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Smita Tripathi

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DYSLIPIDEMIA OF T2DM DOES NOT INCLUDE LP (A) – A CROSS SECTIONAL STUDY IN NORTH INDIAN POPULATION

Smita Tripathi

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ABSTRACT

Background and objectives: Lp (a) concentrations shows considerable variation in healthy individuals and is one of the strongest genetically determined risk factor for development of cardio-vascular disease. People with T2DM have 2-4 fold increase in the risk of developing cardiovascular disease. The possibility that T2DM could influence Lp (a) concentrations has been investigated in past, but the results have been controversial and inconclusive. The purpose of the present study was to measure Lp (a) levels in patients with T2DM and to see that whether there is any correlation with glycemic control and lipid profile in North Indian population. ***Method***: A cross sectional study was conducted on 41 patients with T2DM and 41 age and sex matched healthy controls. Samples were drawn to analyze Lipids, Lp (a)and HbA1c. The data obtained was statistically analyzed using SPSS version 20. Mean and SD for all parameters were calculated between patients and controls using unpaired t test. Correlation between Lp (a) levels and HbA1c and lipids was tested using nonparametric Spearman's correlation formula. P value (2 sided) of <0.05 was considered significant. ***Result***: No significant difference was observed in the level of Lp (a) in patients of T2DM (29.26+21.70 mg/dl) and normal controls (26.80+16.89 mg/dl): p value 0.56, although both mean and confidence interval was higher in diabetic group. The values of HbA1c, serum cholesterol and serum triglycerides were significantly higher in Diabetic group (p value <0.05). Analysis of data using the spearman's correlation coefficient, showed no correlation in value of Lp (a) with HbA1c, cholesterol and triglycerides levels in the study population. ***Conclusion and interpretation***: Lp (a) values do not show any significant association with T2DM and glycemic control in North Indian population of the present study.

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. In India alone the number of diabetics is expected to rapidly increase from 40.6 million in 2006 to 79.4 million by 2030 [1].The risk of cardiovascular disease is increased in T2DM when compared with the non-diabetic subjects [2-4].The role of diabetes as an independent risk factor for cardiovascular disease is well established [5-6] although the excess risk is only partially explained by standard risk factors in these subjects [7].

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), and is considered a pro-atherogenic, pro-thrombotic risk factor for coronary heart disease [8-12]. It is hypothesized that apo(a) which has a striking homology to plasminogen is the cause of increased risk in patients[13]. A clear correlation was found between the serum level of Lp(a) and its accumulation in the vessel wall[11-12]. The level of Lp(a) is genetically determined, and when elevated, cannot be lowered by alterations in food intake or by most of the cholesterol lowering agents [14]. Many prospective epidemiological studies have reported positive associations of baseline Lp(a) concentration with CHD risk[15-16].

Though of high theoretical and practical interest, many aspects of metabolism, function, evolution and regulation of plasma concentrations of Lp(a) are unknown, controversial or enigmatic. There are conflicting reports on the relationship between Lp(a) levels and diabetes. Some studies claim no relation of Lp(a) with metabolic control in diabetics[17-18] while others claim the opposite [19-21]. Some Asian studies showed a strong association between T2DM and elevated Lp(a) levels[22-23] while others don't agree [24-26].The study on relationship between Lp(a) and diabetes needs more evaluation and the data on Lp(a) in Asian Indian diabetics is still meager.

*Corresponding author: ***Smita Tripathi***

MATERIAL AND METHOD

A cross sectional study was performed that enrolled 41 adult patients with T2DM attending medicine OPD at tertiary care hospital, New Delhi. It is a non- randomized study as all the patients coming to medicine OPD within the two months of study period were included. Cases of Type 1 Diabetes and admitted cases of T2DM having coexisting morbidities were excluded from the study group. 41 age and sex matched non diabetic controls from the hospital were also enrolled. Consent was obtained from the patients for enrolling in the study and ethical clearance was obtained from the institutional ethical committee. Samples were drawn from the study population in plain and EDTA vial. Plain vial sample was used to analyze Serum Cholesterol, Serum Triglycerides and Lp (a) and EDTA vial sample was used for estimating HbA1c in the patient. All the analysis was done on Auto-analyzer; AU480- Beckmann Coulter chemistry analyzer.

