IJBPAS, January, 2021, 10(1): 159-169

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

LP(A) LEVELS IN DIABETES AND METABOLIC SYNDROME

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Received 20th Oct. 2020; Revised 19th Nov. 2020; Accepted 15thDec. 2020; Available online 1st Jan. 2021

https://doi.org/10.31032/IJBPAS/2021/10.1.1022

ABSTRACT

Cardiovascular diseases (CVDs) deserve more clinical attention being the primary clinical outcome of metabolic syndrome (MetS). Indians are highly predisposed to MetS, insulin resistance and CVDs. Lipoprotein (a) Lp(a) is a emerging risk factors in the development of CVDs. Lp(a) is an independent determinant of aortic stiffness in elderly patients with diabetes. Type 2 DM is a worldwide endemic disease. Dyslipidemia is also a frequent disorder associated with diabetic patients. Lipid profiles can vary in Diabetes and metabolic syndrome patients. We investigated serum lipid profiles, Lp(a) levels in metabolic syndrome and in type 2 diabetic patients. In this study 220 type 2 diabetic patients and 220 metabolic syndrome patients and 220 healthy control subjects were included. After 12 hours overnight fasting, blood samples were obtained for analyzing the serum lipids, FBS and HbA1C. Type 2 diabetic patients had higher serum total cholesterol, LDL cholesterol, triglyceride and Fasting blood sugar and HBA1C levels and lesser HDL-cholesterol, compared with the Metabolic Syndrome and control group. In

Metabolic syndrome patients had higher serum total cholesterol, LDL cholesterol, triglyceride and Fasting blood sugar and HBA1C levels and lesser HDL-cholesterol, compared with the control group. The serum Lpa was found to be higher levels in metabolic syndrome compared with the type 2 diabetics and control subjects. The serum Lpa was found to be higher levels in diabetics compared with control subjects. Elevated Lp(a) levels is a strong independent predictor of subclinical atherosclerosis.

Keywords: Diabetes mellitus, Metabolic syndrome, Triglycerides, Cardiovascular disorder, Atherosclerosis

INTRODUCTION

The metabolic syndrome is a cluster of metabolic and cardiovascular symptoms that are strongly associated with type II diabetes mellitus. In this kind of diabetes, rather than prolonged high levels of glycemia, there is insulin resistance with secondary hyperinsulinemia, both very frequently associated with, hypertension, dyslipemia, atherosclerosis, and, most importantly, obesity Diabetes Mellitus (DM) is a disorder characterized by persistent hyperglycemia due to insulin resistance. Insulin is a pleiotropic hormone which signals a number of cellular processes such as glucoregulation, lipid metabolism, and protein synthesis in multiple tissues. In patients with DM, these actions of insulin are reduced. Consequently, there is an increase in free fatty acids which promote oxidative stress, endothelial dysfunction, vascular damage, and atheroma formation. The clinical results are high BP, HDL suppression, and high triglycerides (TGL) additionally, DM is associated with macrovascular (myocardial infarction, stroke) and microvascular (retinopathy, neuropathy, renal disease) problems which interfere with blood and nutrient delivery to multiple tissues throughout the body. DM is a crucial factor in Metabolic Syndrome (MetS) and is highly predictive of Cardiovascular Disease (CVD) risk. Much of our knowledge of the relationship between lipids, lipoprotein metabolism and the development of atherosclerosis and cardiovascular disease is based on characterizing metabolic markers.

Lipoprotein(a) Lp(a) consists of an LDL-like particle and the specific apolipoprotein(a) apo (a), which is covalently bound to the apo B of the LDL like particle **[1]**. Elevated levels of Lipoprotein a Lp (a) are found to be independent risk factors for coronary heart disease. The structure of Lp (a) resembles LDL and its atherogenic

properties can be explained by its binding to glycosaminoglycans and inhibition of fibrinolysis. The atherogenic properties of Lp(a) are expressed over 30 mg/dL serum concentration **[2]**. Some reports on serum Lp (a) levels in subjects with type 2 DM show that Lp (a) levels are higher in this group of patients compared with non diabetic healthy controls **[3, 4]**. Patients with type 2 DM have defects in insulin secretion in response to a glucose load and resistance to insulin action **[5, 6]**. Insulin resistance best correlates with metabolic abnormalities and is linked to the development of cardiovascular disease in patients with type 2 diabetes **[7]**. Hyperinsulinemia and insulin resistance have been associated with coronary artery disease (CAD), type 2 DM, dyslipidemia and hypertension **[8]**. Lp(a) has been reported to be an independent risk factor for premature CAD and other thromboembolic disorders **[9]**. Many studies have reported that Lp(a) is elevated in type 2 DM. Moreover, the frequency of high risk levels has been reported to be much higher in type 2 diabetics **[10, 11]**.

