

## Lipoprotein (a) is Associated with Basal Insulin Levels in Patients with Type 2 Diabetes Mellitus

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### Summary

**Background:** It has not been clearly established whether insulin resistance/deficiency leads directly to atherogenesis or through its association with other risk factors such as Lipoprotein(a) [Lp(a)].

**Objective:** This project aimed at studying the association between basal Insulin, Lipids and Lipoprotein(a) levels in Patients with Type 2 diabetes mellitus.

**Methods:** Fasting blood samples were analyzed for Insulin, Lipoprotein(a), total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), glucose and glycosylated hemoglobin (HbA1c) levels in 60 patients with type 2 diabetes mellitus (DM) and 28 healthy subjects. We divided patients into two groups based on basal insulin levels:  $\geq 10 \mu\text{IU/ml}$  and  $< 10 \mu\text{IU/ml}$ .

**Results:** Insulin levels were higher in diabetic versus control individuals [ $p < 0.05$ ]. TC ( $p < 0.01$ ), LDL-C ( $p < 0.05$ ), TC/HDL ratio ( $p < 0.01$ ) and TG levels ( $p < 0.05$ ) were higher and HDL-C levels were significantly lower ( $p < 0.001$ ) in both diabetic groups as compared to control. Lp(a) levels were significantly higher in both diabetic groups, when compared to the control group. Lp(a) levels were significantly lower in diabetics with basal insulin  $\geq 10 \mu\text{IU/ml}$  when compared to those with basal insulin  $< 10 \mu\text{IU/ml}$  ( $p < 0.05$ ). Regression analysis revealed a significant relationship of Lp(a) with insulin levels ( $r = 0.262$ ,  $p < 0.05$ ) and Insulin Glucose ratio ( $r = 0.257$ ,  $p < 0.05$ ).

**Conclusion:** Lp(a) levels correlate inversely with insulin levels in type 2 diabetic patients. Lp(a) may be one of the cardiovascular risk factor in type 2 diabetic patients with longer duration of dm. (Arq Bras Cardiol 2009;93(1):25-30)

**Key words:** Diabetes mellitus; dyslipidemias; lipoprotein (a), insulin.

### Introduction

Among the most common chronic disorders of modern times, diabetes mellitus (dm) remains unique because of its multisystem ramifications. The combination of hypertension, dyslipidemia, insulin resistance, hyperinsulinemia, glucose intolerance and obesity, particularly central obesity, has been termed "metabolic syndrome"<sup>1,2</sup>, which is a powerful determinant of type 2 DM and cardiovascular disease<sup>3</sup>.

Patients with type 2 DM have defects in insulin secretion in response to a glucose load and resistance to insulin action<sup>4,5</sup>. Three phases can be recognized in the pathogenesis of type 2 dm<sup>4,6,7</sup>. In the first phase, plasma glucose remains normal despite insulin resistance because insulin levels are elevated. In the second phase, insulin resistance worsens despite elevated insulin concentration and glucose intolerance manifests as postprandial hyperglycemia. In the third phase, insulin secretion decreases, with progressive loss of beta cells<sup>8</sup>.

Plasma insulin concentrations are determined by both insulin resistance and insulin secretion.

Insulin resistance best correlates with metabolic abnormalities and is linked to the development of cardiovascular disease in patients with type 2 diabetes<sup>9</sup>.

Hyperinsulinemia and insulin resistance have been associated with coronary artery disease (CAD), type 2 DM, dyslipidemia and hypertension. Insulin resistance has been proposed as an independent risk factor for cad<sup>10</sup>.

Lp(a) has been reported to be an independent risk factor for premature CAD and other thromboembolic disorders<sup>11</sup>. 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<sup>12,13</sup>.

The present study aimed at studying the association between basal insulin levels, lipids and lipoprotein(a) concentrations in patients with type 2 diabetes mellitus.

