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LIPOPROTEIN A IN DIABETIC NEPHROPATHY

***[1]Dr. Tamphasana Wairokpam, [2]Dr. Robinson Ningshen, [3]Dr. Kuldeep Singh and [4]Dr. Sanjiv Kumar Sharma**

[1]M. D., Senior Resident in Medicine ,R.I.M.S.
[2]M.D., Professor in Medicine, R.I.M.S.
[3]Post Graduate Trainee in Medicine, R.I.M.S.
[4]Post Graduate Trainee in Medicine, R.I.M.S..

Corresponding Author: Dr. Tamphasana Wairokpam

Deptt. of Medicine, RIMS, Imphal.

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ABSTRACT

Background: Type-2 diabetes mellitus is an increasingly common metabolic abnormality associated with microvascular and macrovascular complications. It is also the most common cause of end stage renal disease (ESRD).(1) Lipoprotein a (Lp a) is a recently discussed important independent and inheritable risk factor for micro/macrovascular complications and also an independent risk factor for the progression of diabetic nephropathy in DM2 patients with overt proteinuria.

KEYWORDS: Lp(a), Diabetic Nephropathy, Microvascular, Macrovascular, Triglycerides, Dyslipidemia, Microalbuminuria, GFR

INTRODUCTION

Diabetic nephropathy is the leading cause of end stage renal disease worldwide.[1] Patients with diabetes currently account for 35% of all patients in ESRD being treated in US and 28% of those in India.

Diabetic nephropathy is characterized by proteinuria, hypertension, progressive loss of renal function, and a high incidence of cardiovascular morbidity and mortality.[3] Of patients with type 2 diabetes, 20–40% develop diabetic nephropathy over a period of 15–20 years after the onset of diabetes.[4] Hyperglycemia, hypertension, hypercholesterolemia, and proteinuria are the most significant risk factors or markers for the development and progression of diabetic nephropathy in type 2 diabetic patients.[3,4,7,8] Nevertheless, in type 2 diabetic patients with proteinuria, delaying the progression to end-stage renal disease remains an elusive goal in clinical setting. Therefore, it is still important to explore other risk factors with possible therapeutic applications in these patients. Abnormal plasma lipoprotein profiles contribute to the increased risk in CAD and diabetic nephropathy. The risk of death from coronary heart disease is substantially increased in diabetic nephropathy compared with normal subjects or diabetes without nephropathy. In diabetic nephropathy, hyperlipidemia has been identified as a risk factor for a more rapid rate of decline in GFR and increased mortality.[5] Patients with nephropathy are found to have significantly higher Lp(a) levels than those without nephropathy in some studies. Also, the serum Lp(a) concentrations increases significantly with increased urinary albumin excretion. However, the effect of Lp(a) on the progression of diabetic nephropathy has not been clearly evaluated yet. Therefore, we took up this prospective study to determine whether Lp(a) is an independent risk factor for deteriorating renal function in type 2 diabetic patients.[1]

AIMS AND OBJECTIVES

The present study is undertaken

- To find out the association of lipoprotein (a) with type 2 diabetic patients with nephropathy and those without nephropathy.
- To assess the role of lipoprotein (a) as a risk factor in diabetic nephropathy.
- To prove that levels of Lp(a) are higher in patients with diabetic nephropathy than those without nephropathy.

MATERIALS AND METHODS

Source of Data

The study is a prospective observational study conducted out at R.I.M.S, Imphal, Manipur for a period of Eight months from march 2016 to October 2016 in patients attending the Hospital. The study population comprised of 100 diabetic patients out of which 50 patients had nephropathy and 50 were without nephropathy.

INCLUSION CRITERIA

Patients diagnosed as type 2 diabetes based on ADA criteria for more than 5 years were included in the study.

EXCLUSION CRITERIA

Patients with diabetes less than 5 years duration, those with chronic liver disease, hypothyroidism, ESRD(non diabetic), pregnant women, gout and patients taking alcohol and drugs affecting Lp(a) levels like niacin, neomycin, oestrogen, hormone replacement therapy, corticosteroids were excluded in this study.

