

Lipoprotein (a) : Role in Diabetes and its Vascular Complications

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Introduction

In 1963, Kare Berg¹ discovered a new antigen lipoprotein (Lp(a)) while working with rabbits immunized with human low density lipoprotein (LDL). He found that the level of this protein was genetically determined by an autosomal dominant mode of inheritance.² During the last two decades, several studies have shown Lp(a) to be a major and independent risk factor for cardiovascular disease particularly coronary artery disease (CAD). However there is very little data regarding its association with diabetes and its other complications. This article will therefore focus on the role of Lp(a) in diabetes and review the available literature on each of the diabetic vascular complications.

Structure and Pathogenicity of Lp(a)

The Lp(a) molecule is formed by the assembly of at least two major proteins, a molecule of apo B100 covalently linked to a molecule of apolipoprotein (a) (apo(a)) by a single disulfide bridge (Fig. 1). It is structurally very similar to low density lipoprotein (LDL) in protein and lipid composition, the essential difference between the two being apolipoprotein apo(a) - a glycoprotein structurally similar to plasminogen, the precursor of plasmin.³ This striking homology endows Lp(a) with the capacity to bind to fibrin and to membrane proteins of endothelial cells and monocytes and thereby to inhibit plasminogen binding and plasmin generation. This inhibition of plasmin generation and the accumulation of Lp(a) on the surface of fibrin and cell membranes favours fibrin and cholesterol deposition at sites of vascular injury. Moreover, insufficient activation of transforming growth factor β (TGF β) due to low plasmin activity may result in migration and proliferation of smooth muscle cells into the vascular intima. These mechanisms may constitute the basis of the

atherothrombotic properties of Lp(a).

Lp(a) in Indians

The coronary artery disease in Indians (CADI) study was the first to report on the existence of high levels of Lp(a) in Asian Indians when compared to whites in the USA.⁴ The Lp(a) distribution is generally skewed in the population and hence medians are used to describe their levels and not means \pm SD. Values $>$ 30 mg/dl are considered high risk for coronary artery disease (CAD).⁵ Another study⁶ has subsequently confirmed the high levels of Lp(a) among Asian Indians living in the UK and in their siblings in India. The SHARE study from Canada also reports that the mean Lp(a) concentration is very high in South Asians (39.1 mg/dl) compared to White Canadians (17.3 mg/dl).⁷ In Singapore, Lp(a) levels were roughly twice as high in Asian Indians compared to Malays and Chinese.⁸ A study of umbilical cord levels of Lp(a) in Indian new born babies reported that Lp(a) levels were significantly higher compared to other ethnic groups like the Chinese or Malays and this seemed to reflect the adult differences in CAD rates.⁹

Studies performed in native Indians in New Delhi showed increased levels of Lp(a) in patients with atherosclerotic vascular disease.^{10,11} However another study from CMC, Vellore reported no such association.¹² We reported high Lp(a) levels in South Indian type 2 diabetic patients with CAD compared to those without CAD.¹³ Recently Lp(a) polymorphism has also been reported in Indians.¹⁴

Thus it appears that Asian Indians have significantly higher Lp(a) levels than other ethnic and racial groups with the exception of blacks. Blacks seem to have a two fold increase in Lp(a) levels as compared to any other racial group and yet have a low prevalence of CAD. This may be due to the black population having a high frequency of intermediate sized alleles of Lp(a).¹⁵ It is also possible that the adverse effects of Lp(a) among Asian Indians are augmented by the concomitant presence of high levels of triglycerides and low levels of HDL cholesterol in

