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BRIEF ARTICLE

Lipoprotein(a) in type 2 diabetic subjects and its relationship to diabetic microvascular complications

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Abstract

AIM: To estimate the level of serum lipoprotein (a) [Lp (a)] in type 2 diabetes mellitus patients and to determine the relationship between Lp(a) in type 2 diabetes mellitus patients and micro-vascular complications.

METHODS: A cross sectional study was performed that enrolled 144 subjects with type 2 diabetes mellitus above the age of 25 years attending outpatient clinic of Government Medical College, Kozhikode. Lp(a) levels were measured quantitatively in venous samples using Turbidimetric Immunoassay in all subjects. Each patient was evaluated for micro vascular complications, namely diabetic retinopathy, nephropathy and neuropathy. The relationship between Lp(a) levels and the micro vascular complications was assessed by univariate analysis.

RESULTS: Mean age of cases was 53.93 ± 10.74 years with a male to female ratio of 1.3:1. Mean duration of diabetes was 9.53 ± 7.3 years. Abnormal Lp(a) levels (≥ 30 mg/dL) were observed in 38 (26.4%) diabetic subjects. Seventy-eight (54.16%) cases had diabetic nephropathy and significantly higher Lp(a) levels were found among these cases [Median 28.2 mg/dL (Interquartile range; IQR 24.4-33.5) *vs* 19.3 mg/dL (IQR 14.7-23.5); $P < 0.05$]. Retinopathy was present among 66 (45.13%) cases and peripheral neuropathy was detected among 54 (37.5%) cases. However, Lp(a) levels were not significantly different among those with or without retinopathy and neuropathy. Positive correlation was found between higher Lp(a) levels and duration of diabetes ($r = 0.165$, $P < 0.05$) but not with HbA1c values ($r = -0.083$).

CONCLUSION: Abnormal Lp(a) levels were found among 26.4% of diabetic subjects. 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.

Key words: Diabetes mellitus; Lipoprotein(a); Micro vascular complications; Diabetic nephropathy; Diabetic retinopathy; Diabetic neuropathy

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INTRODUCTION

There has been a rising epidemic of diabetes mellitus in India in recent years and an alarming increase in the rate

of mortality and morbidity due to coexisting dyslipidemia, atherosclerosis and coronary artery disease. Diabetic micro vascular complications have become a major cause of chronic kidney disease, blindness and diabetic foot problems, which are preventable to some extent. Many risk factors, like the duration of diabetes, degree of glycemic control and age of the patient, are identified in causation of diabetic micro vascular complications.

Lipoprotein(a) [Lp(a)] is a low density lipoprotein-like particle containing Apo-lipoprotein B100 disulphide, linked to one large glycoprotein called Apo-Lp(a), a particle comprised of low density lipoprotein and covalently bound Apo-Lp(a), and is considered a pro-atherogenic, pro-thrombotic risk factor for coronary heart disease (CHD)[1]. Many prospective epidemiological studies have reported positive associations of baseline Lp(a) concentration with CHD risk[2-6].

There are conflicting reports on the relationship between Lp(a) levels and type 2 diabetes. Hyperinsulinemia tends to decrease Lp(a) levels among patients with type 2 diabetes[7,8] and some studies even showed an inverse relationship between Lp(a) levels and incident type 2 diabetes[9,10]. However, some Asian studies showed a strong association between type 2 diabetes and elevated Lp(a) levels[11,12]. Similarly there are conflicting reports on the evidence of association between Lp(a) levels and diabetic micro vascular complications like nephropathy, retinopathy and neuropathy[13-20].

There is insufficient data from the Indian subcontinent on Lp(a) levels and its role in micro vascular complications among patients with type 2 diabetes mellitus. The purpose of the present study was to estimate the serum Lp(a) levels in type 2 diabetic patients and to determine if there is any relationship between serum Lp(a) levels and diabetic micro vascular complications.

MATERIALS AND METHODS

The study included patients with type 2 diabetes mellitus above the age of 25 years who were attending the medical and diabetic outpatient clinics of Government Medical College, Kozhikode, a tertiary-care teaching hospital in northern Kerala, South India. This study was planned with the following aims: (1) to estimate the level of serum Lp(a) in type 2 diabetes mellitus patients; and (2) to determine the relationship between Lp(a) levels and diabetic micro vascular complications. The exclusion criteria were: (1) patients who were already on lipid lowering drugs or glitazones and females taking oral contraceptive pills or hormone replacement therapy; (2) familial hypercholesterolemias; (3) hypothyroidism, including subclinical hypothyroidism (with thyroid stimulating hormone values above 5.5 μIU/mL); (4) those who are seriously ill and/or requiring hospitalization or with chronic liver or kidney disease with serum creatinine ⩾ 2 mg%; and (5) those who were in the habit of alcohol use.

