Review article

Role of serum lipoprotein(a) and its gene polymorphisms in cardiovascular burden among Indians: Coincidental association or causal relationship?

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(Received: July 2022 Revised: September 2022 Accepted: September 2022)

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ABSTRACT

The increase in mortality rate due to coronary artery disease (CAD) is a major public concern among Indians. Smoking, obesity, type II diabetes are strong predisposing factors for CAD. However, the incidences of CAD in patients without these classical risk factors point to the need for identifying novel predictive biomarkers of CAD. The epidemiological studies conducted among European, African, Chinese populations, have demonstrated quite convincingly that Lipoprotein(a) is positively correlated with CAD. However, such studies are very few in the Indian context. It has been suggested that serum Lp(a) at levels more than 20mg/dL is independently associated with the risk of CAD among Indians, particularly in the young and immigrant population. Further, CAD subjects with comorbidities tend to have higher serum Lp(a) level compared to CAD subjects without any comorbidities. Genome wide association studies demonstrated that certain SNPs in the Lp (a) encoding gene (*LPA*), including rs10455872, rs3798220 and rs2266788 are more prevalent among Indians and are found to be strongly associated with CAD complications. Thus, based on the results of limited studies conducted in the Indian population so far, serum Lp(a) appears to be a strong and reliable risk factor for the development of CAD among Indians. However, the role of other factors like serum triglycerides, total cholesterol, homocysteine and CRP also need to be considered in determining CAD risk. The focus in this review is to highlight the recent studies on the role of Lp(a) in cardiovascular diseases in Indian population, particularly in the context of genetic polymorphisms.

Keywords: Coronary artery disease; lipoprotein(a); single nucleotide polymorphism.

INTRODUCTION

According to World Health Organization (WHO), cardiovascular complications are one of the leading causes of deaths worldwide with a loss of 17.9 million lives every year(1). Coronary artery disease (CAD), a type of cardiovascular disease, occurs due to the development of lesions in coronary arteries leading to minimal flow of oxygen to the heart. A number of risk factors have been implicated in CAD. They are classified as modifiable risk factors (obesity, physical inactivity, alcohol consumption, smoking, diabetes mellitus, etc.) which could be modified with effective treatment and lifestyle changes, or non-modifiable risk factors (homocysteine, C-reactive protein, gene polymorphisms etc.,) and which cannot be modified. Studies have shown that non-modifiable risk factors account for about 50% of CAD complications (2).

Lipoprotein(a) [Lp(a)], a low-density lipoprotein variant, has been proposed as an independent risk factor in the development of coronary heart disease and stroke. It has been shown that elevated levels Lp(a) in blood plasma is an inherent trait in some individuals and it does not change due to modifications in lifestyle and environment. Thus, it is conceivable that genetic variations in the *LPA* gene that codes for Lipoprotein (a), may contribute to its elevated level in blood. Indeed, Mendelian randomization studies have demonstrated a correlation between higher Lp(a) level and ischemic heart disease, stroke, and aortic stenosis(3). Further evidence towards a role of elevated Lp(a) levels come from the observations that some individuals within a population have altered serum Lp(a) levels and inter-ethnic differences in Lp(a) levels are seen which may be considered for identifying individuals at risk of cardio metabolic diseases (4).

Although the cardiovascular burden among the Indian population has increased over the past two decades (5,6), studies on the relationship between serum Lp(a) and severity of CAD in the Indian context are limited. In this review, we discuss the structure, pathophysiology and genotypic determinants of serum lipoprotein (a), with a focus on the significance of the genotypic variants of serum lipoprotein (a) in relation to the risk of CAD in Indian population, particularly among young and immigrant Indians.

Lipoprotein(a) structure

Lipoprotein(a) was discovered by Kare Berg, a Norwegian scientist in 1963. Lp(a), synthesized by the liver, is similar to low density lipoprotein (LDL), but contains an additional glycoprotein, apolipoprotein (a),which is linked via B100 moiety of the LDL molecule through a disulphide bond (Fig1). Lipoprotein(a) protein, which is also known as apolipoprotein(a), is encoded by the *LPA* gene located on Chromosome 6. Lp(a) is structurally similar to plasminogen, a protein that plays an important role in fibrinolysis. Lp (a)/Apo(a) consists of two loop-like protein domains called Kringle IV (KIV) and Kringle V (KV). Among them, KIV has 10 subtypes that vary in number of repeats, with each repeat consisting of 114 amino acids. Several isoforms of Apo(a) proteins are present, depending on the number of KIV repeats in each of them. It was shown that there exists an inverse correlation between apo(a) protein size and Lp(a) plasma level and risk of CAD (7).