### Methods

This study was carried out at the department of physiology, army medical college, rawalpindi. This study was approved by the army medical college ethics review board. Sixty patients

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with type 2 DM were selected as per selection criteria and 28 non-diabetic, age and sex-matched healthy individuals were selected for the control group.

The patients participating in the study were diagnosed as having type 2 DM; thirty-two patients were males and twenty-eight were females. Their height was measured in centimeters with patients barefoot and weight was measured in kilograms with patients wearing light clothes.

Clinical information, date of the diagnosis and medical history were obtained through the review of medical files and patients' interviews. All patients presented stable metabolic conditions. Patients presenting any disease that could affect their metabolic status and the parameters studied such as nephrotic syndrome, acute or chronic renal failure, thyroid disorders, acute infections, stroke, diabetic ketoacidosis and nonketotic hyperosmolar syndrome were excluded<sup>11,14</sup>. The patients with history of familial hypercholesterolemia or acute myocardial infarction were also excluded from the study<sup>15,16</sup>. The history of medication was recorded and the patients taking insulin, lipid lowering agents, oral contraceptives and steroids were also excluded<sup>17,18</sup>.

We grouped diabetic subjects based on fasting (basal) insulin concentrations in two groups: insulin levels  $\geq 10 \mu\text{iu/ml}$  and insulin levels  $< 10 \mu\text{iu/ml}$  groups<sup>7,19,20</sup>.

The subjects included in the control group were age and sex matched healthy individuals selected from the staff members of afip (armed forces institute of pathology) and army medical college. They did not present any acute infection or any metabolic or psychological disorder and had no family history of hypercholesterolemia or dm. Their lipid profiles and fasting blood glucose levels were measured, showing they had normal lipid profiles and fasting plasma glucose (fpg) levels  $< 6.1 \text{ Mmol/l}$  (110 mg/dl).

Fasting blood samples were taken from the antecubital vein and the serum was separated, separated in aliquots and then frozen at  $-70^\circ\text{C}$ . Glucose was measured through the GOD-PAP (glucose oxidase phenyl ampyrone) method, an enzymatic colorimetric method with a supplied kit (linear chemicals, barcelona, spain). Total cholesterol was measured by CHOD-PAP (cholesterol oxidase phenol ampyrone), an enzymatic colorimetric kit (linear chemicals). GPO-PAP (glycerol phosphate oxidase), an enzymatic colorimetric kit was used for serum triglycerides measurement (linear chemicals). The CHOD-PAP method was used for HDL-c and LDL-c measurement (merck systems, san antonio, TX, USA). Serum Lp(a) levels were measured immunochemically using a sandwich ELISA method with a mouse monoclonal anti-Apo(a) antibody as the solid phase antibody and a sheep anti-apo B-100 polyclonal antibody (antibody against B-100) as the detection antibody. The antibodies used in this assay identify all known isoforms of Apo(a). There was no cross-reactivity with plasminogen and LDL. The kits used were supplied by innogenetics biotechnology for health care, gent, belgium. Ion exchange resin separation method was used for estimation of glycosylated hemoglobin (stanbio glycohemoglobin, boerne, TX, USA) for which ethylenediaminetetraacetic acid (EDTA)-added whole blood was used. Insulin was measured by a chemiluminescence method, which is a sandwich assay. The

kit was supplied by diagnostic products corporation, usa and instrument used was immulite 2000. The immulite system utilizes assay-specific antibody-coated plastic beads as the solid phase, in a specifically designed test unit. The test unit serves as the reaction vessel for the immune reaction, incubation, washing and signal development. Light emission from the chemiluminescent substrate, which reacts with the enzyme conjugate bound to the bead, is proportional to the amount of analyte originally present in the sample. However, c-peptide levels were not measured in this study.

