Section: Medicine

Original Research Article

A STUDY OF SERUM LIPOPROTEIN (A) LEVEL IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS

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Abstract

Background: Diabetic micro vascular complications have become a major cause of chronic kidney disease, blindness and diabetic foot problems, which are preventable to some extent. 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. The aim is to estimate the serum Lipoprotein (a) levels in type 2 diabetes mellitus patients and to determine if there is any relationship between serum Lp(a) levels and diabetic micro vascular complications. **Materials and Methods:** It is a prospective observational study conducted on 204 patients above the age of 18 years having Type 2 Diabetes mellitus both new and old over a period of two year. **Result:** The mean age was 54.1 ± 8.2 years with 60.3 % females enrolled in the study. The mean duration of DM is 12.3 ± 2.9 years, with mean lipoprotein a, 31.2 ± 12.1 mg/dl. Majority female patients had significantly higher polyuria followed by polyphagia (P< 0.05). They also had significantly higher lipoprotein levels 26.7 ± 10.4 in 18-35 years age group and also in > 60 years age group 46.6 ± 17.2 (P< 0.05). Serum Lp(a) levels showed a significant difference in patients with diabetic retinopathy with a p value 0.022. Various clinical parameters like serum creatinine, HbA1C, diabetic retinopathy and nephropathy showed significant positive correlation with serum lipoprotein levels. **Conclusion:** Abnormal Lp(a) levels were found among the diabetic subjects between the genders. Female patients with diabetic retinopathy had higher Lp(a) levels. An association was found between Lp(a) levels and diabetic retinopathy and nephropathy but not with neuropathy. Longer duration of diabetes and higher Hba1c levels are correlated with higher Lp(a) levels.

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 glycaemic control and age of the patient, are identified in causation of diabetic micro vascular complications. Diabetes mellitus is one of the most seen metabolic disorders which is characterized by hyperglycemia either due to insulin deficiency or insulin resistance.[1]

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein-like particle containing Apo- lipoprotein B 100 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.[2-4] It is associated with microvascular complications like diabetic nephropathy, Diabetic retinopathy, Diabetic neuropathy and macro-vascular complications like coronary artery disease, peripheral vascular disease etc. Because of these complications it is associated with increased morbidity as well as increased mortality. It causes economic burden to the family as well as to society.[1]

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Among all the Dyslipidemias associated with type 2 DM, elevated levels of serum lipoprotein(a) is of much importance because it is an important risk factor for atheromatous complications in diabetes than to non-diabetes.[4] Recently, much interest has been focused on Lp(a) which is a plasma complex composed of apolipoprotein(a) and Apo B -100. Because of structural similarities of Apo(a) to plasminogen, Lp(a) has been suggested to have antifibrinolytic properties.[5]

The characteristic pattern of lipoproteins in type 2 diabetes mellitus includes an increase in Triglycerides, predominance of small dense LDL particles and decrease in HDL cholesterol.[1,3] In type 2 diabetes mellitus, insulin resistance reflects the failure of hyperinsulinemia to suppress the gluconeogenesis, which causes fasting hyperglycemia.[1] Lipoprotein (a) is a risk factor for the progression of diabetic nephropathy with overt proteinuria, arterial stiffness in elderly patient and peripheral arterial disease in type 2 DM patients.[2] Studies have conclusions that lipoprotein (a) is an independent risk factor for coronary artery disease and is a reliable predictor of coronary artery disease severity in type 2 diabetes mellitus patients.[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,[5] and some studies even showed an inverse relationship between Lp(a) levels and incident type 2 diabetes. [6,7] However, some Asian studies showed a strong association between type 2 diabetes and elevated Lp(a) levels.[8,9] Similarly, there are conflicting reports on the evidence of association between Lp(a) levels and diabetic micro vascular complications like nephropathy, retinopathy and neuropathy. Therefore, the present study has been undertaken to assess the serum Lp(a) and the onset and progression of microvascular complications. In a study, Lp(a) levels were lower in subjects with hyperinsulinemia,[10] but in other studies,[11] no significant relation of Lp(a) to insulin was found. There is insufficient data from the Indian subcontinent on Lp(a) levels and its role in micro vascular complications among patients with type 2 DM.

Rationale: We aimed to evaluate the levels of serum lipoprotein a in South East Indian patients with type 2 DM and assess its correlation with diabetic microvascular complications like diabetic nephropathy, Diabetic retinopathy, peripheral neuropathy; and to examine its relation to glycaemic control, metabolic syndrome (MS) and duration of DM.