The present study aimed to study the lipids and lipoprotein(a) concentrations and association in patients with type 2 diabetes mellitus and metabolic syndrome.

MATERIAL AND METHODS

The Present study was carried out in the department of Biochemistry, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry. In this study total number of patients divided in to 3 different groups. The distributions of subjects in the study were as follows

Study group:

Group I- Metabolic syndrome- 220 subjects

Group II- Diabetes mellitus- 220 subjects

Group III- Control group – 220 subjects

The study was approved by the institutional ethical committee of Sri Lakhsmi Naryana Institute of Medical Sciences, Puducherry according Helsiniki 1975 human ethical guidelines. All the data were collected in a prescribed perform and obtained informed consent form.

5ml of the blood samples which were taken for analysis were obtained from the antecubital vein. 5 ml of venous blood samples were collected from patients and controls. Blood samples were centrifuged and plasma was separated. The samples were then centrifuged at 3000 rpm for 15 minutes. The plasma separated and Samples were analyzed Lipoprotein (a)-estimated through the turbidometic method and serum Triglycerides(TGL), Cholesterol, LDL, HDL,

plasma glucose, HbA1c were evaluated by using enzymatic kits on Siemens fully automated analyzer.

Statistical Analysis

All values were expressed as mean ± standard deviation (SD). Independent samples't' test was used to test the significance of difference in means between study group and controls. For men and women, a student t-test or ANOVA test was used to compare between control and MetS participants normal or non-normal distribution, respectively. A P-value less than 0.05 were considered statistically significant. Statistical analysis was done by using Microsoft Excel and SPSS for windows version 11.5 (SPSS, Inc., Chicago).

RESULTS

Table 1: Showing the mean ± SD of biochemical parameters LP (A), cholesterol, TGL, HDL, LDL, FBS and HBA1C levels in Metabolic Syndrome, Diabetics and Controls

S. No.	Parameters	Metabolic Syndrome(n-220) Mean ± SD	Diabetes Mellitus(n-220) Mean ± SD	Control(n-220) Mean ± SD
1	Lp(a)(mg/dl)	35.17±1.30*	27.62±1.22*#	12.93±0.69
2	Cholesterol (mg/dl)	245.52± 13.92*	262.93± 13.55*#	188.63 ±12.80
3	TGL (mg/dl)	241.62±8.63*	257.46±11.81*#	169.67±8.64
4	HDL (mg/dl)	29.91± 2.53*	35.67± 3.29*#	49.59± 4.17
5	LDL (mg/dl)	123.46±3.29*	126±3.11*#	68.52±2.82
6	FBS (mg/dl)	156.77±4.76*	168.83±5.08*#	106.17±1.78
7	HbA1C (gm %)	41.1±1.23*	43.28±1.62*#	3.86±0.02

***Indicates Significant P<0.05 when compared with Control**
#Indicates Significant P<0.05 when compared MetS
***#Represent statistical significance at p<0.05**

DISCUSSION

Lp(a) was initially isolated from human plasma by Berg in 1963, constituted by the association of an LDL-C particle covalently bound to a large glycoprotein, apolipoprotein(a) Apo(a) to apolipoprotein B by a disulfide bridge. The Apo(a) chain contains five cysteine-rich domains known as "kringles", which are coded by a gene localized in the long arm of chromosome 6 (6q26-27) and is subject to multiple polymorphisms, particularly regarding the size of kringle IV. Clinical interest in Lp(a) has grown exponentially in recent times, as an assortment of epidemiological studies has pinpointed the link between plasma Lp (a) concentrations (reported as ≥300mg/L or ≥30 mg/dL) and the risk of suffering coronary events, peripheral artery disease, cerebrovascular disease, and the early development of atherosclerosis in children and adolescents **[12, 13]**. Despite this prominence, the interpretation and application of Lp(a) levels in clinical scenarios remain a controversial issue, since no guidelines have been suggested outlining the profiles of patients whose Lp(a)

concentration should be quantified. As a result, experimental studies are required for the clarification of its role as a CVD risk factor, as well as epidemiological studies evaluating the behavior of its plasma levels regarding other CVD risk factors across differential latitudes in order to effectively direct genetic studies focused on highlighting the true role of the genetic intricacies underlying the greater variations reported among demographics **[14]**.

