.^[5] Lipoprotein(a) [Lp(a)], a subtype of low-density-lipoprotein (LDL) that carries

apolipoprotein(a), has been associated with risk of cardiovascular disease (CVD), [6] but its role in type 2 diabetes is unclear. The risk of developing cardiovascular disease is increased in diabetic individuals. The existence of this relationship has been hypothesized based on the potential for Lp(a) to cause vessel damage through lipoprotein oxidation and on the potential antifibrinolytic property. According to some studies, increased concentrations of Lp(a) have been associated with higher risk of CVD in diabetic patients. [7-9] However, it is unclear if Lp(a) concentrations relate to risk of type 2 diabetes or insulin resistance. [10]

There has been paucity of literature on Lp(a) levels and its role in micro vascular complications among patients with type 2 diabetes mellitus in our population. The objective of this study was to assess the possible relationship between the serum concentrations of Lp(a) and the level of albuminuria in a cohort of type 2 diabetes patients with nephropathy.

MATERIALS AND METHODS

In this cross-sectional hospital based study which was conducted in Era's Lucknow Medical College Lucknow, between January 2013 to December 2013. The study included a cohort of 246 patients with type 2 diabetes mellitus diagnosed according to the American Diabetes Association criteria [11] attending diabetes/Endocrinology clinic of medical college hospital. Presence of albuminuria was assessed according to the albumin/creatinine ratio in spot urine. Level of albuminuria was classified as; normal albuminuria: <30 mg/g creatinine, microalbuminuria: 30-300 mg/g creatinine, macro albuminuria: >300 mg/g creatinine). [12]

We excluded those patients who had (1) an age < 18 years or > 80 years, (2) accelerated hypertension (3) pregnancy, (4) malignancies, (5) patients with end organ diseases such as hepatic failure or heart failure, (6) acute systemic infection, (7) patients with acute complications of

diabetes and (8) patients with h/o non diabetic kidney disease.

All patients provided written informed consent and study was approved by the Institutional Ethics Committee.

The collected data included age, gender, duration of diabetes and history of medication, anthropometric parameters, (which included weight, height, body mass index (BMI), and waist/ hip ratio), systolic and diastolic blood pressures; The BMI was calculated as weight (kg)/height (m²). Hypertension was defined as a blood pressure measurement of above 140/90 mmHg in the right upper limb supine position or when the patient was on anti-hypertensive medication. Biochemical parameters included serum creatinine, albumin, total cholesterol and high-density lipoprotein (HDL) cholesterol, triglyceride, uric acid and glycosylated hemoglobin,

A for estimation of Lp(a) levels. Lp(a) was measured in overnight fasting venous blood sample by a latex-enhanced turbidimetric immunoassay using Latex Daiichi (Sekisui Medical Co., Ltd, Tokyo, Japan). The reference value for Lp(a) level in the normal population was taken as < 30 mg/dl. [13]

Statistical analysis

The statistical analyses were performed using Statistical Package for the Social Sciences 15.0 version software (Chicago, IL, USA). Data are reported as median and inter quartile range (IQR) or mean \pm SD for continuous variables and as proportions for categorical variables. The Student's *t*-test or Mann-Whitney test were used, as appropriate, to determine differences in continuous variables. The Pearson's Chi-square test or Fisher's exact test, as appropriate, was used to determine the differences in categorical variables. Pearson correlation coefficient was calculated to assess correlations between Lp(a) and level of albuminuria. A *P* value < 0.05 was considered to indicate statistical significance.

RESULTS

Our study enrolled 246 patients with type 2 diabetes mellitus. Amongst them, 92 patients had normal albuminuria while 90 patients had micro and 64 had macroalbuminuria. Mean age of our patients was 48 ± 10 years and 56% patients were males. Mean duration of diabetes was 8.5 ± 6 years in our study. Table 1 is showing the clinical characteristics of study patients of diabetes and comparison between patients who had normal albuminuria and those who had nephropathy.

Glycemic status, prevalence of diabetes complications and presence of comorbidities have been depicted in Table 2. We found that 63% patients had

nephropathy, 60% neuropathy and 36 % had macrovascular complications.

Mean lipoprotein (a) levels were significantly high in patients with micro or macroalbuminuria than those who had normal albuminuria. It was also observed that levels of lipoprotein (a) had significant positive correlation with level of albuminuria.

Lp (a) level was measured in all 246 subjects (normal range in serum was up to 30 mg/dL). Lp (a) levels were abnormal in 26.4% cases and normal in 73.6% cases. Higher Lp (a) levels had a significant positive correlation to the duration of diabetes ($r = 0.36$; $P = 0.012$). However, Lp (a) levels did not have a correlation to HbA1c values ($r = -0.063$; $P = 0.67$).

Table 1: Clinical and biochemical characteristics of patients with and without albuminuria

Variable	Normal albuminuria (n=92)	Micro/macro albuminuria (n=154)	P value
Age(years)	52± 13	51±14	0.63
Female, n (%)	40	48	0.02
BMI, kg/m ²	24.6± 2.8	24.3± 3.0	0.12
Systolic blood pressure, mmHg	122± 16	136± 16	0.013
Diastolic blood pressure, mmHg	82± 12	96± 14	0.002
Lipoprotein (a) , mg/dL	18± 4.7	28.6± 6.2	0.01
Serum LDL cholesterol, mg/dL	108± 26	112± 30	0.56
Serum triglyceride, mg/dl	170± 126	182± 134	0.12
Serum HDL, mg/dL	52± 12	50± 12	0.04
Urinary albumin excretion, µg/mi	16.8± 3.6	322± 28	0.001
Estimated GFR ml/min/1.73 m ²	95 ± 26	72 ± 24	0.01
HbA1C	8.6± 2.12	8.8± 2.0	0.7

Values are expressed as means ± SDs, or (%).

