

## Role of serum lipoprotein (a) in type 2 diabetes mellitus and its association with glycemic control

Kavitha MM<sup>1</sup>, JG Ambekar<sup>2</sup>, Nilima Dongre<sup>3</sup>, Kashinakunti SV<sup>4,\*</sup>

<sup>1</sup>PhD Scholar, <sup>2</sup>Professor, <sup>3</sup>Associate Professor, Dept. of Biochemistry, BM Patil Medical College, BLDE Deemed to be University, Vijayapura, Karnataka, <sup>4</sup>Professor, Dept. of Biochemistry, S Nijalingappa Medical College, Bagalkot, Karnataka, India

**\*Corresponding Author:**

Email: mekch@rediffmail.com

Received: 30<sup>th</sup> April, 2018

Accepted: 24<sup>th</sup> May, 2018

### Abstract

Diabetes mellitus (DM) is an established risk factor for cardiovascular disease. At present global risk assessment, lipid profile is only the blood test routinely recommended most commonly. Increased lipoprotein (a) [Lp(a)] contributing factor to accelerated development of macrovascular complications in DM. However Lp(a) and hsCRP evaluation may have the potential to improve cardiovascular risk prediction when used in addition to traditional lipid profile. Hence the study was undertaken to estimate the serum lipoprotein (a), lipid profile, lipid ratios and hsCRP in diabetic patients and their association with glycemic control. Within the diabetic patients we examined Lp(a) levels among controlled and uncontrolled diabetic individuals.

**Materials and Methods:** An observational study comprises of 150 participants. 75 were type 2 diabetic patients and 75 were healthy controls. Diabetic patients were further sub classified into good and poor glycemic control group depending on their HbA1c levels 7.5% as cut-off value. Fasting venous blood sample was collected and used for analysis of fasting glucose, lipoprotein (a), lipid profile, high sensitive C reactive protein (hsCRP) and glycosylated hemoglobin (HbA1c).

**Results:** A significant increase ( $p < 0.05$ ) in Lp(a), TG, LDL, hsCRP and Lipid ratios and significant decrease in HDL in diabetic patients compared to controls. Subjects with poor glycemic control subjects showed significant increase in FBS, HbA1c, TG and hsCRP. Even though, the Lp(a) increased in poor controlled diabetics, but it was not statistical significant. HbA1c shows positive correlation with FBS, TG, HDL, hsCRP and TG/HDL in diabetic patients.

**Conclusion:** The study helps in identification of at risk individuals for CAD beyond the routinely done lipid profile especially in insufficient resource situations. In our study we have higher levels of Lp(a), hsCRP and other atherogenic risk factors cluster more in diabetic patients compared to healthy controls. FBS, TG, hsCRP and TG/HDL are positively correlated with HbA1c. Thus Lp(a) and hsCRP evaluation may have the potential to improve cardiovascular risk prediction when used in addition to traditional lipid profile in diabetic patients. Poor glycemic control subjects have significantly higher hsCRP and TGs compared to good glycemic controls. There is no effect of glycemic control on Lp(a) levels, hence Lp(a) is independent risk factor for CAD in diabetic patients.

**Keywords:** Lipoprotein (a), Glycemic control, Diabetes mellitus.

### Introduction

Diabetes mellitus (DM) is a chronic non-communicable metabolic disorder and is also known as "Iceberg" disease. India has the largest number of diabetic people with 50.8 million and is said to be diabetes capital of the world.<sup>1</sup> Among non-communicable diseases diabetes is considered as high in morbidity and mortality rates. According to WHO reports diabetes will be the seventh cause of death by the end of 2030. As per study 50% of diabetics die due to cardiovascular disease. Diabetic subjects are known to have a two to four times increased risk of developing coronary artery disease (CAD) and CAD occurs two to three decades earlier in diabetic subjects as compared to nondiabetic subjects.<sup>2</sup> It was considered DM is an established risk factor for cardiovascular disease (CVD) and is considered to be CVD equivalent. Thus WHO in 2016 put an effort for sensitizing and bringing awareness about diabetes among people all over the world with theme "Beat Diabetes".

