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Original Research Article

Lipoprotein (a) levels in newly diagnosed treatment naive type 2 diabetics & it's correlation with glycemic & lipid parameters

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ABSTRACT

Background and Aims: Type 2 diabetes mellitus (T2DM) has a high morbidity and mortality mainly due to cardiovascular diseases. Besides traditional risk factors, Lp(a) has recently been emerged as an independent risk factor. This study aimed to evaluate the incidences of elevated Lp(a) levels in newly diagnosed T2DM Pts and to find the pattern of lipid profile abnormalities associated with elevated Lp(a) group of pts & it's correlation with glycemic & lipid parameters.

Materials and Methods: This present study was conducted in newly diagnosed treatment naïve type 2 diabetic patients. After obtaining informed consent, all participants completed a survey to obtain anthropometric & clinical information. Venous blood samples were drawn for fasting plasma glucose, postprandial glucose, HbA1c,lipid profile & Lp(a) measurements.

Results: A total 70 newly diagnosed type 2 diabetic pts & 50 healthy controls were studied. The mean Lp(a)level measured among diabetics was 34.17 ±33.25 mg/dl. The mean concentration of Lp(a) in diabetics was significantly higher than control group(<0.001). Lp(a) was positively correlated with 2hr PP glucose, HbA1c and these correlations were statistically significant. The Lp(a) was negatively correlated with HDLc & this correlation was statistically significant(0.04).

Conclusion: Our study demonstrated Type 2 diabetics had statistically significant higher levels of Lp(a). The residual lipid risk is probably contributed by this molecule So, every diabetic should have checked their level at least once in a lifetime to predict CV risk.

1. Introduction

The traditional lipid profile has served as a mainstay of atherosclerotic cardiovascular disease (ASCVD) risk assessment parameter for decades. Even targeting these traditional lipid parameters, a considerable number of patients are still continue to have cardiovascular events. This invoke investigators to search for new contributors to address the residual lipid risk. Lipoprotein a has recently been emerged as a new risk predictor of major adverse cardiovascular events.[1] Lipoprotein(a) (Lp(a)) was described nearly 50 years ago by Kare Berg and has been considered to be a genetic variant of low-density lipoprotein.[1] Lipoprotein(a) is a low-density lipoprotein (LDL) particle with an added apolipoprotein(a) (apo[a]) attached to the apoplipoprotein(b) (apo[b]) component of the LDL particle via a disulfide bridge. The structure of Lp(a) is highly heterogeneous secondary to many different apo(a) isoforms within the population.[2] An individual's Lp(a) level is 80-90% genetically determined in an autosomal codominant inheritance pattern.[3] Apo(a) has homology with plasminogen and has been shown in vitro to inhibit fibrinolysis but is not an active protease able to degrade fibrin.[4] This homology prevents the activation of plasminogen by tissue plasminogen activator (t-PA) partly

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by competing with plasminogen for binding to the fibrin or endothelial cell surface and also by stimulating endothelial cell synthesis of plasminogen activator inhibitor (PAI-1) possibly hindering fibrinolysis.[5] Moreover, lipoprotein (a) has been demonstrated to bind and inhibit tissue factor pathway inhibitor (TFPI), a potent inhibitor of the tissue factor-mediated coagulation cascade thus perhaps directly promoting thrombosis.[6,7] Therefore, it could hypothetically promote thrombosis at vulnerable arterial plaques. Lp(a) has an affinity for many components of the sub endothelial matrix including proteoglycans, fibrinogen and fibronectin.[6] Indeed, studies in rabbits have shown that Lp(a) can be retained in the arterial wall to a greater extent than LDL. Lp(a) also binds to triglyceride-rich lipoproteins, a property which may contribute to the accumulation of lipid in the arterial wall. Lp(a), like LDL, is subject to oxidative modification to become a substrate for uptake by macrophages thereby fuelling the formation of foam cells.[7] Also like oxidised LDL, Lp(a) seems to have inflammatory properties promoting the chemotaxis of monocytes and inducing the expression of vascular adhesion molecules.[7] One meta-analysis showed an increased risk of CHD and MI with concentrations >30 mg/dL (62 nmol/L) while the INTERHEART trial showed Lp(a) >50 mg/dL was associated with increased risk of MI (OR 1.48; 95% CI 1.32-1.67; P < 0.001).[8,9] The same meta-analysis showed increased risk of stroke at Lp(a) <50 mg/dL and another showed a 2x higher risk of ischemic stroke with smaller apo(a) isoforms and higher Lp(a) concentrations.[8] In many studies elevated plasma Lp(a) levels have been shown to contribute significantly to the incidence of CVD.[10] Lp(a) may be a new metabolic syndrome risk factor and it may be useful as a cardiovascular risk biomarker in future clinical practice. The intent of this study was to check it's level in newly diagnosed type 2 diabetics and to see its correlation between blood glucose & lipid parameters.