In the present study both the cases and controls were randomly selected. Then two groups were matched with respect to age and sex. No specific age group was selected.

METHODS

All biochemical assays were carried out with Automated Random access clinical chemistry analyzer ERBA XL-600 with ERBA TEST REAGENT. The lipid profile, urea, creatinine, liver function tests were measured. Fasting blood sugar was measured on fasting blood sample i.e. after 8-10hrs of overnight fast. Postprandial blood glucose was measured 2-hr after an oral load of 75g glucose, as recommended by WHO for glucose tolerance test.

The separated lipoproteins are stained with a lipid specific Sudan black stain. The excess of stain is removed with an alcoholic solution.

The resulting electrophoregrams were evaluated visually for pattern abnormalities or by densitometry to obtain relative quantification of individual zones.

Electrophoresis on HYDRAGEL 7 LIPO ± Lp (a) and HYDRAGEL LIPO ± Lp (a) 15/30 gel presents a particular advantage: it permits simultaneous determination of the lipoprotein profile and the fast pre-beta or Lp (a) fraction.

RESULTS AND ANALYSIS

In the present study it is found that shorter the duration of type-2diabetes lesser is the chance of developing nephropathy. As the duration of type-2 diabetes increased development of nephropathy increased. Incidence of Diabetic nephropathy significantly more in patients with duration >10 years of DM with P=0.000. majority of patients with diabetic nephropathy are with duration of DM type 2 of 11- 15 yrs.

In the present study all the lipid parameters were abnormally elevated and the values were statistically significant in the nephropathy group as compared to controls except HDL values which were decreased in both the groups but more in the diabetic nephropathy subjects. It was not statistically significant (p-0.111).

In the present study Triglycerides were elevated in both the groups but even more so in the nephropathy group. Also Total-Cholesterol and LDL-C were increased in the nephropathy group. It was not statistically significant (p-0.111).

In Diabetic nephropathy patients, Mean value of Lp (a) was 11.4 mg/dl as compared to non-nephropathy patients where Mean value of Lp (a) was 5.773mg/dl Inference-Lipoprotein (a) is significantly elevated in patients with Diabetic Nephropathy with P<0.000.

Inference- DM Poor control was the lone significant predictor of Elevated L(a) followed by Duration of Diabetic >10 years. Inference- DM Poor control was the lone significant predictor of Elevated L(a) followed by Duration of Diabetic >10 years.

In the present study, poor control and duration of diabetes, more than 10 years, are significantly associated with abnormal elevation of Lp (a) levels.

TABLE 1: ASSOCIATION OF DURATION OF DM WITH DIABETIC NEPHROPATHY

Duration of DM	Diabetic Nephropathy		Total (N=100)	p - value
	Absent (N=50)	Present (N=50)		
5 - 10 Years	34 (68.0%)	13 (26.0%)	47 (47.0%)	0.000**
11 - 15 Years	14 (28.0%)	31 (62.0%)	45 (45.0%)	
16 - 20 Years	2 (4.0%)	6 (12.0%)	8 (8.0%)	