Abnormalities in lipid metabolism i.e dyslipidemia and lipoproteins are the established traditional risk

factors for CAD. Elevated cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and low levels of high density lipoprotein cholesterol (HDL-C) are characteristic of typical dyslipidemia. Several intervention studies revealed reduction of serum TC and TG levels inturn reduction of mortality due to CAD.<sup>3,4</sup>

Lipoprotein (a) [Lp(a)] type of low density lipoprotein cholesterol (LDL-C) called little rascal. It was first identified by K Berg in 1963.<sup>5</sup> Lp(a) composed of an LDL-C like particle and apolipoprotein(a) which is covalently bound to apo B of LDL-C particle. Lp(a) is structural analogue and competitive inhibitor of plasminogen leading to impaired fibrinolysis. Lp(a) accumulates in the vessel wall; inhibits binding of plasminogen to cell surface. This inhibition also promotes proliferation of smooth muscle cells. Hence Lp(a) has atherogenic and thrombotic properties.<sup>6</sup> Studies reveal that diabetic patients are reported to have higher Lp(a) values than non diabetic controls and still higher values found in diabetics with complications.<sup>7,8</sup> Increased Lp(a) levels

confer genetic predisposition to CVD and may be related to accelerated atherogenesis in DM.

Recent data support that lipid ratios are more meaningful than individual lipid parameters. They help in early prevention and diagnosis of CHD than the individual serum lipids.<sup>9</sup>

High sensitivity C-reactive protein (hsCRP) is an acute phase protein, biomarker of inflammation and as an independent predictor for CAD. hsCRP levels increase with inflammation and insulin resistance. Measurement of hsCRP may be considered marker for better prediction of cardiovascular risk.<sup>10</sup>

Glycosylated hemoglobin (HbA1c) reflects the cumulative blood glucose over period of 8-10 weeks. It is an important indicator of long term glucose control and thus part of continuing care in diabetics.<sup>11,12</sup> Elevated HbA1c concentration has been considered an independent risk factor for coronary artery disease in diabetic patients.<sup>13</sup> It is reported that good glycemic control is associated with reduction in CVD.<sup>14</sup> Studies reveal that decrease Lp(a) levels with improved glycemic control in diabetic patients.<sup>15</sup>

There are very few and controversial data on Lp(a) in diabetics and its relationship with glycemic control in Indian population. Hence the present study was conducted to estimate the serum Lp(a) levels, lipid profile, lipid ratios and hsCRP in diabetic patients and to compare with healthy controls. Within the diabetic patients we examined Lp(a) levels among controlled and uncontrolled diabetic individuals by taking HbA1c 7.5% as cut-off value and also to see the relationship between Lp(a), lipid profile, lipid ratios and hsCRP with glycemic control.

## Materials and Methods

This is a hospital based observational case-control study, conducted in the department of Biochemistry, S Nijalingappa Medical College and Hanagal Sri Kumareshwara Hospital Research Centre, Bagalkot, a teaching Centre in Karnataka, India. The study protocol was approved by institutional ethics committee (IEC). Study was conducted over a period of one year from January to December 2016. The study comprises of 150 subjects, 75 were clinically diagnosed diabetic patients attending the medical OPD and admitted patients. Age and sex matched 75 healthy controls of the age group between 30 to 60 years. Diabetes was diagnosed on the basis of WHO criteria (FBS > 126 mg/dL or PPBS > 200 mg/dL or HbA1c > 6.5%). Diabetic patients were further subdivided into two groups as good and poor glycemic control depending on HbA1c levels 7.5% as cut-off levels. Patients with thyroid disorders, nephrotic syndrome, chronic liver, renal diseases, diabetics with any complications and pregnant ladies were excluded from the study.