2. Materials and Methods

2.1. Statistical analysis

Statistical Analysis was done by using STATA- software. All continuous variables were summarized as number, mean, standard deviation and all categorical variables were summarized as frequency and percentages. Differences in various parameters between diabetes & control groups and degree of correlation between Lp(a)and some clinical and biochemical parameters were estimated by using Analysis of Variance(ANOVA) and Person Correlation Coefficient test and results were presented as correlation coefficient (r) and p-value and P-value <0.05 was considered as statistically significant.

3. Results

A total 70 newly diagnosed treatment naive type 2 diabetic pts were studied of whom 50(71.43%) were males & overall mean age was 46.20±10.95yrs with minimum & maximum age of study population were 20yrs, 65yrs respectively.Majority of the pts were between 30-40yrs and 51-60yrs age group (28.57%). The mean BMI of diabetic study population was 26.20±2.87kg/m^2 with maximum BMI of 33.10kg/m^2 was observed. Forty six pts (65.71%) were addicted to some form of tobacco. About one fourth of study population (25.71%) had positive family h/o diabetes. Clinical characteristics and glycemic status of diabetics and healthy control subjects are shown in Table 1. There was no statistically significant difference in age, gender & smoking habit between study and control groups.Diabetic patients had significantly higher blood fasting glucose, 2hr post prandial glucose,HbA1c,HsCRP levels as compared to healthy control subjects. The lipid parameters and Lp(a) levels of diabetic and control subjects are shown in Table 2. The mean levels of Serum total cholesterol, triglycerides,low density lipoprotein cholesterol, high density lipoprotein cholesterol were significantly higher in study population compared to control subjects. As shown in Table 2, the mean concentration of Lp(a) in diabetics was significantly higher than control group(<0.001). The mean Lp(a)level measured among diabetics was 34.17 ±33.25 mg/dl with minimum level 2.53 mg/dl & maximum level 150mg/dl were measured. Out of 70 diabetics 42(60%) pts had Lp(a) level within normal range that is below 30mg/dl. & remaining 28pts (40%) had elevated levels in their blood. Out of them five pts (7.14%) had very high level >100mg/dl. Most commonly observed lipid profile abnormality among Lp(a) elevated group of diabetics was isolated low HDLc level(16pts,57.14%), the second common form of lipid profile abnormality was isolated high LDLc level that is more than 130mg/dl(15pts,53.57%) followed by combined high triglyceride level with low HDLc level(11pts,39.29%). A summary of the correlations among Lp(a) and some clinical and biochemical parameters in diabetic patients is demonstrated in Table3. In diabetic patients, Lp(a) level was positively correlated with 2hr PPsugar, HbA1c,HsCRP and the correlation was statistically significant. The Lp(a) level was negatively correlated with HDLc & this correlation was statistically significant(0.04). However, no statistically significant correlations were seen between Lp(a) and age, BMI,FPG,Total cholesterol level,LDLc,Triglyceride. (Table 3) The correlations of Lp(a) with LDLc and with HDLc were shown in Figures 1 and 2.

4. Discussion

We all know that T2DM is now considered as coronary heart disease(CHD) equivalent & 80% of deaths among them are from cardiovascular diseases.Besides traditional modifiable

Table 1: Clinical characteristics and glycemic status among study & control groups.