Serum Cholesterol was measured using enzymatic end point method (combining both esterase and oxidase activities for total cholesterol estimation). The system reagent is only for determination on Beckman Coulter AU analyzers .The method has a coefficient of variation less than 3% and has been certified to meet NCEP performance criteria for accuracy. The method is linear from 25 to 700mg/dl [27, 28].

Serum Triglycerides were measured by method using series of coupled enzymatic reaction. The system reagent is only for determination on Beckman Coulter AU analyzers. The method is linear from 10 to 1000mg/dl and has coefficient of variation less than 5% [29].

HbA1c was analyzed using latex agglutination inhibition assay (Randox kit, U.K).The method has coefficient of variation less than 5% and range from0.25 to 2.4gm/dl. It had a correlation coefficient of 0.998 when compared with other commercially available methods.

Lp(a) was analysed using latex enhanced immune-turbidimetric method (Diazymekit, USA). It had cv less than 2.6% and linear from 0.544 to 100mg/dl. It had a correlation coefficient of 0.98 with other available methods.

All the parameters except Lp(a) were analyzed immediately as a part of routine analysis. Sample for Lp(a) estimation were preserved at -20 °C and batch analysis was performed after adequate numbers were collected. The data obtained was statistically analyzed using SPSS (statistical package for social sciences) version 20. Mean and SD for all parameters were calculated between patients and controls using unpaired t test (Data was continuous and unpaired). Correlation between Lp(a) levels and HbA1c and lipids was tested using nonparametric Spearman's correlation formula. P value (2 sided) of <0.05 was considered significant.

RESULTS AND DISCUSSION

In present study, 41 T2DM patients (22 M; 19 F) and 41 non diabetic control subjects (20M; 21F) visiting the hospital OPD were included. Duration of T2DM ranged from 1 year to 25 years in the cases group.

Serum Lp (a) levels of T2DM patients was higher than the control group [(29.26±21.70 mg/dl) vs. (26.80±16.89 mg/dl),p=0.56]respectively, although the increase was not significant in our study.The Serum Cholesterol of T2DM patients was significantly higher than the control group [(240.41±60.24mg/dl vs. 204.70±62.49mg/dl), p=0.01], respectively. The serum Triglyceride level of diabetics was significantly higher than that of control [(217.78±102.73mg/dl vs. 153.90±72.23mg/dl)p=0.00] respectively. Also HbA1c levels were significantly higher in cases of T2DM [(8.56±1.82%) vs. (5.34±0.64%) p=0.00]. (Table 1)

However, analysis of data using the spearman's correlation coefficient, showed no correlation in value of Lp (a) with HbA1c, Cholesterol and Triglycerides levels in the study population i.e. both cases and control.(Table 2)

An increased levels of Lp(a)>30 mg/dl has been accepted as an isolated risk factors for CAD and myocardial infarction (MI). In our study the level of Lp (a) more than 30mg/dl in cases and controls was 13 and 10 respectively.

If we try to understand the findings of other similar studies: A study done on 50 diabetic patients, with 30 controls in India showed that mean serum Lp(a) level in diabetes mellitus patients was 44.2±35.8 mg/dl, which was significantly higher when compared to controls (mean 21.1±11.2 mg/dl, $p < 0.05$).Their patients were admitted in hospital either due to Diabetes or its complications. Also 50 diabetic patients (cases) included both Type 1 and Type 2. In this study 30 Diabetics had Lp(a) more than 30 mg/dl[30].

In a Turkish study, 709 T2DM patients (407 F; 302 M) and 157 healthy control subjects (91F; 66M) living in the same geographic region were included. Serum Lp(a) levels of diabetic patients were not significantly different from the control group [(33.3 ± 46.4 mg/dl) vs. (35.9 ± 46.7 mg/dl) p=0.519] respectively. The total cholesterol of 709 diabetic patients was significantly higher than that of control group (202.2 ± 41.5mg/dl vs. 189.0 ± 30.5 mg/dl, p<0.001), respectively. The serum triglyceride level of diabetics was found to be significantly higher than that of control (196.9 ± 121.9 mg/dl vs. 123.7 ± 76.1 mg/dl, p<0.001). As in the present study dyslipidemia and metabolic syndrome was found to be higher in diabetic patients with respect to healthy controls, however, serum Lp(a) levels were not significantly different in both groups[31].