Informed written consent was taken from all participants. All care was taken to maintain the confidentiality of the patients as per Helsinki declaration.

For each patient detail history was taken, general physical examination and anthropometric measurements like height and weight are recorded. Body mass index (BMI) was calculated using the formula  $Wt (Kg)/Ht (m)$ .

Under aseptic precaution 5 mL of fasting venous blood was drawn. Out of this 2 mL was EDTA sample used for estimation of HbA1c by high performance liquid chromatography (HPLC) method in D-10 Bio-Rad instrument. Remaining 3 mL was allowed to clot and serum was separated. The serum was used for analysis of biochemical parameters like fasting blood glucose (FBS), lipid profile, lipoprotein (a) and hsCRP. Glucose was estimated by glucose oxidase and peroxidase method. TG's by glycerol phosphate method, HDL-C estimated by direct method. LDL-C was calculated by Friedewald's formula i.e  $LDL=TC-TG/5-HDL$ . Lp(a) and hsCRP was estimated by immunoturbidimetric method. All parameters were measured in fully automated analyser, Biosystem A25 using Biosystem kits. Lipid ratios were calculated i.e TC/HDL, LDL/HDL, and TG/HDL.

## Statistical Analysis

Statistical analysis was carried out using software SPSS version 19. Quantitative data were expressed as mean $\pm$ SD. Student 't' test was applied for comparison of two groups and Pearson's correlation test was applied for correlation.  $p < 0.05$  is considered as statistically significant.

## Results

Demographic characters of cases and control was shown in table 1. There was significant increase in BMI, FBS and HbA1c in cases compared to controls. There was no difference ( $p=0.16$ ) in age among two groups.

Table 2 shows the comparison of lipid profile, Lp(a), hsCRP and lipid ratios between cases and controls. In the present study diabetic subjects have significantly higher ( $p<0.05$ ) serum TG's, LDL-C, Lp(a) and hsCRP compared to controls. There was significant decrease in HDL-C levels in cases compared to controls. There was significant increase ( $p<0.000$ ) in lipid ratios in diabetics compared to controls.

Comparison of lipid profile, Lp(a), hsCRP and lipid ratios among type 2 diabetic patients with good and poor glycemic control are depicted in table 3. Diabetic patients with poor glycemic control showed significant ( $p=0.0001$ ) increase in FBS, HbA1c, TGs, and hsCRP compared to good glycemic control group. Although, the Lp(a) levels in poor glycemic patients are increased compared to good glycemic control subjects ( $29.8 \pm 16.47$ , vs  $23.69 \pm 14.23$ ) it was not statistical significant.

Pearson correlation of HbA1c with FBS, lipid profile, Lp(a), hsCRP and lipid ratios was shown in table 4. There was significant positive correlation between HbA1c with FBS ( $r = 0.38$ ,  $p=0.001$ ) Fig. 1, TGs ( $r=0.234$ ,  $p=0.04$ ), HDL ( $r=0.277$ ,  $p=0.01$ ) hsCRP ( $r=0.780$ ,  $p=0.0001$ ) Fig. 2 and TG/HDL ( $r=0.14$ ,  $p=0.001$ ).

**Table 1: Table showing clinical characteristics, FBS and HbA1c in controls and cases**

	Control N=75	Cases N=75	t	p-value
Age in Year	52.74 ± 16.69	56.45 ± 16.3	1.39	0.16
BMI Kg/m <sup>2</sup>	24.98 ± 1.41	26.34 ± 2.08	4.61	0.000**
FBS mg/dL	87.79 ± 17.37	165.73 ± 58.91	10.98	0.000**
HbA1c %	5.28 ± 0.61	8.51 ± 1.96	13.58	0.000**