### Statistical analysis

The data were analyzed by the computer software program "statistical package for social sciences" (spss version 10). Data were expressed as means and standard error of the mean (sem). The tests applied for statistical analysis were ANOVA and bonferroni (multiple comparisons). A value of  $p \leq 0.05$  Was considered statistically significant. Spearman's correlation coefficients were also determined between basal insulin levels, insulin glucose ratio and clinical characteristics. Levels of Lp(a), insulin and insulin glucose ratio were also analyzed by linear regression analysis with 95% confidence intervals after log transformation of insulin and insulin glucose ratio.

## Results

### Clinical characteristics

Clinical characteristics of the control group and diabetic patients are shown in table 1. SBP (systolic blood pressure), DBP (diastolic blood pressure) fasting plasma glucose and hba1c were significantly higher in both groups of diabetic patients ( $p < 0.0001$ ), When compared to the nondiabetic, healthy subjects. There was a non-significant difference regarding age and BMI between the diabetic patients and the control group ( $p > 0.05$ ). Diabetics with insulin  $< 10 \mu\text{iu/ml}$  were significantly older and had longer duration of DM when compared to the patients with insulin levels  $\geq 10 \mu\text{iu/ml}$  ( $p < 0.05$ ).

### Insulin levels

Serum insulin levels were significantly higher in diabetic patients ( $16.94 \pm 3.21$ ), When compared with the nondiabetic, control subjects ( $7.88 \pm 1.01$ ) [ $P < 0.05$ ].

The serum insulin/glucose ratio, which is a marker of insulin resistance, was significantly higher in diabetic patients with insulin levels  $\geq 10 \mu\text{iu/ml}$  ( $p < 0.0001$ ) When compared to the group with insulin levels  $< 10 \mu\text{iu/ml}$ . Moreover, HOMA-ir values were significantly higher in the group with higher insulin levels, when compared to the control group ( $p < 0.0001$ ) And the diabetic patients with lower insulin levels ( $p < 0.01$ ).

### Lipid profile and Lp(a) profile

Total cholesterol ( $p < 0.01$ ), LDL-c ( $p < 0.05$ ), Total cholesterol /HDL ratio ( $p < 0.01$ ) And TG ( $p < 0.05$ ) Were significantly higher and HDL- c was significantly lower ( $p < 0.001$ ) In both groups of diabetic patients when compared to the control group.

Lp(a) was significantly higher in patients with basal insulin

< 10  $\mu$ iu/ml ( $p < 0.01$ ) And in those with insulin levels  $\geq 10$   $\mu$ iu/ml ( $p < 0.05$ ) When compared with the control group [table 2]. Lp(a) levels were significantly lower in DM patients with basal insulin  $\geq 10$   $\mu$ iu/ml, when compared to the ones with insulin levels < 10  $\mu$ iu/ml ( $p < 0.05$ ).

Insulin glucose ratio was negatively correlated with fpg ( $r = -0.49$ ,  $P < 0.001$ ) And HbA1c levels ( $r = -0.343$ ,  $P < 0.01$ ). Serum insulin levels were negatively correlated with age ( $r = -0.300$ ,  $P < 0.05$ ) And positively correlated with HDL ( $r = 0.306$ ,  $P < 0.05$ ). The logistic regression analysis revealed a significant association between Lp(a) as a dependent variable and the insulin levels as an independent variable ( $r = 0.262$ ,  $P < 0.05$ ) (Figure 1). The association with insulin/glucose ratio was also significant ( $r = 0.257$ ,  $P < 0.05$ ) (Figure 2).

## Discussion

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<sup>21</sup>.

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)<sup>11</sup>. 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 insulin, insulin glucose ratio and Lp(a) levels. A study carried out with elderly individuals also showed that fasting insulin was inversely correlated with Lp(a) levels. Lp(a) was significantly associated with tc and LDL-c, tg and Apo B. These results suggest that fasting insulin levels significantly influence LDL-c metabolism in the elderly. Although Lp(a) levels seem to be mostly genetically inherited, an indirect relation with insulin through adiposity and/or other associated lipid abnormalities cannot be ruled out<sup>22</sup>. Fasting insulin has also been shown to be inversely correlated with Lp(a) in both sexes. However, the reported coefficients were weak<sup>23</sup>.