Variables	Diabetics(N=70)	Control(N=50)	p value
Age(yrs)	46.20±10.95	44.33±9.17	0.326
Gender M/F	50/20	35/15	0.865
BMI(kg/m^2)	26.20±2.87	24.48±1.32	<0.001
Smoker	46(65.71%)	32(64%)	0.846
FPG(mg/dl)	137.89±58.80	89.4±5.56	<0.001
2hr PPG(mg/dl)	217.16±85.93	124±15.50	<0.001
HbA1c(%)	7.67±0.83	4.88±0.57	<0.001
HsCRP(mg/L)	2.59±0.80	0.18±0.14	<0.001

BMI:Body mass index,FPG:Fasting plasma glucose,2hr PPG:post prandial glucose,HbA1c:Glycated Hemoglobin,HsCRP:High sensitive c reactive protein. Datas are expressed as mean+/-standard deviation(SD),no & %. N=Number of subjects.

Table 2: Lipid parameters & Lp (a) levels in diabetic & control subjects

Parameters	Diabetics(N=70)	Control(N=50)	p value
Total Cholesterol(mg/dl)	207.04±52.39	163±17.56	<0.001
Triglycerides-(mg/dl)	292.16±85.49	109.5±31.4	<0.001
LDLc(mg/dl)	121.65±49.40	91.51±14.25	<0.001
HDLc(mg/dl)	34.84±8.19	42±4.12	<0.001
Lipoprotein(a) (mg/dl)	34.17±33.25	22.87±5.86	<0.001

LDLc: Low density lipoprotein cholesterol,HDLc:High density lipoprotein cholesterol. Datas are expressed as mean+/-standard deviation(SD) N=Number of subjects.

Table 3: Pearson correlation (r) between lipoprotein (a) and some clinical and biochemical parameters in type 2 diabetic patients.

Parameter	Person Correlation (r)	p-value
Age	0.1043	0.3901
BMI(kg/m^2)	-0.0849	0.4844
FPG	0.2325	0.0527
2Hr PP	0.3517	0.0033
HbA1c	0.2829	0.0177
Total Cholesterol	0.0277	0.8199
HDL	-0.2440	0.0418
LDL	0.2225	0.0642
TAG	-0.1216	0.3159
Hs-CRP	0.3786	0.0012

*BMI:Body mass index *FPG: Fasting Plasma Glucose *2Hr PP: Two-Hour Postprandial Glucose *HbA1c: Glycated Hemoglobin *T2DM: Type 2 Diabetes Mellitus *HDL:High-Density Lipoprotein *LDL: Low-Density Lipoprotein*TAG: Triglycerides *LP (a): Lipoprotein (a) *Hs-CRP: High-sensitivity C-Reactive Protein

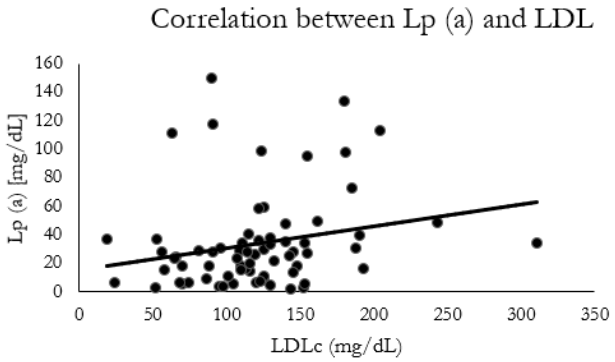

Fig. 1: Correlation between lipoprotein (a) and low-density lipoprotein in diabetics.