\*\* - Highly significant

**Table 2: Table showing the lipid profile, Lp(a), hsCRP and lipid ratios in control and cases**

Parameters	Control N=75	Cases N=75	t	P value
TC mg/dL	153.97 ± 35.1	163.49 ± 47.10	1.45	0.16
TGs mg/dL	112.32 ± 54.95	128.98 ± 41.26	2.09	0.03*
HDL-C mg/dL	39.2 ± 9.69	33.17 ± 9.88	3.71	0.002**
LDL-C mg/dL	92.3 ± 28.74	104.52 ± 42.1	2.07	0.03*
Lp(a) mg/dL	17.20 ± 3.98	26.87 ± 15.63	5.19	0.001**
hsCRP mg/L	1.28 ± 0.37	3.93 ± 0.98	21.71	0.001**
TC/HDL	4.04 ± 0.95	5.22 ± 1.73	5.19	0.001**
LDL/HDL	2.43 ± 0.81	3.37 ± 1.51	4.75	0.001**
TG/HDL	3.01 ± 1.5	4.27 ± 1.84	4.11	0.001**

**Table 3: Table showing the lipid parameters, Lp(a), hsCRP and lipid ratios in good and poor glycemic control diabetic patients**

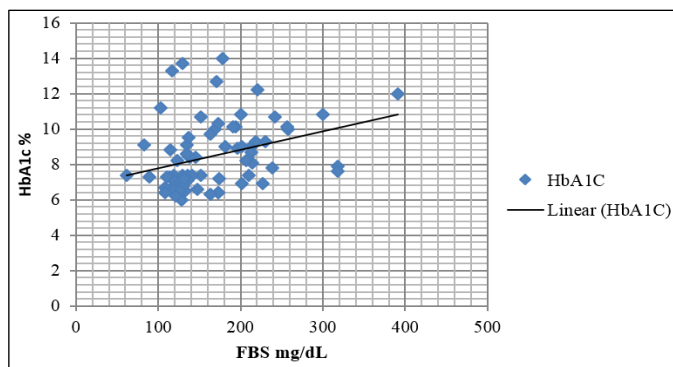
Parameters	HbA1c < 7.5 % N=36	HbA1c > 7.5% N=39	t value	P value
FBS mg/dL	136.81 ± 31.92	182.41 ± 65.46	4.2	0.0001 *
HbA1c %	6.98 ± 0.45	9.84 ± 1.65	13.4	0.0001 *
TC mg/dL	162.06 ± 48.31	160.78 ± 46.83	1.06	0.84
TG mg/dL	125.74 ± 32.83	137.36 ± 47.38	2.08	0.03 *
HDL-C mg/dL	35.83 ± 8.64	30.18 ± 9.68	1.25	0.49
LDL-C mg/dL	101.13 ± 61.03	103.2 ± 52.67	1.34	0.37
Lp(a) mg/dL	23.69 ± 14.23	29.8 ± 16.47	1.257	0.49
hsCRP mg/L	3.29 ± 0.56	4.57 ± 0.93	2.758	0.003 *
TC/HDL	4.52 ± 1.83	5.32 ± 1.4	1.653	0.1
LDL/HDL	2.82 ± 0.94	3.42 ± 1.0	1.403	0.3
TG/HDL	3.51 ± 1.29	4.51 ± 2.1	3.062	0.001**

\* - Statistical significant, \*\* - Highly significant

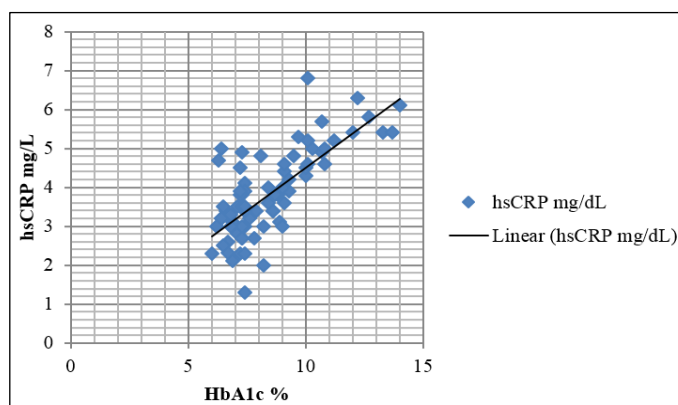
**Table 4: Correlation of HbA1c with other lipid parameters**