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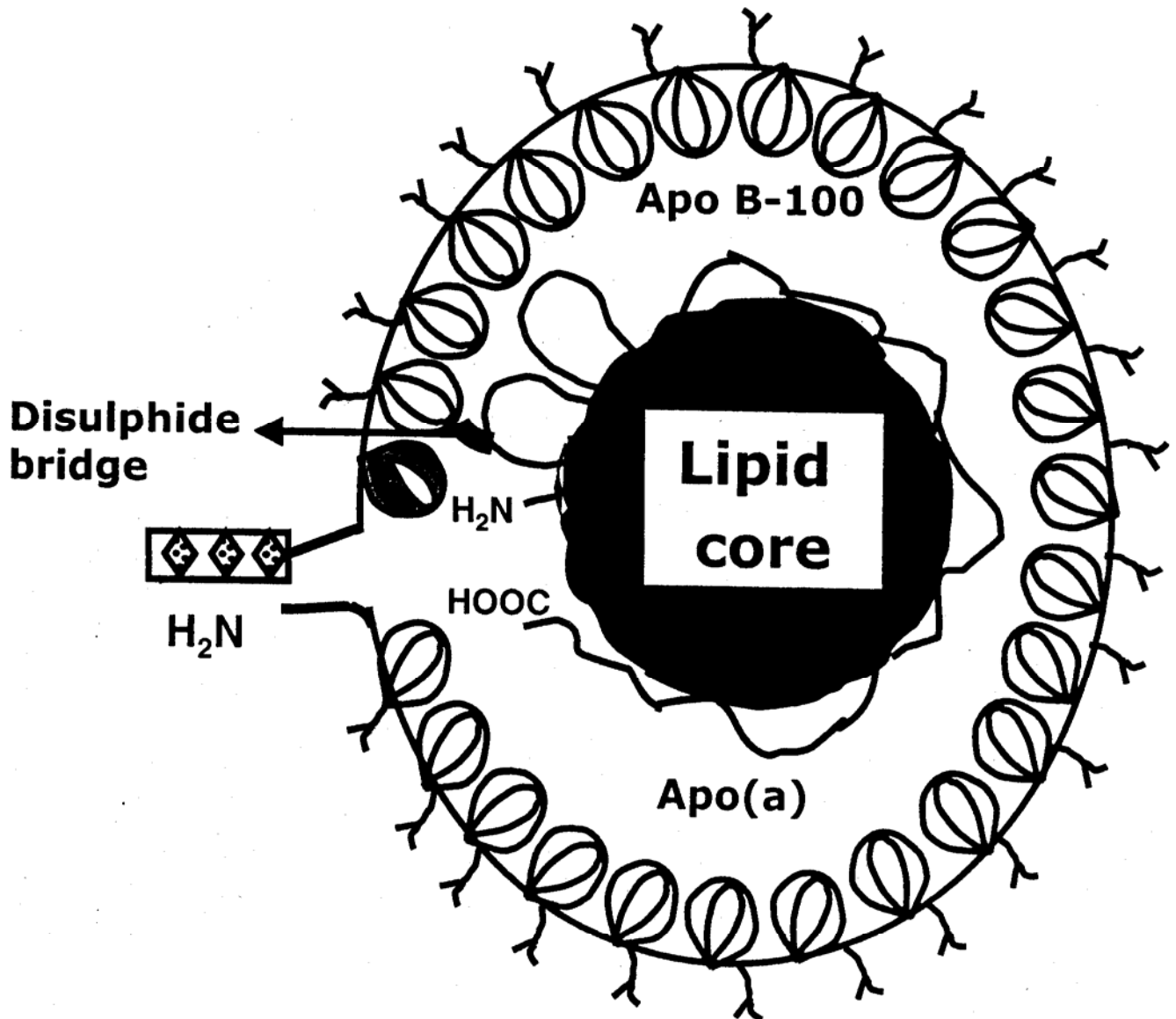


Fig. 1 : Structure of Lipoprotein(a).

the face of even modest LDL elevations.