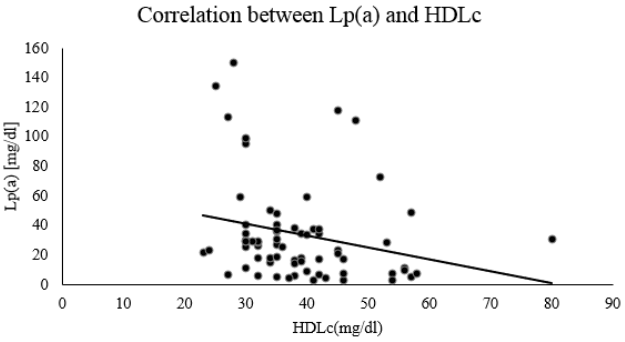

Fig. 2: Correlation between lipoprotein (a) and high-density lipoprotein in diabetics.

risk factors researchers have come up with few new novel risk factors that are consistently associated with ASCVD events.LP(a) is one of this molecule. It is well documented that despite achievement of target LDLc goal, a considerable no of diabetics continue to get ASCVD events, so residual lipid risk does exist in those subset of pts. This residual lipid risk is largely contributed by Lp(a). So,we tried to find out the incidence of elevated Lp(a) level in our study population. We found that incidence of elevated level that is above 30mg/dl was as high as in 40% cases (28pts). The mean Lp(a)level measured among diabetics was 34.17 ±33.25 mg/dl. This significant finding is consistent with results reported by several studies.[11] The effect of hyperglycemia on the rate of Apo(a) synthesis is still not exactly known. It is evident from many studies that glycosylation prolongs the half-life of lipoproteins. This may be applicable for Lp(a) where many studies have shown diabetic patients have an increased concentration of glycosylated hemoglobin, which may contribute to their higher level of Lp(a).[12]

Plasma Lp(a) concentrations are primarily regulated at the level of the Apo(a) gene, and an inverse relationship was found between plasma Lp(a) concentration and Apo(a) size which may result from an inefficient secretion of larger Apo(a) isoforms from the hepatocytes.[13] A study of Ribault

et al.[14] found that type 2 diabetic patients have a higher expression of low molecular weight isoforms of Apo(a), raising the possibility of which diabetic patients in the present study may have small size isoforms of Apo(a), resulting in higher levels of Lp(a).

Most commonly observed lipid profile abnormality among Lp(a) elevated diabetics was isolated low HDLc level(16pts,57.14%). This finding is contrary to known fact of high triglyceride combined with low HDLc that we commonly observed & expected in Indian type 2 Diabetics. Changes in Lp(a) concentrations relative to glycemic control remain controversial; however, most studies have failed to show any correlation between Lp(a) levels and glycemic control in patients with T2DM.[14] In our study, in diabetic patients, Lp(a) was positively correlated with 2hr PPsugar,HbA1c,HsCRP and the correlation was statistically significant. The Lp(a) was negatively correlated with HDLc & this correlation was statistically significant. (p=0.04) Diabetic study population had statistically significant higher HsCRP levels as compared to control cohort & it implies type 2 Diabetics had ongoing low grade inflammation. As we know atherosclerosis is a smouldering thromboinflammatory process and in diabetes there is accelerated atherosclerosis. The association of Lp(a) levels in DM has been a matter of some controversies. The major reasons for the inconsistent results of the prospective studies have been attributed to the variations in study design. Collection and storage of samples, analytical techniques used, and methods used for statistical analysis and population differences reflect the known ethnic variability in the Apo(a) size isoforms and distribution of plasma Lp(a) levels. Our study has got certain limitations like we recruited modest no. of pts, it was a single centre study, we didn't correlate high value with cardiovascular events, we also didn't do qualitative estimation of LP(a) considering apo(a) polymorphism.

5. Conclusion

From the recent literatures, CVD risk in type 2 diabetic patients could be dependent on additional lipid risk factors. Recent studies suggest Lp(a) may be an independent risk factor in type 2 diabetes mellitus patients for the development of cardiovascular disease. Lp(a) may be a new member of metabolic syndrome and it may be useful in routine clinical practice as a biomarker for determining cardiovascular risk. Our study demonstrated,TYPE2 diabetics have higher incidence of Lp(a)level & probably residual lipid risk is mostly contributed by this molecule.Hence every diabetic pt should check their Lp(a) level once in a lifetime for predicting their future cardiovascular events. Lp(a) level measurement should be incorporated in traditional lipid profile parameters. The impact of Lp(a) in T2DM needs to be further investigated by prospective studies with assessment of apo(a) polymorphism.

6. Source of Funding

None.

7. Conflict of Interest

None.

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