HbA1c	Parameters	r	p-value
	FBS	0.380	0.001 *
TC	0.182	0.114	
TG	0.234	0.043 *	
HDL-C	0.277	0.01*	
LDL-C	0.142	0.218	
hsCRP	0.780	0.000 *	
Lp(a)	0.125	0.287	
TC/HDL	0.019	0.873	
LDL/HDL	0.018	0.87	
TG/HDL	0.243	0.03*	

\* - Statistical significance



**Fig. 1: Correlation graph of HbA1c with FBS in diabetic patients**



**Fig. 2: Correlation graph of hsCRP with HbA1c in diabetic patients**

## Discussion

In our study FBS and HbA1c are significantly increased in diabetic patients compared to controls. Increased TG's, LDL-C and decreased HDL-C are well known risk factors for CAD in diabetic patients. In our study we did not find any difference in TC. High prevalence of dyslipidemia in subjects with type 2 diabetes mellitus, our study is in accordance with other studies.<sup>16,17</sup> In diabetic subjects, high TG levels tend to coexist with low HDL levels.<sup>18,19</sup>

Lp(a) is variant of LDL-C emerging as a strong biomarker of CAD. Our results show that diabetic patients have high Lp(a) levels compared to controls. The increased Lp(a) levels in diabetic subjects may be due to increased concentration of glycated Lp(a) in the circulation.<sup>20,21</sup> Glycosylation increases the half-life of lipoproteins i.e Lp(a). Reports say that Lp(a) levels above 20 mg/dL are associated with high risk of CAD.<sup>22</sup> A south Indian study on 300 participants, reports Lp(a) had an independent association with CAD in type 2 diabetes patients. An increase Lp(a) levels was found to be associated with increase in carotid intimal thickness. Hence, Lp(a) is associated with CAD even at an early stage of atherosclerosis.<sup>23</sup>

A cross sectional study by Anthonia OO<sup>24</sup> et al carried out on 200 Nigerian patients with type 2 DM, reported that elevated serum Lp(a) levels are higher in subjects with DM than in people without DM. It also showed positive association with most of the

atherogenic profile parameters in type 2 DM individuals. A study by Gazzaruso C et al<sup>25</sup> reported that estimation of Lp(a) and apo (a) phenotypes may be used not only as predictor of CAD and also predictor of CAD severity in type 2 diabetic patients. A south Indian study by Mohan V et al,<sup>26</sup> reports that Lp(a) is an independent association with CAD in type-2 diabetic patients. Haffner et al<sup>14</sup> says contradictory statement that, slightly lower Lp(a) levels in diabetic patients than non diabetic subjects and there was no statistical significance.

Data support that lipid ratios have been reported more sensitive in reflecting the morbidity and severity of CHD than individual lipid parameters. Our study shows that there was significant increase in lipid ratios in diabetic patients compared to controls. Among the lipid ratios TG/HDL showed positive correlation with HbA1c. According to Shai et al<sup>27</sup> TC/HDL, LDL/HDL and apoB/apoA ratios are more susceptible to increased CVD mortality than individual lipid. According to Imran AS et al<sup>28</sup> atherogenic index (AI) can be used to indicate the presence of increased cardiovascular risk in patients with type 2 DM and as a guide for the aggressive therapeutic approach. The TG/HDL ratio is cheap and easy to calculate and is a good predictor of LDL size. In current strategies of global risk assessment, lipid profile is only the blood test routinely recommended most commonly in all setups. Calculation of lipid ratios is very easy and can be done

routinely from lipid profile parameters especially in Indian set up where new tests are not routinely possible because of cost factor.