** Significant at 0.01 level.

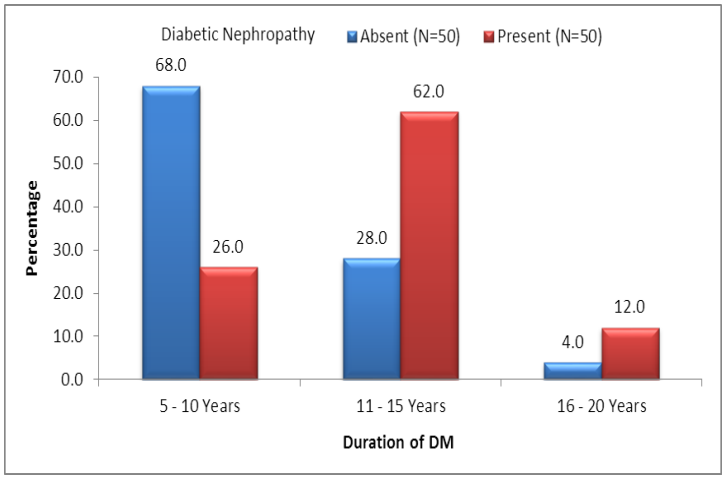

FIGURE 1: ASSOCIATION OF DURATION OF DM WITH DIABETIC NEPHROPATHY

TABLE 2: ASSOCIATION OF LIPID PARAMETERS WITH DIABETIC NEPHROPATHY

Lipid Parameters	Diabetic Nephropathy		Total (N=100)	p - value
	Absent (N=50)	Present (N=50)		
TC (> 200 mg/dl)	0 (0.0%)	36 (72.0%)	36 (36.0%)	0.000**
LDL (> 130 mg/dl)	25 (50.0%)	43 (86.0%)	68 (68.0%)	6.143 (0.000)**
HDL (< 35 mg/dl)	33 (66.0%)	26 (52.0%)	59 (59.0%)	1.904 (0.120) NS
TGL (> 150 mg/dl)	38 (76.0%)	50 (100.0%)	88 (88.0%)	0.000**
Lipoprotein (> 10 mg/dl)	0 (0.0%)	47 (94.0%)	47 (47.0%)	0.000**

** Significant at 0.01 level
NS ➔ Not Significant(4)

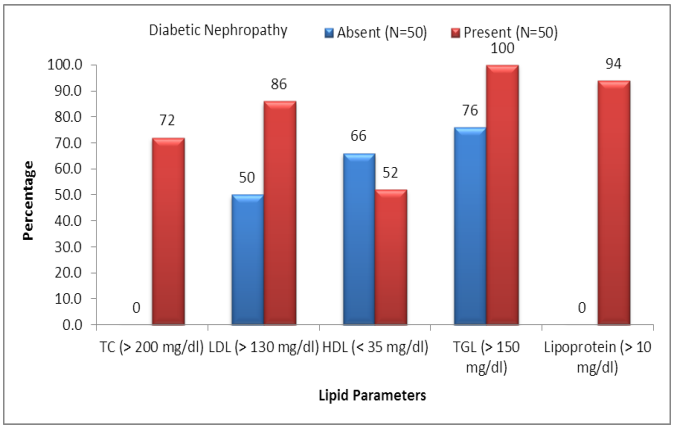

FIGURE 2: ASSOCIATION OF LIPOPROTEINWITH DIABETIC NEPHROPATHY

TABLE2B: COMPARISON OF LIPID PARAMETERS

Lipid Parameters	Diabetic Nephropathy		Total (N=100)	p - value
	Absent (N=50)	Present (N=50)		
Total Cholesterol	170 ± 11.0	205 ± 20.8	187 ± 24.1	0.000**
LDL Cholesterol	127 ± 8.09	148 ± 15.4	137 ± 16.1	0.000**
HDL Cholesterol	33.8 ± 2.77	34.8 ± 2.93	34.3 ± 2.88	0.111 NS
Triglycerides	178 ± 31.7	255 ± 30.7	216 ± 49.7	0.000**
Lipoprotein	5.77 ± 0.72	11.4 ± 0.79	8.40 ± 2.75	0.000**

** Significant at 0.01 level.
NS ➔ Not Significant.

TABLE 2C: ASSOCIATION OF LIPOPROTEIN WITH DIABETIC NEPHROPATHY

Lipoprotein	Diabetic Nephropathy		Total (N=100)	p - value
	Absent (N=50)	Present (N=50)		
< 10 mg/dl	50 (100.0%)	3 (6.0%)	53 (53.0%)	0.000
> 10 mg/dl	0 (0.0%)	47 (94.0%)	47 (47.0%)	