MATERIALS AND METHODS

This is a prospective study carried in the Dept. of General medicine, MKCG Medical College and Hospital during the period of November 2020 to October 2022.

Sample Size: The sample size N was calculated using the formula $N=Z^2\times P\times(1-P)/d^2$ Where, Z=1.96 (standard deviation at 95% confidence interval); P= Expected percentage from population; d=0.05(Expected margin of error) and is around 150.

Inclusion Criteria

All patients of Type 2 Diabetes mellitus both new and old.

Exclusion Criteria

Patients with Type 1 Diabetes mellitus, age <18-year, chronic liver disease, End stage renal disease, pregnant women, chronic alcoholics, chronic inflammatory conditions, Hepatitis, Hypothyroidism/Hyperthyroidism

Study Population: The diagnosed cases of type 2 DM (ADA guidelines 2015) who will come to OPD or Inpatients in Department of Medicine in accordance with inclusion and exclusion criteria.

Data Collection and Intervention: All patients fulfilling the inclusion criteria were included in the study after taking written informed consent. The data was collected according to a pretested proforma in terms of detailed medical history, clinical examination and the necessary investigations. The patients were subjected to complete clinical examinations like clinical tests for assessment of Neuropathy by Semmes Weinstein monofilament test, ankle reflex, vibration perception by 128Hz tuning fork test. Ocular fundi examination was done for assessment of Retinopathy. Spot urine Albumin Creatinine ratio was measured for Nephropathy. Measurement of serum lipoprotein a level was done and intimated by Randox immunoturbido- metric immunoassay method.

Statistical Analysis: The continuous data were expressed as mean ± SD and the categorical data expressed as proportions. The difference between the groups for continuous data was analyzed by t-test or Mann-Whitney U test based on the normality of the data. Normality was assessed by Shapiro-Wilk test. The difference in the categorical data between the two groups was analyzed by Fisher's exact test. The continuous score was analyzed by repeated measures ANOVA for within the group analysis and generalized mixed effect modeling for between the group analysis. Both per-protocol and intention to treat analysis was done. The missing values were treated by multiple imputation techniques. $P < 0.05$ was considered significant. The data was analyzed using SPSS 24 version program. Laboratory parameters were obtained. Data was analysed by descriptive Statistics; Pearson coefficient of correlation is used to identify relationship between Quantitative variables.

Ethical Issues: Approval of the study was taken from the Institutional Ethics Committee of MKCG Medical College, Berhampur. Before enrolment of study subjects, registration for clinical trial was done in CTRI.

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RESULTS

The mean age of the study population was 54.1 ± 8.2 years. Out of which 123 are females and 81 are males. The mean Lipoprotein A was 31.2 mg/dl. The mean FBS was found to be 195.1 ± 64.1, the mean PPBS, 265.2 ± 76.1and mean HbA1c was 9.2 ± 1.8. Majority of the patients had polyuria (89.7%) followed by retinopathy 142 (69.6%) and paresthesia of extremity in 138 (67.4 %). Polyuria was very common in females followed by retinopathy and paresthesia of extremity.

The evaluation of Lipid parameters showed the mean HDL to be 30.2 ± 7.2, LDL to be 145.6 ± 47.89 and VLDL, 59.6 ± 67.89. The triglycerides are 247.5 ± 88.89 and total cholesterol was 225.3 ± 44.31. In the study population the renal parameters were evaluated the mean serum creatinine was 1.4 ± .28 with Effective Creatinine clearance 52.3 ± 20.8 and the Urine Albumin Creatinine Ratio, 82.1 ± 43.2. The Lipoprotein levels were high in >60 years age group in both the genders (0.001) followed by 35-60 years (P= 0.458).

The serum lipoprotein levels were evaluated in patients with microvascular complications like diabetic retinopathy and diabetic nephropathy and on evaluation it showed significantly higher values in patients with complications than without these complications. Diabetic neuropathy did not show significant increase in lipoprotein levels. The Lipoprotein levels were evaluated in various HbA1c subgroups and found significantly high in >9.1 % groups in both the genders followed by 8.1-9% [Table 7]. Serum lipoprotein levels were evaluated based on the albumin creatinine ratio and significantly higher values were seen in macro albuminuria (>300) 43.6 ± 31.2. Clinical parameters like serum creatinine, HbA1C and diabetic retinopathy showed significant positive correlation with serum lipoprotein levels. The correlation was evaluated using Pearson's correlation test [Table 9].