In the later stages of type 2 DM, insulin secretion declines, with progressive loss of beta cells as well as worsening of the glycemic control<sup>12</sup>. The risk of cardiovascular mortality and morbidity also increases with longer duration of DM<sup>24</sup>.

In united kingdom prospective diabetes study (UKPDS) 9 years of follow up showed that regardless of the assigned therapy, fasting plasma glucose and HbA1c levels increased, with the increased duration of DM, and maintaining near-normal glycemia was difficult. Not even with insulin therapy

**Table 1 - clinical characteristics, glycemic status of control individuals and dm patients based on insulin levels**

	Control	Dm patients with insulin levels $\geq 10$ Miu/ml N = 26	Dm patients with insulin levels < 10 $\mu$ iu/ml n = 34
Gender M/F	15/13	13/13	19/15
Age (years)	44.54 $\pm$ 1.13	47.38 $\pm$ 2.48 *	52.88 $\pm$ 1.44
Bmi ( kg/ m <sup>2</sup> )	23.90 $\pm$ 0.39	27.47 $\pm$ 0.82 ***	26.44 $\pm$ 0.82 ¶
SBP	125.67 $\pm$ 1.53	144.42 $\pm$ 3.02 #	144.56 $\pm$ 2.30 #
DBP	77.83 $\pm$ 1.19	89.23 $\pm$ 2.01 #	85.74 $\pm$ 1.39 #
FPG (mmol/l)	5.06 $\pm$ 0.09	9.53 $\pm$ 0.66 #	10.17 $\pm$ 0.49 #
HbA1c %	4.83 $\pm$ 0.08	7.30 $\pm$ 0.30 #	7.33 $\pm$ 0.26 #
Serum Insulin ( $\mu$ IU/ml)	7.88 $\pm$ 1.01	30.74 $\pm$ 6.51 #	6.39 $\pm$ 0.42
Serum Insulin/Glucose	1.57 $\pm$ 0.22	3.99 $\pm$ 1.20 **	0.70 $\pm$ 0.06
HOMA-IR	0.90 $\pm$ 0.08	2.55 $\pm$ 0.48#	1.00 $\pm$ 0.05\$
Duration		5.60 $\pm$ 0.78 *	7.85 $\pm$ 0.94

**Table 2 - lipid and Lp(a) profile of control individuals and dm patients.**

	Controls N = 28	Dm patients with insulin levels $\geq 10$ $\mu$ iu/ml N = 26	Dm patients with insulin levels < 10 $\mu$ iu/ml N = 34
Gender M/F	15/13	13/13	19/15
Total Cholesterol (mmol/L)	4.36 $\pm$ 0.11	4.99 $\pm$ 0.20 **	4.97 $\pm$ 0.18 **
LDL Cholesterol (mmol/L)	2.73 $\pm$ 0.10	3.14 $\pm$ 0.19 *	3.16 $\pm$ 0.16 *
HDL Cholesterol (mmol/L)	1.21 $\pm$ 0.07	1.01 $\pm$ 0.05 ***	0.98 $\pm$ 0.04 #
Triglycerides (mmol/L)	1.36 $\pm$ 0.03	1.76 $\pm$ 0.19 *	1.99 $\pm$ 0.24 *
T Cholesterol/HDL	3.62 $\pm$ 0.11	5.38 $\pm$ 0.43 #	5.60 $\pm$ 0.43 #
LDL/HDL	2.27 $\pm$ 0.09	3.45 $\pm$ 0.35 ***	3.65 $\pm$ 0.34 ***
Lp(a) [mg/dL]	19.29 $\pm$ 3.54	30.62 $\pm$ 4.42 * ¶	53.87 $\pm$ 9.33 **