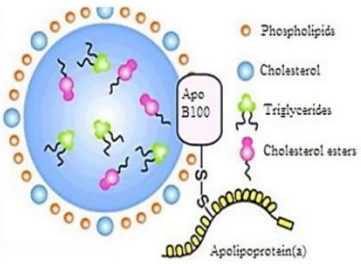

Fig. 1: Components and structure of lipoprotein(a)(8)

Lipoprotein(a) determinants

Genetic setup

Several studies have revealed that the level of serum Lipoprotein(a) is largely influenced by LPA gene variants and also depends on the size of apo(a) isoforms (9-10).

Steroidal hormone

Apart from the variation in genetic setup, other factors are also associated with increase in the level of serum Lp(a). Steroidal hormones have a role in Lp(a) concentration. A prospective study by Sowers *et al.*, among premenopausal women population demonstrated a modest association between Lp(a) and estrogen (11). In another study conducted among 3712 female CAD subjects showed that, post-menopausal group had a higher Lp(a) level compared to pre-menopausal group (12). However exact mechanism of action of steroid hormone on serum Lp(a) metabolism is not understood.

Plasma glucose

Increase in plasma glucose level can affect Lipoprotein(a) concentration and increase the risk of CAD. A study by Kotani *et al*., among female subjects showed positive correlation between Plasma glucose and higher Lp(a) concentration. It was suggested that higher plasma glucose level can cause oxidative modification of Lp (a), which facilitates Lp(a) deposition In coronary arteries, that leads to atherosclerosis (13).

Pathophysiology

Despite considerable research, the functions of serum Lp(a) and the pathological manifestations associated with increased serum Lp(a) levels are not fully understood to date. A few studies have stated that serum Lp(a) is both atherogenic and thrombogenic in nature and several mechanisms have been proposed in favour of its participation in these two processes. Serum Lp(a) concentrations are measured by its synthesis in hepatocytes and its clearance. LDL-R, Scavenger receptor Class B type I(SR-BI) are the major receptors found to play important role in Lp(a) clearance. However a study reported that familial hypercholesterolemia (FH) patients who carried a loss of function mutant LDL-R showed elevated Lp(a) levels. A study suggested that proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) has a significant role in regulating serum Lp(a) level . It was demonstrated that PCSK-9 reduces Lp(a) clearance by LDL-R degradation(14). It has been shown that an increase in homocysteine level can affect Lp(a) concentration. Homocysteine facilitates Lp(a) binding to fibrin by exposing the lysine domain of apo(a) leading to decrease in fibrinolytic activity by inhibiting tissue plasminogen activator (tPA1) which finally triggers thrombosis (15).

Oxidized phospholipids present in Lp(a) has major contributions in atherogenic properties. Pattern recognition receptors like toll like receptors (TOR-2) and CD36 recognise the Oxidized phospholipids which leads to secretion of cytokines like IL-1, IL-6, IL-8. This elicits nuclear factor (NF)kB signalling pathway which speedup immune response. Further this mechanism triggers necrosis of atherosclerotic plaque caused by macrophage apoptosis, which finally causes plaque destabilization (16).

***LPA* gene polymorphism and its impact on serum lipoprotein (a) concentration**

Genome wide association studies have identified three regions in the human chromosome, namely 6q26-27, 9p21, and 1p as regions associated with predisposition to CAD (9). Among these, the region 6q26-27, which harbours the *LPA* gene, is considered to be strongly associated with risk of CAD. Genetic and epidemiology data have identified the *LPA* gene to be highly polymorphic, varying across different populations, due to the variable number of repeats of KIV domain (17). In humans, the *LPA* gene polymorphism has been shown to have evolved due to duplication, deletion and gene conversion events of the PLG gene that codes for plasminogen. The *LPA* gene

has 78% structural similarity to the *PLG* gene(18). *PLG* gene consists of five Kringle domains namely KI, KII, KIII, KIV, and KV (Protease domain).During evolution, the *LPA* gene lost the KI, KII and KIII domains, and the KIV domain diversified into KIV-1 to KIV-10 domains (Fig.2). The KIV-2 domain contains a variable number of repeats and variation in the copy number of these repeats (from 1-40) accounts for apo(a) isoforms (19). Higher copy number variation leads to larger apo (a) isoforms and vice versa. Multiple studies have suggested that the apo(a) isoform sizes are inversely proportional to serum Lp(a) concentration(20, 21).*LPA* gene is highly expressed in hepatocytes. Studies that looked at post translational modification in apo(a) isoforms, have revealed that apo(a) isoforms with smaller sizes tend to have a shorter retention time in the endoplasmic reticulum thereby, being more efficiently secreted compared to the larger isoforms (22, 23). This mechanism clearly explains the inverse relationship between apo(a) isoforms size and Lp(a) concentration.