Subjects who were taking medications for hyperlipidemia or medications known to affect the lipid profile were excluded. Subjects with familial hyperlipidemia, pregnancy, hypothyroidism, alcoholism, as well as those with signs and/or symptoms of active infection or stressful conditions were excluded as they are known to alter the Lp(a) levels.

This was a cross sectional study. Informed consent was obtained from each of the participants and the study was approved by the Institutional Review Board. A detailed history including dietetic history was taken. Physical examination included height, weight and body mass index (BMI). BMI was calculated by determining weight in kilograms and dividing by the height in meters squared. Waist circumference was measured using a measuring tape in centimeters at the point where the mid axillary line touches the highest point of iliac crest. The plane of the tape was held parallel to the floor with the tape snug but without compression of the skin. The measurement was made at a normal minimal respiration.

Neuropathy assessment was done in both feet with vibration perception using a tuning fork of 128 Hz, elicitation of ankle jerks and testing with monofilament of 5.07 size (thickness), equivalent of 10 gm of linear force. If any two of the three tests were positive, the patient was considered to have neuropathy after excluding other causes for neuropathy with a reasonable clinical and appropriate laboratory evaluation. Examination of the retina was done through dilated pupils to determine the level of non-proliferative diabetic retinopathy, proliferative diabetic retinopathy (PDR) and macular edema by a qualified ophthalmologist. The definitions were based on the International Classification of Diabetic Retinopathy. Screening for microalbuminuria can be performed by measurement of the albumin-creatinine ratio in a random, spot collection (preferred method); the analysis of a spot sample for the albumin-creatinine ratio is strongly recommended by most authorities. In the present study, two of three specimens collected within a 3 to 6 mo period were used for quantification to include in the respective group.

A venous blood sample was collected after a 12 h overnight fasting for estimation of Lp(a) levels. The measurement is performed with the person in a baseline stable condition. Lp(a) level was measured by turbidimetric immunoassay. The reference value for Lp(a) level in the normal population is < 30 mg/dL. HbA1c was estimated using high performance liquid chromatography method. Other laboratory investigations, including fasting and post prandial blood sugars, blood urea, serum creatinine and thyroid stimulating hormone, were done in all the patients.

Statistical analysis

Data are reported as median and inter quartile range (IQR) or mean ± SD for continuous variables and as proportions for categorical variables. Continuous variables were analyzed by *t*-test and Pearson's correlation when data was normally distributed and by Mann Whitney *U* test when data was not normally distributed. A *P* value

Table 1 Lipoprotein(a) levels among patients with or without retinopathy and neuropathy

	No. of cases	Lp(a) level (mg/dL)	
		Median	Inter quartile range
Retinopathy present	66	24.8	16.1-29.4
Retinopathy absent	78	22.9	14.9-27.6
Neuropathy present	54	23.2	18.1-27.3
Neuropathy absent	90	24.6	17.6-28.1

Lp(a): Lipoprotein(a).

Table 2 Definitions of abnormalities in albumin excretion and lipoprotein(a) levels with albumin-creatinine ratio

Albumin/creatinine ratio (μgm/mg creatinine)	No. of cases	Lp(a) levels (mg/dL)	
		Median	Inter quartile range
Normal (< 30)	66	19.3	14.7-23.5
Micro (30-299)[a,b]	58	26.4	20.2-32.8
Macroalbuminuria (≥ 300)[a]	20	33.2	30.3-36.1

[a]$P < 0.05$ *vs* normal; [b]$P < 0.05$ *vs* macroalbuminuria. **Lp(a): Lipoprotein(a).**

< 0.05 was considered to indicate statistical significance. Statistical analysis was done using SPSS version 13.0 for Windows.