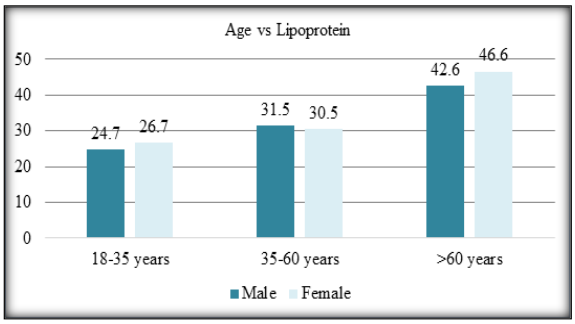

Figure 1: Age in relation to Lipoprotein level

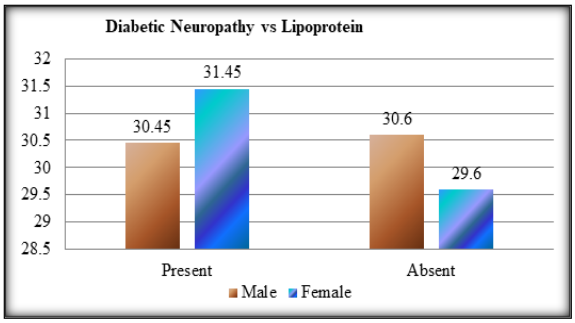

Figure 2: Diabetic Neuropathy in relation to Lipoprotein level

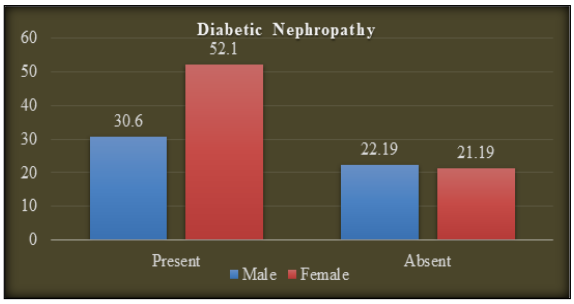

Figure 3: Diabetic Nephropathy in relation to Lipoprotein level

Table 1: Demographic Characteristics Study Participants N=204

Demographic Characteristics		Study Participants N=204
Mean Age (Years)		54.1 ± 8.2
Sex	Female	123 (60.3 %)
	Male	81 (39.7 %)
Mean BMI (kg/m2)		31.2 ± 3.9
HbA1c (%)		9.2 ± 1.8
Mean Duration of DM (years)		12.3 ± 2.9
Mean Lipoprotein A (mg/dl)		31.2 ± 12.1

Table 2: Clinical Symptoms associated with Diabetes

Clinical Symptoms	Male (N=81)		Female (N=123)		Total
Polyuria	63	77.78	120	97.56	183 (89.7 %)
Polyphagia	20	24.69	31	25.20	51 (25 %)
Paraesthesia of extremity	18	22.22	120	97.56	138 (67.4 %)
Retinopathy	13	16.05	129	104.88	142 (69.6%)

Table 3: Lipid Parameters

Lipid Parameters	Male	Female	Study participants (N=204)
HDLc (mg/dl)	29.2 ± 8.2	33.2 ± 7.8	30.2 ± 7.2
LDLc (mg/dl)	125.6 ± 17.89	165.6 ± 27.89	145.6 ± 47.89
VLDLc (mg/dl)	63.6 ± 77.09	67.6 ± 55.89	59.6 ± 67.89
TG (mg/dl)	207.5 ± 58.39	257.5 ± 76.69	247.5 ± 88.89

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Total cholesterol	205.3 ± 34.31	255.3 ± 34.31	225.3 ± 44.31

Table 4: Renal Parameters

Renal Parameters	Male	Female	Study participants (N=204)
Serum Creatinine (mg/dl)	1.7 ± .28	1.9 ± .18	1.4 ± .28
Effective Creatinine clearance (ml/min)	51.3 ± 12.8	55.3 ± 23.8	52.3 ± 20.8
Urine Albumin Creatinine Ratio	87.1 ± 33.21	84.1 ± 44.2	± 43.2

Table 5: Comparison of serum Lipoprotein levels between the age groups

Age group	Male	Female	P value@
18-35 years	24.7 ± 11.4	26.7 ± 10.4	0.028
35-60 years	31.5 ± 14.2	30.5 ± 17.2	0.458
>60 years	42.6 ± 21.2	46.6 ± 17.2	0.001

Table 6: Comparison of serum Lipoprotein levels between microvascular complications