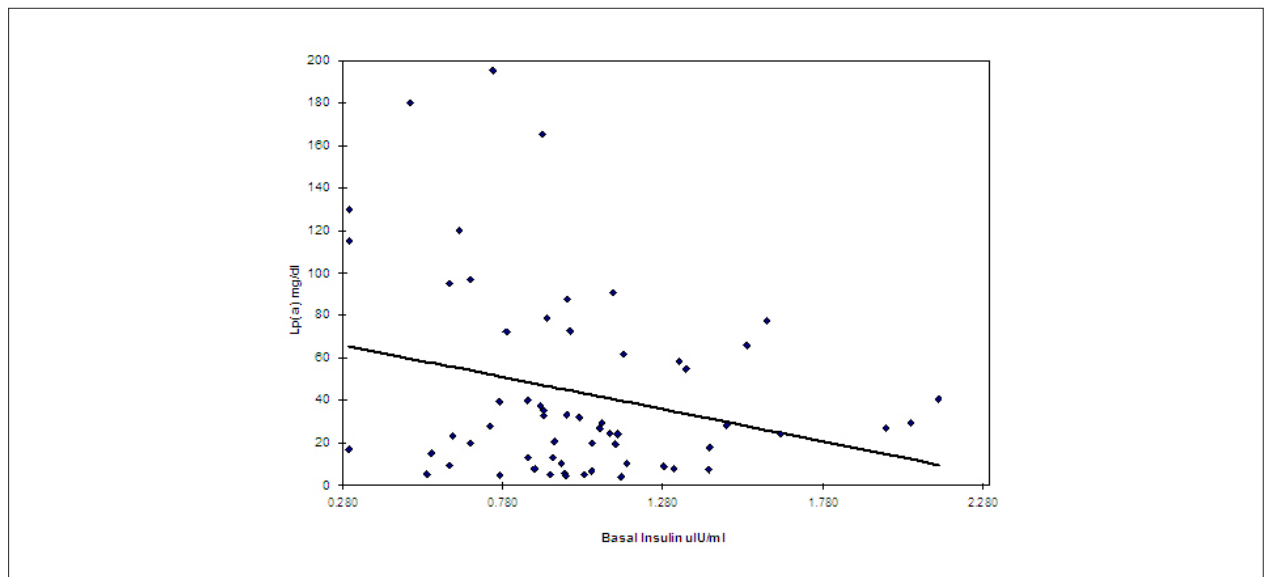


Figure 1 - Regression analysis between Lp(a) and Insulin.