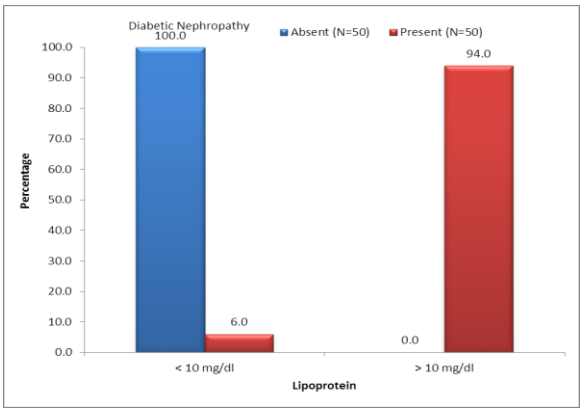

FIGURE 2b: ASSOCIATION OF LIPOPROTEIN WITH DIABETIC NEPHROPATHY

DISCUSSION

Type-2 diabetes mellitus is a metabolic disorder affecting carbohydrate, fat and protein metabolism. An estimated 50% of all diabetic patients, either type 1 or type 2 are dyslipidemic.[5] Dyslipdemia is observed in patients with diabetic nephropathy significantly when compared to those without nephropathy and in those who has long term diabetes more than 10 yrs and in whom the glycemic control was poor.[6] In diabetic nephropathy, hyperlipidemia has been identified as a risk factor for a more rapid decline in GFR and increased mortality.[7]

Type 2 diabetes with nephropathy is associated with several lipid abnormalities including hypertriglyceridemia, reduced HDL level, an increased proportion of small, dense LDL particles and elevated Lp(a).[6]

Lp(a) has been identified an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with proteinuria. Lp(a) levels were increased in diabetic nephropathy compared to diabetes without nephropathy.[9] Levels greater than 30mg/dl are associated with two fold greater risk for coronary artery disease.[10]

Many risk factors like the duration of diabetes, degree of glycemic control and age of the patient and are identified in the causation of the diabetic microvascular complications. Abnormal plasma lipoprotein profiles contribute to the increased risk in CAD and diabetic nephropathy. The risk of death from coronary heart disease is also substantially increased in diabetic nephropathy compared with normal subjects or diabetes without nephropathy.[12,13, 18 ,21]

In diabetic nephropathy, hyperlipidemia has been identified as a risk factor for a more rapid rate of decline in GFR and increased mortality.[12,13] Lipid abnormalities in diabetes can be due to intrinsic abnormality of the disease process, induced by complications of diabetes like nephropathy or genetically determined.[13]

Kare Berg detected Lp(a) in 1963 in Norway.[15, 16] .Lp (a) is assembled from two different components. One is an LDL and contains all the lipid with hydrophobic apo B-100; other is a hydrophilic glycoprotein apo (a). Both LDL and apo (a) are believed to be linked by a single disulphide bond.[13]

A breakthrough in Lp (a) research was the cloning and sequencing of Apo (a) by Mc Lean et al, which revealed a high degree of homology of Apo (a) with plasminogen and that their genes are adjacent on chromosome 6.[15,16,14]

Plasminogen is a plasma serine protease of the fibrinolytic system. Although the normal function of Lp (a) is unknown, the close homology between Lp (a) and plasminogen has raised the possibility that this lipoprotein may inhibit endogenous fibrinolysis by competing with plasminogen for binding on the endothelial surface.[14, 16, 18]

Apo (a) may also induce monocyte chemotactic activity in the vascular endothelium.[15,18] This mechanism may contribute to a role of Lp (a) in atherothrombosis which may have a significant role in the development of diabetic nephropathy. In addition to vascular injury, Lp(a) might be implicated in glomerular injury. Lp(a) and oxidized Lp(a) have been shown to induce activation of reactive oxygen metabolites in isolated rat glomeruli.[21]

Patients with nephropathy are found to have significantly higher Lp(a) levels than those without nephropathy. Also, the serum Lp(a) concentrations increases significantly with increased urinary albumin excretion.[19,20]

CONCLUSION

Hence, we conclude that:

Serum Dyslipidemia is much more common in type-2 diabetes with nephropathy compared to those without nephropathy.

Serum Dyslipidemia (hypertriglyceridemia) is one important risk factor for the coronary heart disease and Increased Lp (a) and Triglycerides may be the reason for increased prevalence of coronary heart disease in nephropathy patients.

Poor control of DM is the lone significant predictor of elevated Lipoprotein (a) followed by duration of Diabetic >10 years.

Lp (a) values are significantly elevated in Diabetic Nephropathy.

Thus it is essential to include Lp(a) in a battery of tests for evaluation of macro and microvascular complications in type 2 diabetes.

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