However, copy number variation of the kringle domain accounts for only 70% of variation in Lp(a) concentration as it has been shown that individuals with similar isoform sizes have variation in their Lp(a) serum levels (24). Besides the variable repeats in the Kringle IV domain, pentanucleotide polymorphism and single nucleotide polymorphism have been also reported to be associated with variations in Lp(a) levels.

Several single nucleotide polymorphisms (SNPs), identified across different ethnic groups, have been implicated in CVD. Among these SNPs, rs10455872 and rs3798220 located in non-coding regions of the gene, are extensively studied and have been shown to account for 30% of Lp(a) variations with a positive correlation with the risk of CVD. These two SNPs have also been shown to be inversely correlated to kringle IV2 repeats, reduced copy number variations, and small apo(a) size and higher Lp(a) levels(25-27). In addition, previous case-control studies have suggested that besides CAD, rs10455872 and rs3798220 are also associated with obstructed coronary artery number, atherosclerotic burden and calcification of aortic valve (28).

These findings highlight the fact that the presence of specific SNPs results in the expression of genetic variants in the *LPA* gene and these variants contribute to variable Lp(a) concentrations across different populations, which in turn predispose individuals to the risk of CAD.

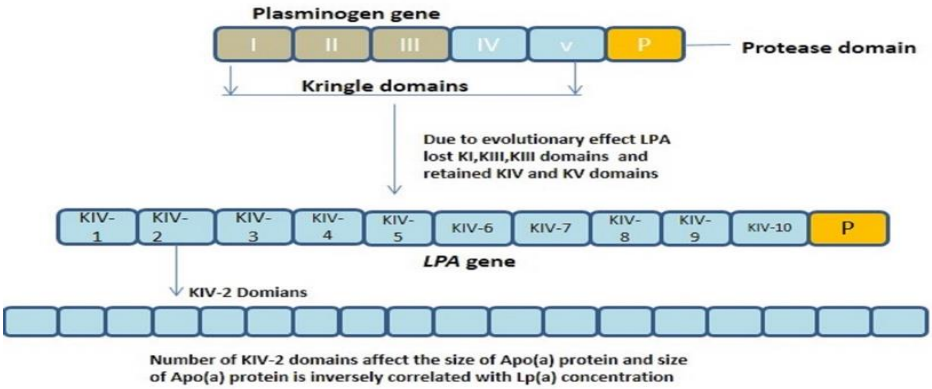

Fig. 2: Structural comparison between *PLG* and *LPA* gene and evolution of *LPA* gene from *PLG* gene (3)

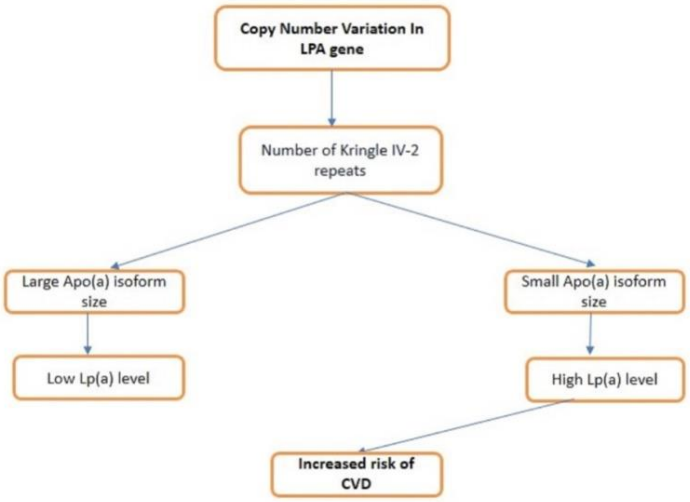

Fig.3: Schematic flow chart of relationship between apo(a) isoform size, Lp(a) level and risk of CVD