Table 2: Prevalence of Co-morbidities and diabetes related complications in Patients with type 2 diabetes mellitus(n=246)

Name of the complication	Prevalence (%)
Hypertension	45
Dyslipidemia	40
Macrovascular complications (ischemic heart disease/peripheral artery disease/cerebrovascular disease)	36
Retinopathy	42
Nephropathy	63
Neuropathy	60
Foot ulcers	12

Table 3: Lipoprotein (a) levels according to stages of albuminuria

Albuminuria	N=246	Lipoprotein (a), mg/dl Median (inter quartile range)	P value
Normal (< 30)	92	22.4(18-26.6)	
Micro (30-299) ^{a, b}	90	28.7(22.4-34)	a, 0.002 ,b 0.001
Macroalbuminuria (≥ 300)	64	36(30-50.6)	c, 0.001

a. Difference between micro and normal albuminuria b. Difference between mac

DISCUSSION

Diabetic nephropathy is a common and serious complication of diabetes associated with adverse outcomes of renal failure, cardiovascular disease, and premature mortality. [14]

Lipoprotein (a) has been identified as an independent, causal risk factor for cardiovascular disease. There are conflicting reports on the relationship between Lp(a) levels and type 2 diabetes. [15-17] Since diabetes predisposes individuals for

cardiovascular disease, a similar association between circulating Lp (a) levels and risk of type 2 diabetes was expected. However, studies have shown contradictory results. Early studies have indicated that Lp(a) concentrations were elevated in subjects with type 2 diabetes, [18] especially those with poor metabolic control, and that improved metabolic control resulted in decreases of serum Lp(a) [19] While others found either unchanged [20] or decreased [21] concentrations of serum Lp(a) in patients with type 2 diabetes versus nondiabetic subjects.

These conflicting reports on the association between Lp(a) levels and type 2 diabetes prompted us to estimate the Lp(a) levels in this diabetic cohort. We conducted this study to assess Lp(a) levels in patients of diabetes with nephropathy who had different levels of albuminuria.

Lp (a) is an important cardiovascular risk factor in the general population. [22,23] However, data on the risks conferred by Lp(a) in patients with diabetes mellitus specially in diabetic nephropathy are scarce and controversial and it is not well known, It was assumed that, glycation of proteins, i.e., nonenzymatic glycosylation resulting from the high plasma glucose levels found in diabetes, is thought to be one of the factors contributing to the severity of this disease. Indeed glycation produces modest increases in the degradation rate of Lp (a). However, glycation does not appear to enhance the atherogenic potential of unmodified Lp (a) significantly. [24]

Kapelrud et al. in their study in patients with type1 diabetes found that serum concentration of Lp (a) was twice as high in insulin dependent diabetic patients with microalbuminuria as in those without microalbuminuria. They concluded that increased concentrations of Lp (a) lipoprotein might partly explain the increased morbidity and mortality of cardiovascular disease observed among patients with diabetic nephropathy. [25]

In an Indian study by Chandni et al abnormal Lp (a) levels were found among

26.4% of diabetic subjects. [26] Patients with diabetic nephropathy had higher Lp (a) levels. No association was found between Lp (a) levels and diabetic retinopathy or neuropathy. Longer duration of diabetes correlated with higher Lp (a) levels similar to our study

showed a statistically significant association between higher Lp (a) levels and diabetic nephropathy (both microalbuminuria and overt proteinuria) which is in concordance with Tseng et al. [27] They also reported high Lp (a) levels among type 2 diabetic patients with overt proteinuria although contradictory results were shown by another study [28] did not show such an association. Song et al have demonstrated in their study that Lp (a) level might be an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria. [29] Our observation of high Lp (a) levels among those with overt proteinuria and positive correlation with levels of albuminuria has important clinical implication.

Type 2 diabetes is considered a cardiovascular equivalent and confers very high risk for causation of atherosclerosis. Lipoprotein also being cardiovascular risk factor and albuminuria can further contribute to occurrence of cardiovascular events. Increased concentrations of Lp (a) lipoprotein might partly explain the increased morbidity and mortality from cardiovascular disease observed among patients with diabetic nephropathy and Lp (a) - lowering therapy might offer benefits in subgroups of patients with high Lp (a) levels. Despite the recognition of the role of Lp (a) as an independent risk factor of CVD events, irrespective of other coexisting risk factors, physician knowledge regarding Lp(a) is limited. Consequently, Lp(a) is measured infrequently. One of the reasons for this is associated with the lack of clear recommendation associated with the Lp(a) cut-off values, another relates to the cost and difficulties associated with diagnostic methods, and a third reason is the lack of recommendations on management and

therapy of patients with high levels of this biomarker. [30]

Limitations of study were small sample size and cross sectional design. It is important that more prospective studies are warranted on large number of patients that would shed light on the roles of Lp (a) in pathogenesis of complications of type 2 diabetes.

CONCLUSION

We observed high Lp(a) levels in patients of diabetes who had micro or macro albuminuria than normal albuminuria. Lp (a) level might be an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria. More evidence is needed to establish this fact. Larger studies are also necessary to elucidate the cardiovascular risk related to Lp (a) levels in Indian patients with type 2 diabetes to tackle this issue.

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