Lp(a) and Diabetes

The literature regarding the association of Lp(a) with diabetes mellitus shows highly conflicting observations. Numerous groups have reported that Lp(a) concentrations are increased in patients with type 1 diabetes¹⁶⁻¹⁸ and that the Lp(a) concentration is related to the degree of glycaemic control.^{16,19,20} However other studies have reported that there is no association between the Lp(a) concentration and the degree of glycaemic control.^{21,22} Some studies have in fact reported that Lp(a) concentrations are not increased in type 2 diabetic patients compared to healthy control subjects.²³⁻²⁵

In a study done at an out-patient diabetes centre at Parkland, 93 white patients with diabetes mellitus were studied.²⁶ Forty nine of these patients had type 1 diabetes mellitus and 44, type 2 diabetes mellitus. All the patients with type 1 diabetes and 18 patients with type 2 diabetes mellitus were on insulin, while the others were either on sulphonylureas or diet modification only.²⁶ The study showed that the patients with poor glycaemic control (as measured by a HbA_{1c} level of $\geq 8.0\%$) had significantly higher levels of Lp(a) as compared to those patients with better metabolic control (HbA_{1c} level of $< 8.0\%$) and also the non-diabetic control subjects.

With regard to type 2 diabetes, there seems to be

general agreement that the Lp(a) concentration is not increased in type 2 diabetic patients.^{21,23-25} However there are exceptions to rule as some have reported that there is an increase in Lp(a) levels.^{18,26} Some studies even report that the Lp(a) levels are lower in diabetic patients without complications when compared to normal control subjects.²⁷

Lipoprotein(a) - relationship with insulin and oral hypoglycemic agents

To evaluate the effect of insulin therapy on Lp(a) levels in patients with type 2 diabetes mellitus, a study was taken up by Caiscas *et al*²⁸ in which they looked at 60 poorly controlled type 2 diabetic patients. Patients previously treated with oral hypoglycemic agents received one or two insulin doses and those previously on insulin received multiple insulin doses. After three months of therapy, the Lp(a) levels were measured. The study showed that the improvement of glycemic control by insulin therapy did not influence plasma Lp(a) levels in type 2 diabetes mellitus.²⁸

In another study done by Haffner *et al*,²⁹ the relationship of Lp(a) with a number of variables including the type of therapy in type 2 diabetic patients was studied. It was shown that patients on oral hypoglycemic agents had lower levels of Lp(a) as compared to those on insulin or diet therapy. Thus we conclude that OHAs seem to have some effect in the reduction of Lp(a) levels in type 2 diabetic patients. However no such effects have been found with insulin.

Lp(a) and coronary artery disease

Serum levels of Lp(a) have been shown to correlate with the presence,^{30,31} extent³² and severity³³⁻³⁵ of coronary artery disease as well as the occurrence and recurrence of myocardial infarction and cardiac deaths.³⁶⁻⁴⁰ Since stable adult levels are reached early in infancy, the pathological processes associated with elevated levels of Lp(a) start soon after birth or nearly two decades earlier than most other risk factors.^{41,42} Child-parent associations specifically looking for CHD in parents and lipid levels in the offspring in the Bogalusa Heart Study⁴³ indicate that Lp(a) is a marker of CAD in adulthood.

The PROCAM study provides independent evidence that a high Lp(a) level is a significant CAD risk factor.⁴⁴ Similar results were also obtained in the Framingham study⁴⁵ and several others.^{27,28,46,47} However the Quebec Cardiovascular Study reports that Lp(a) is not an independent risk factor for CAD but appears to increase the risk associated with other lipid risk factors.⁴⁸ Other studies report that there is no

association between Lp(a) and CAD.^{49,50} But the general agreement seems to be that Lp(a) is strongly associated with CAD and that it is a powerful independent risk factor for the same.

Studies done in native Indians as well as immigrant Indians show that the incidence, prevalence, hospitalization and mortality rates from CAD in Asian Indians is three to four times higher than in their European and American counterparts, inspite of the traditional risk factors being significantly less in Indians.⁵¹⁻⁵³ Lp(a) is shown to be a powerful independent risk factor for CAD in type 2 diabetic patients. Moreover, this association was independent of total and LDL cholesterol, HDL cholesterol, triglycerides and other cardiac risk factors. There are also some studies which do not show any association⁵⁴ but overall, Lp(a) seems to be an independent risk factor for CAD in Indians.