Serum Lp(a) levels in relation to CAD among the South Indian population

The prevalence of CAD burden is not uniform among the Indian population. For instance, it has been reported that South Indians have two-fold higher risk of CAD as compared to the North Indian population (29). A study conducted by Medha *et al.,* on association of Lp(a) with CAD and non-insulin dependent diabetes mellitus (NIDDM) in 158 south Indian subjects reported significantly higher mean Lp(a) level (67.12mg/dL) among NIDDM with CAD, compared to subjects with only NIDDM. In addition, the study also found a positive correlation of total cholesterol and LDL with Lp(a) concentration among NIDDM with CAD subjects (30). Moreover, the correlation between Lp(a) and angiographic lesion severity among South Indians has also been reported in the literature. In the case-control study conducted by Rajasekhar *et al.,* on 200 individuals of South Indian origin, the serum Lp(a) level was found to be higher (24.79mg/dL) among CAD subjects compared to controls (16.04mg/dL). In the same study, it was reported that subjects had coronary artery stenosis (Triple vessel disease-TVD) with a higher Lp(a) levels when compared to those with single and double vessel disease. It showed a significant positive correlation between Lp(a) level and vessel severity (31). However, in another case-control study that involved both the North and South Indian population, CAD subjects in both the populations had higher Lp(a) level compared to controls (32). Taken together, these findings strongly suggest a role of Lp(a) in increased risk of CAD among subjects with co-morbidities and the level correlated with the severity of the angiographic lesions. The salient findings of these studies are presented in Table 1.

Serum Lp(a) levels in relation to CAD among North Indian population

A study on 101 Indian patients from a tertiary care hospital in North India, revealed a significantly higher mean Lp(a) level among CAD subjects (26.83±22.09mg/dL) compared to subjects with controls (15.07mg/dL). In addition, the Lp (a) levels showed a trend for the degree of severity with moderate (27.4mg/dL) and severe CAD subjects showing higher Lp(a) levels compared to the mild CAD subjects (24.3mg/dL) (33). Earlier literature suggested Lp(a) value >30 mg/dl is an independent risk factor for CVD (34). These differences could be attributed to ethnicity, age, environmental and genetic factors.

In another study, Ashfaq *et al.,* observed elevated Lp(a) level was among triple vessel subjects (69.2±24.13mg/dL) compared to double vessel (58.01±22.98) and single vessel disease (39.28±18.41mg/dL. This study also proposed that Lp(a) level above 21 mg/dL as an independent predictor for severity of coronary atherosclerosis (35). These findings highlight that serum lipoprotein(a) with lower cut-off value (<20mg/dL) to be positively correlated with risk of CAD and Lp(a) to be an independent predictor for CAD. The salient findings of these studies are presented in Table 2.

Table 1: Study highlights, study group and findings undertaken for south Indian population

Author and year	Study type	Study group	Findings
Rajappa (2006)	Case control	1. CAD with NIDDM-53 2. NIDDM-53 only 3. Control-52	Higher mean Lp(a) level(67.12) among CAD with NIDDM group. Positive correlation between Lp(a) and total cholesterol among CAD with NIDDM
Rajasekhar (2004)	Case control	CAD-151 Control-49	CAD subjects had higher Lp(a) level(24.03 mg/dL) compared to control(16.04 mg/dL)
Geetanjali (2003)	Case control	North India(cases-133 , control-122 South India(cases-121, control-358)	CAD subjects had higher Lp(a) level(23.8 mg/dL and 31.2mg/dL) compared to control(19.5mg/dL and 17.9mg/dL) among both South and North Indians

Table 2 : Study highlights, study group and findings undertaken for north Indian population

Author (year)	Study type	Study group	Findings
Yusuf *et al.,* (2014)	Case control	Case:450 Control:150	Regression analysis showed that Lp(a) was independently associated with CAD
Ashfaq *et al.,*(2013)	Cross sectional	CAD:270 Non CAD:90	Regression analysis showed that Lp(a) above 21 mg/dL was significantly associated with CAD
Gupta *et al.,* (1996)	Cross- sectional	CAD:77 Normal coronary:24	CAD subjects had significantly higher Lp(a) compared to control subjects

CONCLUSION

The studies among the Indian population reviewed here suggests Lp(a) to be a strong risk factor for CAD, either as an independent or an associated factor with obesity, smoking, homocysteine, CRP and traditional lipids like LDL-C, TG, and TC. Variations in copy number of the encoding gene and the presence of single nucleotide polymorphisms within the coding and the non-coding regions of the gene have also been suggested to contribute to higher levels of Lp(a) and CAD risk among Indians. Studies have identified SNPs like rs10455872, rs3798220 and rs2266788 to be more prevalent and strongly associated with CAD complications. In addition, CAD subjects with comorbidities like diabetes mellitus, hypertension had a higher Lp(a) level compared to CAD subjects without any co-morbidities. Based on the studies discussed here, it appears that Lp(a) is a better predictor of CAD among the Indian population irrespective of age and ethnicity. However, there were conflicting reports too, mainly because of lack of homogeneity in assay method, and selection of subjects. Therefore, studies with large sample size and valid assay methods would be necessary to systematically assess the Lp(a) on CAD.

ACKNOWLEDGEMENT

The authors sincerely thank Dr. Malathi Shekar for editing and improving the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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