RESULTS

A total of 144 subjects satisfying the inclusion criteria were included in the study. The mean age was 53.93 ± 10.74 years and the male to female ratio was 1.3:1. Mean duration of diabetes was 9.53 ± 7.3 years. Mean BMI was 25.16 ± 3.9 kg/m^2 with a waist circumference of 91.94 ± 8.8 cm. Mean systolic blood pressure was 134.12 ± 17.1 mmHg and mean diastolic blood pressure was 83.12 ± 9.2 mmHg. Mean HbA1c was 8.01% ± 2.15%. With regard to current diabetic management: 3% of patients were on diet alone; 70% were on oral antidiabetic drugs like metformin and/or sulfonylurea; 19% were on oral antidiabetic drugs (metformin and/or sulfonylurea) and insulin; and 8% were on insulin alone (Patients on glitazones were not included in the present study).

Lp(a) level was done in all 144 subjects (normal range in serum is up to 30 mg/dL). Lp(a) levels were abnormal in 38 (26.4%) cases and normal in 106 (73.6%) cases. Higher Lp(a) levels had a significant positive correlation to the duration of diabetes ($r = 0.165$; $P < 0.05$). However, Lp(a) levels did not have a correlation to HbA1c values ($r = -0.083$; P = insignificant).

Lp(a) levels and micro vascular complications

Retinopathy was assessed in all 144 patients. 78 (54.2%) did not have retinopathy. 66 (45.8%) cases had evidence of diabetic retinopathy, of whom 40 (27.8%) cases had mild non-proliferative retinopathy, 13 (9%) had moderate non-proliferative retinopathy and 8 (5.6%) had severe non-proliferative retinopathy. Five (3.4%) cases had PDR. There was no statistically significant difference in Lp(a) levels among patients with and without diabetic retinopathy (Table 1).

Diabetic neuropathy was present in 54 (37.5%) patients and absent in 90 patients (62.5%) but there was no statistically significant difference in Lp(a) levels among patients with and without diabetic neuropathy (Table 1).

Lp(a) levels and diabetic nephropathy

Seventy-eight (54.16%) cases had diabetic nephropathy (microalbuminuria or overt proteinuria). Median Lp(a) levels in this group was 28.2 mg/dL (IQR 24.4-33.5), whereas those without nephropathy had a median Lp(a) level of 19.3 mg/dL (IQR 14.7-23.5) and this difference was statistically significant ($P < 0.05$). Intergroup comparison of median Lp(a) levels between patients with microalbuminuria and macroalbuminuria also showed statistical significance (Table 2).

DISCUSSION

Diabetes mellitus confers a two-fold higher risk for a wide range of vascular diseases, independent of other conventional risk factors[21]. Any additional risk factor along with diabetes would increase the vascular risk that might prove to be catastrophic to the sufferer. High Lp(a) level has been proven to be a risk factor for atherosclerosis and related morbidity and mortality in many studies[2-6]. It would be logical to consider higher vascular risk among diabetic patients with elevated Lp(a) levels although such an association is yet to be proven in controlled trials.

Type 2 diabetics are usually hyperinsulinemic and insulin tends to lower the Lp(a) levels[7,8]. Large population-based studies have even shown an inverse association between Lp(a) levels and incident diabetes[9,10]. However, some Asian studies clearly showed higher Lp(a) levels among type 2 diabetics[8,11,12]. 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.

A significant proportion of type 2 diabetics (26.4%) had elevated Lp(a) levels, as observed by other workers[8,11,12]. Higher Lp(a) levels were observed among those with a longer duration of diabetes in this study, similar to the observations made by Habib *et al*[8]. Higher Lp(a) levels among patients with a longer duration of diabetes may be related to lower plasma insulin levels in such individuals. Because vascular risk is directly related to the duration of diabetes, the possible contribution of elevated Lp(a) levels to higher vascular risk among type 2 diabetics demands investigation in future clinical trials. A cross sectional analyses of two community-based studies showed that Lp(a) is a strong independent predictor of CHD risk in type-2 diabetic women, but not in men or in men or women without type-2 diabetes[22]. Already there is some evidence showing a strong association between peripheral occlusive arterial disease (a marker of systemic

atherosclerosis) and serum Lp(a) levels in patients with diabetes[23]. The present study did not show any relationship of Lp(a) levels to glycemic control, as in one previous study[24].

The present study showed a statistically significant association between higher Lp(a) levels and diabetic nephropathy (both microalbuminuria and overt proteinuria). Tseng[14] from Taiwan also recently observed high Lp(a) levels among type 2 diabetic patients with overt proteinuria although an earlier study[13] did not show such an association. Our observation of high Lp(a) levels among those with overt proteinuria in the present study has important clinical implications as Lp(a) level is an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria, as shown by Song *et al*[25].