Many reports on Lp (a) levels however indicate higher prevalence rates of elevated Lp (a) in people with type 2 DM compared to healthy non diabetic subjects and type 1 DM patients **[15, 16]**. Previous reports were prevalence rate of elevated Lp (a) is much lower than that who reported a prevalence rate of 43.4% in people with type 2 DM. It is of note that elevated serum TG is a prominent feature of patients with type 2 DM who have elevated Lp (a) levels and this is evident by the results we obtained when we compared biochemical and clinical parameters between type 2 DM patients with elevated LP (a) levels and those with normal Lp (a) levels. Serum Lp (a) levels are transiently or chronically increased.

We have noted in this study that serum LP (a) had significantly associated with CVS risk factors namely, LDL-C, LDL/HDL and TG. A positive correlation of Lp (a) with total cholesterol and LDL-C but not with triglycerides and HDL-C. We have also shown in this study that over half of our patients with type 2 DM have elevated LDL-C and reduced HDL-C levels. Hypertension is a CVS risk factor and metabolic syndrome defining criteria is a commonly documented co-morbidity of DM **[17]**.

The presence of elevated Lp (a) levels had no bearing with glycaemic control and the mean HbA1c levels were comparable in DM patients with and without elevated Lp (a) levels, Some studies have shown similar results with our findings on the relationship between glycaemic control and Lp (a) **[18-20]**. In these studies (there was found no relation between HbA1c and Lp(a) concentrations in subjects with type 2 DM. It has been observed that patients with type 2 DM have increased morbidity and mortality due to coronary risk events. This increased risk has been shown to be independent from conventional risk factors. Different factors have been found to be responsible for an increased prevalence of CAD in DM. One of these are the elevated levels of serum lp(a). Our study has revealed that Lp(a) levels were significantly elevated in DM patients. Type 2 diabetic patients with hypoinsulinemia had longer duration of diabetes and higher

concentrations of Lp(a), when compared to those with hyperinsulinemia. The present study also showed a significant inverse relationship between serum glucose and Lp(a) levels. Lp(a) was significantly associated with total cholsterol and LDL-c, TG. These results suggest that fasting blood sugar levels significantly influence LDL-c metabolism in the elderly, the level of Lp(a) in human plasma is largely unaffected by diet, physical activity, and conventional hypolipidemic therapy.

Lp(a) has been found to be metabolized differently from triglyceride-rich lipoproteins. Acute hyperglycemia-induced hyperinsulinemia has a different effect on Lp(a) levels in healthy subjects. Previous study reports **[21]**, it was observed that unlike LDL, Lp (a) production, and not catabolism, determined plasma concentrations and the inverse association of Lp (a) concentrations with Apo(a) isoforms was due to differences in production and not catabolism. One of the risk factors in long standing DM may be increasing Lp (a) levels. The association of Lp(a) levels in DM has been a matter of some controversies.

As a component of MS, Dyslipidemia represents one of the fundamental pillars in its ethiopathogenics. Dyslipidemia and inflammation. Lp(a) plays an important role at the molecular level both for CVD and MS when its plasmatic concentration is elevated, being able to generate both of the aforementioned basic disturbances **[22-24]**. It is important to highlight the lack of differences of Lp(a) levels between genders in previous study reports, as has been outlined in previous investigations; therefore, most comparisons were done utilizing the general population. Exhibiting a qualitative association with Lp(a), subjects with MS also showed higher levels than healthy subjects, similar to the results of Bozbaş H *et al*., 2008, in 355 Turkish individuals. Nevertheless, this behavior differs from that described for older Japanese adults, whose plasmatic concentrations were not statistically different **[25]**. Notably, notwithstanding the escalating tendency of Lp (a) levels as the number of criteria increased, it is not the amount of criteria expressed but the actual diagnosis of MS that appears relevant regarding the presence of elevated Lp(a) concentrations. With reference to the analysis by individual diagnostic criteria, previous studies evaluating the relationship between Lp(a) and the isolated components MS are not abundant, and very few include all criteria in their analyses. In our univariate estimations, subjects displaying each of the components

appeared to have higher serum Lp(a) concentrations in contrast to those without these conditions, except those with elevated glycemia, where differences were not statistically significant. These results differ from those depicted by Candido *et al*. **[26]** in 400 Brazilian individuals, who did not find such association with these criteria in an analysis akin to ours. It is important to acknowledge that the variables demonstrating the greater differences in Lp(a) levels (waist circumference and elevated TAG) are the most associated with systemic inflammatory state characteristic of MS [27, 28]. These findings may underline the role of Lp(a) in this process, whether as an active molecule or as a potential pro inflammatory companion of these risk factors **[29, 30]**.