Microvascular complications	Cases	Serum Lipoprotein Mean ± SD		P value@
Diabetic Retinopathy				
	N	**Male**	**Female**	
Present	142	33.60 ± 17.27	43.60 ± 15.03	0.022
Absent	62	23.19 ± 9.80	21.19 ± 7.12	0.054
Diabetic Nephropathy				
	N	**Male**	**Female**	
Present	137	30.60 ± 12.43	52.10 ± 21.03	0.001
Absent	67	22.19 ± 2.50	21.19 ± 7.12	0.674
Diabetic Neuropathy				
	N	**Male**	**Female**	
Present	138	30.45 ± 12.38	31.45 ± 12.11	0.054
Absent	66	30.6 ± 20.05	29.6 ± 15.05	0.076

Table 7: Comparison of serum Lipoprotein levels with HbA1c

HbA1c	N		Lp (a)	P value@
< 6	22	10.7 %	23.19 ± 9.80	0.001
6.1-7	45	22.1%	30.23 ± 7.11	
7.1-8	67	32.8 %	32.45 ± 8.38	
8.1-9	42	20.6 %	37.12 ± 5.03	
>9	28	%	43.60 ± 15.03	

@ One Way ANOVA

Table 8: Comparison of serum Lipoprotein levels with albumin creatinine ratios

Microvascular complications	Cases	Mean ± SD		P value@
	N=204	**Male**	**Female**	
Normal (< 30)	77 (37.7%)	26.7 ± 10.4	28.7 ± 12.5	0.034
Micro (31-299)	112 (54.9%)	32.5 ± 16.2	34.5 ± 10.2	0.043
Macro albuminuria (≥300)	15 (7.3%)	43.6 ± 31.2	45.6 ± 21.2	0.023

@ One Way ANOVA

Table 9: Correlation of serum Lipoprotein levels with various clinical parameter

Clinical Parameters	Correlation Coefficient	P value@
S-Creatinine (mg/dl)	.343*	0.03
HbA1c (%)	.326*	0.04
Retinopathy	.343*	0.03
Nephropathy	.440*	0.022
Duration of Diabetes	.409*	0.009
Age	.386*	0.014

*p value < 0.05, @ Pearson's Correlations statistics

DISCUSSION

In recent years, there has been an alarming rise in the rate of mortality and morbidity due to concomitant dyslipidaemia, atherosclerosis, and coronary artery disease in India, as well as a burgeoning epidemic of diabetes mellitus. In some cases, preventable diabetic foot issues, chronic renal disease, and blindness are now mostly due to diabetic micro vascular complications. In our study the mean age of the study population was found to be 54 years. It has been found that T2DM presenting at a young age is of aggressive nature by the landmark Search for Diabetes in Youth study. In studies by Chandni et al. as well a similar prevalence of T2DM was seen in age group as mentioned in our study.[12] Our study showed the majority of the patients were females. Women show more dramatic changes in hormones and body due to reproductive factors during lifetime. Gender differences arise from sociocultural processes, such as different behaviours of women and

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men, exposition to specific influences of the environment, different forms of nutrition, life styles or stress, or attitudes towards treatments and prevention.[13] An increase in body fat is generally associated with an increase in risk of metabolic diseases such as type 2 diabetes mellitus, hypertension and dyslipidaemia. Body mass index (BMI) criteria are currently the primary focus in obesity treatment recommendations, with different treatment cut-off points based upon the presence or absence of obesity-related comorbid disease. We found the mean BMI was found to be 31kg/m2 which included patients with pre and obesity criteria. Studies by Bayes et al. and Mayers et al. have shown extensive correlation between increased BMI and diabetes. [14,15]

In our study the mean HBA1C levels were around 9 with a mean duration being 12 years suggestive of long duration of diabetes and will be associated with various micro vascular complications. Diabetes and related complications are associated with long-term damage and failure of various organ systems. Hyperglycaemia is the principal cause of micro vasculopathy but also appears to play an important role in causation of macro vasculopathy.[16]

Clinical Symptoms: Due to the chronic nature of the condition, many people ignore the signs and symptoms of diabetes. Because the effects of hyperglycaemia take time to appear, unlike many other diseases, many do not view this as a severe issue. In our study majority of the female patients had polyuria followed by paraesthesia and retinopathy associated signs and symptoms. Studies by Ramachandran et al. showed results consistent with our study.[17]