We did not observe any statistically significant association between Lp(a) levels and diabetic retinopathy in this cohort. Some previous studies have shown an association between Lp(a) levels and retinopathy[15,16], while others have not[17,18]. Similar to the observations made by earlier workers[19,20], we were also unable to find any association between diabetic neuropathy Lp(a) levels.

The small number of subjects selected for evaluation of a common clinical problem like type 2 diabetes mellitus is an important limitation of this study. However, the observation of high Lp(a) levels in a significant proportion of cases and the association between Lp(a) levels and diabetic nephropathy were especially noteworthy. Larger studies are necessary to elucidate the vascular risk related to Lp(a) levels in Indian patients with type 2 diabetes for strategic planning of preventive measures.

In conclusion, Lp(a) levels were abnormal in 26.4% of type 2 diabetic patients in the present study. A significantly higher proportion of patients with diabetic nephropathy had higher Lp(a) levels compared to those without nephropathy. Lp(a) levels were comparable among patients with or without diabetic retinopathy and diabetic peripheral neuropathy. A longer duration of diabetes had a positive correlation with higher Lp(a) levels. However, higher HbA1C levels did not have any correlation with Lp(a) levels.

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COMMENTS

Background

There has been a rising epidemic of diabetes mellitus in India in recent years. Diabetic micro vascular complications have become a major cause for chronic kidney disease, blindness and diabetic foot problems, which are preventable to some extent. Many risk factors, like the duration of diabetes, degree of glycemic control and age of the patient, are identified in the causation of diabetic micro vascular complications. There are conflicting reports on the evidence of the association between lipoprotein(a) [Lp(a)] levels and diabetic micro vascular complications like nephropathy, retinopathy and neuropathy. The purpose of the present study was to estimate the serum Lp(a) levels in type 2 diabetic patients and to determine if there is any relationship between serum Lp(a) levels and diabetic micro vascular complications.

Research frontiers

High Lp(a) levels among those with overt proteinuria in the present study has important clinical implications as Lp(a) level is an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria. Larger studies are necessary to elucidate the vascular risk related to Lp(a) levels in Indian patients with type 2 diabetes for strategic planning of preventive measures. 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.

Innovations and breakthroughs

Lp (a) level is an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria, as shown by Song *et al*. The observation of high Lp(a) levels among those with overt proteinuria in the present study, as shown in some previous studies, has important clinical implications. This may help to identify the high risk group to implement intensive follow up.

Applications

This study suggests that Lp(a) may be an independent risk factor for the progression of diabetic retinopathy, apart from other known risk factors like the duration of diabetes, degree of glycemic control and age of the patient.

Terminology

Lp(a) is a low density lipoprotein-like particle containing Apo-lipoprotein B100 disulphide, linked to one large glycoprotein called Apo-Lp(a).

Peer review

The study offers an interesting insight into the correlation between Lp(a) levels and proteinuria in type 2 diabetes mellitus and progression of nephropathy.

REFERENCES

1 **Albers JJ**, Cabana VG, Warnick GR, Hazzard WR. Lp(a) lipoprotein: relationship to sinking pre-beta lipoprotein hyperlipoproteinemia, and apolipoprotein B. *Metabolism* 1975; **24**: 1047-1054
2 **Marcovina SM**, Koschinsky ML. A critical evaluation of the role of Lp(a) in cardiovascular disease: can Lp(a) be useful in risk assessment? *Semin Vasc Med* 2002; **2**: 335-344
3 **Craig WY**, Neveux LM, Palomaki GE, Cleveland MM, Haddow JE. Lipoprotein(a) as a risk factor for ischemic heart disease: metaanalysis of prospective studies. *Clin Chem* 1998; **44**: 2301-2306
4 **Danesh J**, Collins R, Peto R. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. *Circulation* 2000; **102**: 1082-1085
5 **Bennet A**, Di Angelantonio E, Erqou S, Eiriksdottir G, Sigurdsson G, Woodward M, Rumley A, Lowe GD, Danesh J, Gudnason V. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. *Arch Intern Med* 2008; **168**: 598-608
6 **Erqou S**, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* 2009; **302**: 412-423
7 **Rainwater DL**, Haffner SM. Insulin and 2-hour glucose levels are inversely related to Lp(a) concentrations controlled for LPA genotype. *Arterioscler Thromb Vasc Biol* 1998; **18**: 1335-1341
8 **Habib SS**, Aslam M, Shah SF, Naveed AK. Lipoprotein (a) is associated with basal insulin levels in patients with type 2 Diabetes Mellitus. *Arq Bras Cardiol* 2009; **93**: 28-33
9 **Kamstrup PR**, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City