Likewise, when assessing its plasmatic concentration according to the possible specific diagnostic combinations for MS criteria, a large heterogeneity was found concerning these levels and the amount of criteria; yet, the greatest values were found in subjects with more than 3 alterations. Notoriously, the high basal glucose/low HDL-C/ hyper triacylglyceridemia combination displayed the highest Lp(a) values, with high waist circumference/high blood pressure/ hypertriacylglyceridemia/low HDL-C combination; in addition, these patients also had higher LDL-C levels. These phenomena turn all of patients into potential candidates for the application of therapeutic measures aimed to the decrease of Lp(a) values, particularly with an increment in the degree of physical activity performed, since it has been associated with normal levels of this lipoprotein. These patients are also ideal candidates for the investigation of genetic disorders which may be responsible for this dyslipidemia. Alterations linked to plasma lipoproteins, especially those regarding low-density lipoproteins (LDL-C) are particularly notable within the physiopathologic aspects of MS, showcasing its genetic implications.

Indeed, the decisive role played by genetic factors regarding Lp(a) is broadly known; nonetheless, several conditions, alterations, and molecules can influence and generate important variations in its plasmatic concentration. In our study population, age appears to be one of the main risk factors for presenting elevated Lp(a), resembling previous reports on the Taiwanese population and on Swedish subjects from a Monica study **[31]**. Moreover, despite the cardiovascular consequences generated by high levels of this molecule, when it coexists with specific Apo (a) isoforms, it has been associated with longevity.

On the other hand, in the multivariate analysis of all diagnostic criteria for MS, only patients with hypertriacylglyceridemia exhibited a greater risk of presenting elevated Lp(a). However, after adjusting the model for LDL-C categories, not only is it apparent that this lipoprotein boasts the closest association with high levels of Lp(a), but the effects of TG seem to disappear; it is important to highlight that this tendency was only observed with LDL-C adjusted for Lp(a)-C, not priorly.

This pattern deviates from those portrayed by rainwater in healthy subjects (Rainwater D L 1996) and Other study in diabetic patients **[32]**, who both found a positive (Lp(a)−LDL-C) relationship and an inverse (Lp(a)−TG) relationship. Therefore, future studies should focus on the evaluation of the behavior of Lp(a) with respect to the various types of dyslipidemia, the understanding of molecular mechanisms explaining the proportionality of LDL-C/Lp(a) concentrations, and the therapeutic considerations that may be established for these patients **[33]**.

Elevated Lp(a) level is associated with various complications including microalbuminuria, nephropathy, retinopathy, heart attack, stroke and death among patients with diabetes.

CONCLUSION

Serum LP (a) is significantly and positively associated with most of the atherogenic profile defining parameters in type 2 DM of which elevated TG is prominent. Type 2 DM is associated with atherogenic lipid disorder and high fasting glucose, Lp(a) levels inversely correlate with glucose levels in type 2 diabetic patients. Lp(a) may be one of the cardiovascular risk factors in type 2 diabetic patients with longer duration of DM. This study may partially explain the higher incidence of cardiovascular problems with the increasing duration of DM. However, long-term prospective studies are needed in diabetic patients to disclose the true mechanistic links to cardiovascular problems.

Diabetes and Lp(a) increase severity of atherosclerosis, cardio vascular disorders and those with both conditions have extremely severe atherosclerosis. A high prevalence of this combination is a major contributes to the heart disease among Indians.

This analysis demonstrates that MS is yet another disease to consider among disorders involving high Lp(a) levels; future studies are required for discerning whether this relationship represents a state previous to the widely recognized cardiovascular

consequences of this molecule, or if they each stand as independent outcomes. Likewise, the presence of MS influences the plasmatic concentration of Lp(a), but this effect is irrespective of the amount of diagnostic criteria. Although these criteria seem to modify levels when they are present, when assessed in conjunction, their effects appear to be attenuated. The only component to show an association despite several statistical adjustments is impaired fasting glucose, which, by virtue of being related to a hyperinsulinemic state, appears to diminish the probability of presenting elevated Lp(a), an association that had previously only been suggested for DM2.

Conflict of interest: Nil

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