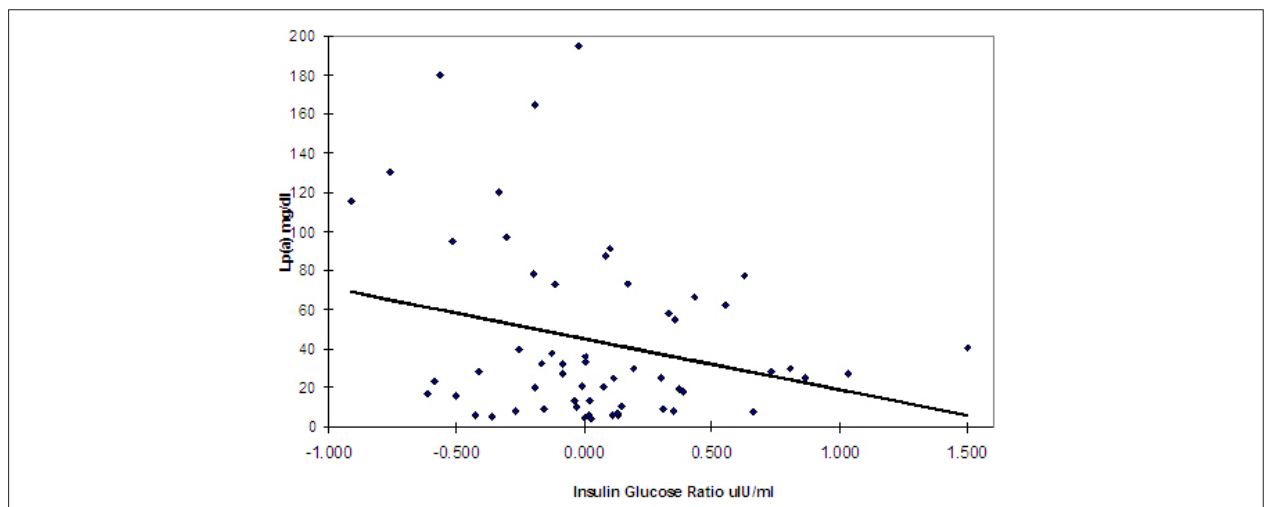


Figure 2 - Regression analysis between Lp(a) and Insulin Glucose ratio.

the therapeutic goal of near-normal glycemia was achieved due to the difficulty in treating marked hyperglycemia and the risk of hypoglycemic episodes<sup>25</sup>.

The concentration of glycosylated Lp(a) is increased in the circulation of diabetic subjects. It is evident that glycosylation prolongs the half-life of lipoproteins and likewise for Lp(a). This can lead to elevated levels of Lp(a) in diabetic individuals<sup>26</sup>.

In a study by alagozlu et al<sup>27</sup>, non-obese type 2 DM patients were studied. They were divided into 3 groups according to the type of treatment administered: i.e. Insulin, sulphonylureas and an untreated group. There was no significant difference in Apo A I, Apo B and triglyceride levels in the different groups of diabetic individuals. Hdl levels were significantly lower and Lp(a) levels were significantly higher in the untreated group. It was concluded that gaining metabolic control may also have favorable effects on Lp(a) levels<sup>27</sup>.

Plasma Lp(a) concentrations are primarily controlled at the level of the gene that encodes Apo(a), and an inverse correlation has been shown between plasma Lp(a) concentration and Apo(a) size that may arise, at least in part, from the relatively inefficient secretion of the larger Apo(a) isoforms from the hepatocytes. Additionally, the level of Lp(a) in human plasma is largely unaffected by diet, physical activity, and conventional hypolipidemic therapy<sup>28</sup>.

In a study by haffner and colleagues, no association was found between Lp(a) concentrations and insulin levels<sup>29</sup>. In most cases, diabetic dyslipidemia is preceded by hyperinsulinemia, resulting from insulin resistance. Because patients with type 2 diabetes and insulin resistance are at a markedly increased risk of atherosclerosis, and because strict control of glycemia has proved beneficial in reducing microangiopathy but not macroangiopathy, the treatment of diabetic dyslipidemia

should be aggressive<sup>30</sup>.

The insulin resistance syndrome (IRS), which is very common in subjects with type 2 diabetes, has been suggested to be one of the factors increasing the cardiovascular risk in type 2 diabetic men and predicted CHD events in elderly diabetic men<sup>31</sup>. The mechanisms by which IRS enhances atherothrombosis are largely unknown, but adverse changes, indirectly through cardiovascular risk or directly through hyperinsulinemia, may accelerate atherothrombosis<sup>32</sup>.

Lp(a) has been found to be metabolized differently from triglyceride-rich lipoproteins. Acute hyperglycemia-induced hyperinsulinemia has a different effect on plasma Apo B and Lp(a) levels in healthy subjects<sup>33</sup>. In a study by Klaus G. Parhofer et al<sup>34</sup>, 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. The major reasons for the discrepant results of the prospective studies have been attributed to the variation in study design, collection and storage of samples, methods used for statistical analysis and population differences that reflect the known ethnic variability in the distribution of Lp(a) levels and Apo(a) size isoforms<sup>35</sup>.

## Conclusions

Type 2 DM is associated with atherogenic lipid disorder and high fasting insulin/glucose ratio. Lp(a) levels inversely correlate with insulin 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.

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## Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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## Study association

This study is not associated with any post-graduation program.

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