Lp(a) and peripheral vascular disease

A cross-sectional study of type 1 and type 2 diabetic patients showed that Lp(a) was strongly associated with peripheral vascular disease (PVD) in both subsets of patients.⁵⁵ Similar results showing an association between Lp(a) and PVD were also obtained by many other workers.^{49,56-59} There are however a few studies which report a lack of association between Lp(a) and PVD.

In Indians, PVD is less common and its association with Lp(a) is yet to be determined.

Lp(a) and cerebrovascular Disease

There is very little data on Lp(a) and stroke. In one study, Lp(a) was observed to be increased in about one-third of patients with acute cerebral ischaemia but did not correlate with the stroke characteristics or prognosis.⁶⁰ In another study⁴⁷ which included 355 type 2 diabetic patients and 145 type 1 diabetes patients, Lp(a) concentrations were found to be significantly higher in patients with cerebrovascular disease.

Lp(a) and retinopathy

The literature regarding the association of Lp(a) with retinopathy appears to be contradictory. One study showed no association between Lp(a) and retinopathy in younger or older onset diabetic subjects.⁶¹ However studies done by Marisaki and co-workers⁶² and Onuma and colleagues⁶³ show that Lp(a) is an independent risk factor for diabetic retinopathy. A study done on Korean type 2 diabetic reports that Lp(a) might play a role in the occlusion of the retinal capillaries leading to proliferative diabetic retinopathy.⁶⁴

Another study looked at the relationship between Lp(a) and diabetic complications including diabetic polyneuropathy, autonomic neuropathy, nephropathy, peripheral vascular disease, diabetic gangrene, coronary heart disease and retinopathy. No significant association was seen between Lp(a) and any of these complications except for retinopathy and this correlation was also not significant when the duration of diabetes was included in the logistic regression analysis.⁶⁵ In a more recent study,⁶⁶ Lp(a) levels and apo(a) isoforms of low molecular mass were found to be associated with the presence of proliferative retinopathy.

Thus with respect to retinopathy no definite conclusions can be drawn with regard to its association with Lp(a).

Lp(a) and nephropathy

Several studies have shown Lp(a) levels to be increased in non diabetic subjects with treated and untreated chronic renal failure.⁶⁷⁻⁶⁹ A number of studies have shown increased Lp(a) concentrations in type 1 diabetic patients with proteinuria.⁷⁰⁻⁷² On the contrary, other studies found no such association.^{73,74} In three studies of subjects with type 2 diabetes, one study found that microalbuminuria was associated with increased Lp(a) concentrations while the remaining two studies reported the opposite finding.⁷⁵⁻⁷⁷ Another study reported significant reduction of Lp(a) concentrations in a patient with nephrotic syndrome after remission.⁷⁸ The majority of these studies did not control for ethnicity. Among the few that did, sample sizes were too small to be meaningful.

Most of the studies however share a similar finding that both diabetic and nondiabetic patients with proteinuria have higher levels of Lp(a) compared to those without proteinuria. This may suggest that metabolic conditions in patients with renal disease and proteinuria may cause plasma Lp(a) to rise. However larger studies are needed to define the true role of Lp(a) in renal disease both in diabetic and non-diabetic subjects. In Indians, there are no studies to our knowledge which report on Lp(a) either with retinopathy or nephropathy.

Conclusion

In conclusion, Lp(a) has a fairly strong association with diabetic macrovascular complications and it appears to be an independent risk factor particularly for CAD. However its association with microvascular complications is far from clear and more studies need to be done. As both coronary artery disease and diabetes are very common among Indians, a number of

investigators are currently studying Lp(a) in Indian diabetics. Hence knowledge of the current status of Lp(a) in diabetes and its various complications could help to avoid confounder bias in future studies (e.g. diabetes with nephropathy would be a potential confounder as Lp(a) levels could be elevated in both these conditions).

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