Blood parameters: Dyslipidaemia is commonly associated with diabetes. This has been demonstrated for the Caucasian population, but few data are available for Asian Indians. In our study the various lipid parameters were significantly deranged with high LDL, triglyceride levels and total cholesterol levels along with low mean LDL levels which is consistent with a meta-analysis done on similar lines in TYPE 2 DM patients.[18] Diabetic nephropathy is the kidney disease that occurs as a result of diabetes. Cardiovascular and renal complications share common risk factors such as blood pressure, blood lipids, and glycaemic control. James Sowers et al reviewed aspects of the association of diabetes with renal disease, emphasizing that CKD and albuminuria are associated with increased rates of cardiovascular disease (CVD) and mortality. In our present study the majority of the patients had micro as well as macroalbuminuria with a moderately high serum creatinine level and a moderately high eGFR as well with a higher mean value seen in females as compared to males. Our study was consistent with studies by James et al. which showed diabetes associated nephropathy in many patients.[19]

Dyslipidaemia and lipoprotein (a): In our study there was significantly higher lipoprotein (a) levels in elderly population as compared to the younger generation with a higher value in females as compared to males. Studies by Akita et al. has shown Lipoprotein(a) as a risk factor for atherosclerosis and increases with age.[20] Association with various microvascular complications showed a significantly higher value of Lp(a) in females as compared to males but neuropathies did not show a significant increase in lipoprotein levels. Studies by Tseng et al,[21] showed consistently high values for diabetic patients but did not show any association in contrast to our study which a showed a significant association in case of retinopathy. 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 Tseng et al.

Lipoprotein (a) with diabetic retinopathy: In developed countries, diabetic retinopathy (DR) is the leading cause of vision loss in adults of working age. The prevalence rates of DR ranged from 7% to 12%. Lp(a) plasma concentrations are highly heritable and mainly controlled by the apo(a) gene located on chromosome 6q. Study by Malaguarnera et al has showed a significant association with high lipoprotein a level with diabetic retinopathy which is consistent with our study where in patients with DR have shown an increase Lp(a) levels.[22]

Lipoprotein (a) with diabetic nephropathy: In our study there was a significantly higher Lipoprotein (a) levels in patients with nephropathy as compared to those without nephropathy. This is similar to various previous studies study on 76 insulin dependent diabetic patients, Kapelrud et al. found that serum concentration of Lp(a) lipoprotein are twice as high in insulin dependent diabetic patients with microalbuminuria as in those without microalbuminuria. It seems that serum Lp(a) can be considered as a promising predictive factor for the diagnosis of earlier nephropathy.[24]

Lipoprotein (a) with diabetic neuropathy: Microvascular disease in type 2 diabetes is a significant cause of end-stage renal disease, blindness and peripheral neuropathy. In a study on by Lakotia et al. Lp (a) levels in type 2 DM subjects in relation to diabetic microvascular complications on 200 patients the mean Lp (a) in patients with neuropathy and without neuropathy were similar (28.9 mg/dL) vs 29.3 mg/ dL ($p>0.92$). In our study although there has been an increase in Lipoprotein (a), but it is not significantly higher as compared to patients without peripheral neuropathy.[25] There are conflicting reports and further studies are needed in this aspect.

Comparison of serum Lipoprotein levels with HbA1c: Lipoprotein (a) levels are elevated in poorly controlled diabetic patients which may be a contributing factor to the high risk for atherosclerosis observed in diabetic patients. In our present study there was significant correlation HbA1C level with Lipoprotein (a). Similar findings were observed when mean Lp (a) levels were compared with HbA1c,

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statistically significant trend was observed, where the HbA1c levels increased, mean Lp(a) levels also increased linearly. In a study on Lipoprotein(a) concentration in non-insulin-dependent diabetes mellitus and borderline hyperglycaemia there was no correlation between Lp (a) levels and FPG (p=.030) and they concluded that Lp (a) levels are similar in individuals with NIDDM, borderline hyperglycaemia and normoglycemia. [26]

CONCLUSION

The correlation association of various clinical parameters showed a significant association with serum creatinine, HbA1c, retinopathy and also age and duration of diabetes. In conclusion, lipoprotein levels were significantly higher females as compared to males with significant association was seen in diabetic retinopathy and with nephropathy but not with neuropathy. There was higher serum lipoprotein a level in patients with macro albuminuria as compared to micro albuminuria. A longer duration of diabetes had a positive correlation with higher Lp(a) levels also a high HbA1c and higher age.

This is the first study in east India to evaluate the association between the lipoprotein a level and its association in diabetic patients. The small number of subjects selected for evaluation of a common clinical problem like type 2 DM 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 retinopathy were especially noteworthy. Further studies are needed in similar line to generalise the study data.

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