A study done on 144 T2DM patients in Kerala, having a mean duration of diabetes as 9.53±7.3 years showed only 26% of patients had Lp(a)levels above 30mg/dl (which they are considering as cut off). They also found no correlation between Lp(a) levels and glycemic control. But they found correlation between duration of diabetes and Lp(a) levels[32].

A study done on OPD patients at Parkland coming for treatment of T2DM shows no significant increase of Lp(a) compared to the control population[23]. However patients with poor glycemic control (HbA1c≥8%) had significantly higher Lp(a) compared to those with better metabolic control(HbA1c<8%) and also non diabetic control subjects. A study by Caixas *et al*, took 60 poorly controlled T2DM patients. They were put on therapy of oral hypoglycemic or insulin for 3 months. This study however, showed that improvement of glycemic control did not influence Lp(a) levels in T2DM[33].

Using a different approach to analyze the interaction between Lp(a) and diabetes, a more recent prospective study of healthy US women aged 45 years or older (Women's Health Study [WHS]) revealed an inverse association between Lp(a) and the risk of incident type 2 diabetes[34,35]. The authors replicated their findings in a Danish population-based cohort (Copenhagen City Heart Study [CCHS]) with prevalent diabetes. These findings suggest that Lp(a) has opposite effects on the risks of cardiovascular disease and diabetes, increasing the former and decreasing the latter[36].

As seen in the above examples the variations in results of studies regarding Lp (a) and T2DM are many. Most of these studies including the present one are cross-sectional. In some studies the diabetic patients are admitted patients due to co-morbidities. In some both type 1 and type 2 DM cases are included. In our study the age group range and duration of Diabetes range was wide, narrowing this may lead to more conclusive data. Many studies have also stated that percentage of diabetics with >30mg/dl of Lp (a) was actually less than 50%.More over variation in results could also be attributed to variation in study design, collection and storage of samples, methods used for statistical analysis. We can also not ignore population differences that reflect the known ethnic variability in the distribution of Lp (a) levels and Apo (a) size isoforms.

In theory, either diabetes by itself or any accompanying condition could contribute to increase Lp(a) levels over the lifespan of each individual. To what extent transcription and translation of apo(a) are affected by hyperglycemia is still not exactly known. The concentration of glycosylated Lp(a) is increased in circulation in diabetic patients and it would also lead to prolongation of half-life of this protein[37, 38]. However, it is well established that Lp(a) concentrations are not significantly affected by environmental factors. Instead, most of the variance in plasma Lp(a) is determined genetically [39]. Diabetes is inherited and so is Lp(a). Alternatively, because both Lp(a) and diabetes increase the risk of cardiovascular disease, mortality rates may be increased at earlier ages in subjects with both risk factors. It is thought provoking thattherapies could be developed to reduce cardiovascular risk in population if it was possible to modify Lp(a) levels by non-genetic factors.

CONCLUSION

An observational study can show correlation between potential risk factors and disease but not causality. We must keep in mind that the disease status might itself alter features of putative risk factor which might result in spurious associations. The data obtained from the present study shows that there is increase in Lp (a) levels in cases of T2DM compared to non-Diabetics, but the increase is not significant. Hence we cannot conclusively include increased Lp(a) in Diabetic dyslipidemia from the present study. A follow up study of Diabetic patients in larger number, with periodic estimation of Lp(a) levels is suggested to understand the change of Lp(a) levels with duration of Diabetes. Also estimation of GlycatedLp(a) levels along with total Lp(a) levels will also throw more light on subject.

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No funding was required for the study as all the tests performed are routinely done in the hospital for patient care.

Compliance with Ethical standard

All procedures performed in the study involved human subjects and were in accordance with the ethical standards of institutional research committee.

Informed consent

Informed consent was obtained from all individual participants included in the study

Conflict of interest

No conflict of interest exists for any of the authors of the study.

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