Heart Study. *Circulation* 2008; **117**: 176-184
10 **Mora S**, Kamstrup PR, Rifai N, Nordestgaard BG, Buring JE, Ridker PM. Lipoprotein(a) and risk of type 2 diabetes. *Clin Chem* 2010; **56**: 1252-1260
11 **Habib SS**, Aslam M. Lipids and lipoprotein(a) concentrations in Pakistani patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2004; **6**: 338-343
12 **Singla S**, Kaur K, Kaur G, Kaur H, Kaur J, Jaswal S. Lipoprotein (a) in type 2 diabetes mellitus: Relation to LDL: HDL ratio and glycemic control. *Int J Diabetes Dev Ctries* 2009; **29**: 80-84
13 **Heesen BJ**, Wolffenbuttel BH, Leurs PB, Sels JP, Menheere PP, Jäckle-Beckers SE, Nieuwenhuijzen Kruseman AC. Lipoprotein(a) levels in relation to diabetic complications in patients with non-insulin-dependent diabetes. *Eur J Clin Invest* 1993; **23**: 580-584
14 **Tseng CH**. Differential dyslipidemia associated with albuminuria in type 2 diabetic patients in Taiwan. *Clin Biochem* 2009; **42**: 1019-1024
15 **Kim CH**, Park HJ, Park JY, Hong SK, Yoon YH, Lee KU. High serum lipoprotein(a) levels in Korean type 2 diabetic patients with proliferative diabetic retinopathy. *Diabetes Care* 1998; **21**: 2149-2151
16 **Chopra R**, Saramma JG, Mary J, Rebecca A. Lipoprotein(a) as a risk factor for diabetic retinopathy in patients with type 2 diabetes mellitus. *Indian J Ophthalmol* 2007; **55**: 195-198
17 **Deepa R**, Mohan A, Rema M, Haranath SP, Saravanan G, Mohan V. Lipoprotein(a) in South Indian type 2 diabetic subjects in relation to diabetic vascular complications. *J Assoc Physicians India* 2002; **50**: 657-661
18 **Ergün UG**, Oztüzün S, Seydaoglu G. Lipoprotein (A) levels in type 2 diabetic patients with diabetic retinopathy. *Med J Malaysia* 2004; **59**: 406-410
19 **Maser RE**, Usher DC, DeCherney GS. Little association of lipid parameters and large sensory nerve fiber function in diabetes mellitus. *J Diabetes Complications* 1996; **10**: 54-59
20 **Tarkun I**, Cetinarslan B, Cantürk Z. Lipoprotein(a) concentrations in patients with type 2 diabetes mellitus without cardiovascular disease: relationship to metabolic parameters and diabetic complications. *Nutr Metab Cardiovasc Dis* 2002; **12**: 127-131
21 **Sarwar N**, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375**: 2215-2222
22 **Qasim AN**, Martin SS, Mehta NN, Wolfe ML, Park J, Schwartz S, Schutta M, Iqbal N, Reilly MP. Lipoprotein(a) is strongly associated with coronary artery calcification in type-2 diabetic women. *Int J Cardiol* 2011; **150**: 17-21
23 **Wollesen F**, Dahlén G, Berglund L, Berne C. Peripheral atherosclerosis and serum lipoprotein(a) in diabetes. *Diabetes Care* 1999; **22**: 93-98
24 **Westerhuis LW**, Venekamp WJ. Serum lipoprotein-a levels and glyco-metabolic control in insulin and non-insulin dependent diabetes mellitus. *Clin Biochem* 1996; **29**: 255-259
25 **Song KH**, Ko SH, Kim HW, Ahn YB, Lee JM, Son HS, Yoon KH, Cha BY, Lee KW, Son HY. Prospective study of lipoprotein(a) as a risk factor for deteriorating renal function in type 2 diabetic patients with overt proteinuria. *Diabetes Care* 2005; **28**: 1718-1723

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