We know that hsCRP is the inflammatory biomarker. In our study there was significant increase in hsCRP in diabetic patients compared to controls. Evaluation of hsCRP may have potential to improve cardiovascular risk prediction when used along with other traditional lipid profile. It was considered as single strongest predictor of risk.<sup>29</sup> In our study it was also increased in poorly controlled diabetic individuals compared to good glycemic diabetic individuals. It was positively correlated with HbA1c levels. Many trials and studies reveal that hsCRP is an independent predictor of future cardiovascular events in diabetes and significantly correlates with HbA1c.<sup>30,31</sup>

Hyperglycemia enhances glycosylation of proteins particularly lipoproteins. Glycosylation of LDL has been shown to enhance its susceptibility to oxidation, which triggers the atherosclerotic processes. In present study subjects with poor glycemic control showed significantly higher levels of FBS, HbA1c and TGs compared to good control diabetics. Dyslipidemia increases with increasing blood glucose levels and thus cardiovascular risk would be high with poor glycemic control.<sup>32</sup> Data reveals 25% reduction in microvascular complications with improved blood glucose control in type 2 diabetics was demonstrated in United Kingdom Prospective Diabetic Study (UKPDS).<sup>33</sup>

In our study there is relatively higher Lp(a) levels in poorly controlled glycemic diabetics compared to good controls but it is not statistically significant. SS Habib<sup>34</sup> in his study reported that diabetic patients have higher levels of Lp(a) and hsCRP. Diabetic patients with poor glycemic subjects have significantly higher hsCRP levels compared to those with good glycemic control and there is no effect of glycemic control on Lp(a) levels. Our results are in accordance with few other studies.<sup>35,36</sup> Poorly controlled diabetes mellitus is associated with high Lp(a) levels and this metabolic abnormality contributes to elevated coronary risk in diabetic individuals. According to few hypotheses there is defect in the clearance of the apoprotein B-100 in diabetic individuals. Few say decrease in LDL-C in cellular metabolism in diabetes mellitus is proposed to be due to glycation of LDL particle and LDL receptors.<sup>35</sup> In our study there is no significant association of Lp(a) with glycemic control which is in accordance with Smaoui et al.<sup>37</sup>

In our study there was significant positive correlation of HbA1c with FBS, TGs hsCRP and TG/HDL which are significantly associated with CVD risk factors. The findings by Habib<sup>30</sup> and Heller<sup>7</sup> showed that positive correlation of Lp(a) with TC and LDL-C but not with TGs and HDL-C. Study by Elizabeth et al<sup>38</sup> LDL and HDL cholesterol significantly associated with HbA1c. HDL-C was inversely

associated with HbA1c and LDL-C positively associated with HbA1c in diabetic patients.

## Conclusion

Increased levels of Lp(a), hsCRP and dyslipidemia in diabetic patients compared to healthy controls. FBS, TG, HDL-C and hsCRP are positively correlated with HbA1c. Thus Lp(a) and hsCRP evaluation may help in early cardiovascular risk prediction when used in addition to other traditional lipid parameters in diabetic patients. Poor glycemic control subjects have significantly higher hsCRP and TGs compared to good glycemic controls. There is no effect of glycemic control on Lp(a) levels, hence Lp(a) is an independent risk factor for CAD in diabetic patients.

**Limitation of the Study:** Small sample size.

**Further Scope of the Study:** Genetic factor should be taken into consideration while estimating the Lp(a) levels.

**Conflict of Interest:** There is no conflict of interest among the authors.

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**How to cite this article:** Kavitha MM, Ambekar JG, Dongre N, Kashinakunti SV. Role of serum lipoprotein (a) in type 2 diabetes mellitus and its association with glycemic control. *Int J Clin Biochem Res.* 2018;5(3):435-440.