RESEARCH ARTICLE

Association of lipoprotein(a) with lipid profile and response to statin treatment in hyperlipidaemic patients

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Abstract

Objectives: To determine serum levels of lipoprotein(a) in the local population, its relationship with other parameters of lipid profile and statins' response to lipoprotein(a).

Method: The cross-sectional analytical study was conducted at the Pak-Emirates Military Hospital and Army Medical College, Rawalpindi, Pakistan, from March 2018 to March 2019, and comprised of healthy controls in group I, persons with hyperlipidaemia without medications in group II, and diagnosed cases of hyperlipidaemic on statin therapy in group III. The samples were studied using enzyme-linked immunosorbent assay for lipoprotein(a) estimation, and an automated chemistry analyser for lipid profile estimation. Data was analysed using SPSS 21.

Results: Of the 90 subjects with a mean age of 43±5 years, 30(33.3%) were in each of the three groups. Mean body mass index, total cholesterol, triglycerides and low-density lipoprotein were significantly different among the groups. Lipoprotein(a) level was not correlated with statins ($p>0.05$), but had a positive correlation with low-density lipoprotein.

Conclusion: Lipoprotein(a) was found to be raised even in the absence of dyslipidaemia, and it was controversially raised with statin therapy. Lipoprotein(a) can very well be regarded as an independent risk factor for all the known complications of hyperlipidaemia.

Keywords: Hyperlipidemia, BMI, Statins, Lipid profile, Lipoprotein(a). (JPMA 72: 1031; 2022)

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Introduction

Cardiovascular diseases have been a major source of morbidity and mortality worldwide. About 4.5% deaths and 2% disability-adjusted life years (DALYs) worldwide happen due to raised cholesterol levels.[1] Hyperlipidaemia is a leading cause of cardiovascular diseases (CVDs). It is a vast spectrum of genetic or acquired disorders that result in CVDs due to raised levels of lipids and lipoproteins in blood which accumulate in vascular walls and initiate the disease process. Lipid profile is routinely done for diagnosis and prognosis of hyperlipidaemia, which includes measuring levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL).

In the past few decades, the incidence of CVDs remained high despite low or normal lipid profile. The discovery of lipoprotein(a) (Lp[a]) in1963 by Kåre Berg, led to the recognition of its role in CVD risk independent of the lipid profile.[2]

Lp(a) consists of LDL-like particle bound with apo B-100, which, in-turn, is bound covalently via a disulfide linkage with apo-a. It is 10 times more atherogenic than LDL and its levels are determined genetically, with South Asians being the second most vulnerable population.[3]

Lp(a) was found to be a possible risk factor for the development of CVDs.[4] Lp(a) has also shown to increase relative risk of coronary atherosclerosis by 2 folds when its concentration is >30mg/dl. The relative risk increases 5 folds when LDL is high along with high Lp(a).[5] Lp(a) has been established as an acute phase reactant[4] found raised in individuals with infections, post-operative patients, and individuals with chronic disorders, like diabetes, renal failure and malignancies.[6] Increased levels of pro-inflammatory cytokines tumour necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-β), and interleukin-6 (IL-6) tend to increase gene expression for Apo(a) and, hence, there is higher concentration of Lp(a) causing oxidation of the already-formed Lp(a) and making it pathogenic.[7] Lp(a) oxidises more rapidly than LDL, making it an increased threat[7] Oxidised Lp(a) is taken up by macrophages which change into foam cells and the conventional process of atherogenesis ensues.[8] Lp(a) is a competitor for binding site on tissue plasminogen activator. It prevents activation of plasminogen, decreases fibrinolysis, stimulates secretion of plasminogen activator inhibitor-1 (PAI-1), thus promoting thrombogenesis.[9]

To date, statins were used as the first line of treatment for hyperlipidaemia. But the role of statins against Lp(a) is

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controversial. Some studies even showed that statins increased Lp(a) concentration instead of decreasing it.[10]

There is lack of baseline data regarding Lp(a) concentrations in the local population. The current study was planned to find out serum Lp(a) levels in the local population in healthy and hyperlipidaemic patients, with or without statin therapy, and to assess the response of statin therapy to Lp(a).

Patients and Methods

The cross-sectional analytical study was conducted at the Pak- Emirates Military Hospital and Army Medical College (AMC), Rawalpindi, Pakistan, from March 2018 to March 2019, after approval from the institutional ethics review board. Keeping in view the novelty of the study, unavailability of local data regarding prevalence of Lp(a) and its reported international prevalence, the sample size was calculated using an online calculator[11] by employing confidence interval (CI) 95%, margin of error 10% and estimated population proportion 37% having the chance to be exposed to high levels of Lp(a). Individuals were sampled on the basis of non-probability purposive sampling. After taking informed consent from the subjects, the sample was raised, comprising healthy controls in group I, persons newly diagnosed with or suspected of having hyperlipidemia without medications in group II, and diagnosed cases of Hyperlipidaemics on statin therapy for at least 4 weeks in group III. Individuals with liver, renal and endocrine disorders, acute infections, smokers, pregnant females and those with positive family history of CVDs were excluded. Basic data was collected using a structured proforma. Blood samples were collected. Serum was separated and stored following the standard protocol. Parameters of interest were TC, TG, HDL, LDL, Lp(a) and body mass index (BMI). TC, TG, LDL and HDL levels were calculated using fully automated chemistry analyser (Roche/Hitachi cobas c311) using homogenous enzymatic colorimetric method. Lp(a) levels were calculated by human Lp(a) enzyme-linked immunosorbent assay (ELISA) kit. For BMI, overweight was defined as BMI 23-24.9 kg/m2, while obesity was BMI >25kg/m^2.[12]

Data was analysed using SPSS 21. Data were evaluated for normality prior to the application of Pearson correlation and analysis of variance (ANOVA). Mean and standard deviation were calculated and variables were compared using ANOVA. Correlation of Lp(a) with other variables was assessed by Pearson correlation coefficient and $p<0.05$ was taken as significant.

Results

Of the 90 subjects with a mean age of 43±5 years, 30(33.3%) were in each of the three groups. Mean BMI in group I was 22.03± 2.22kg/m^2, while in group II it was 25.4±4.59kg/m^2 and in group III it was 25.9±4.12kg/m^2.

TC, TG and LDL levels were significantly different among the groups ($p<0.05$), while there was no significant difference in terms of HDL and Lp(a) ($p>0.05$).

Dyslipidaemia was most pronounced in group II, whereas statin treatment improved mean lipid profile values, and the mean Lp(a) levels were high across all the three groups (Table-1). TG level in group 1 was significantly different from group III ($p=0.03$). HDL level in group 1 was

Table-1: Mean values of lipid profile and Lipoprotein(a) in the study groups.

Parameters (mean)	Healthy individuals (n = 30)	Hyperlipidaemics without statins (n = 30)	Hyperlipidaemics with statins (n = 30)	p-value*
TC (mg/dl)	150.8 ± 0.88	243.6 ± 0.79	203.4 ± 0.72	0.001
TG (mg/dl)	95.66 ± 0.26	225 ± 1.04	137.3 ± 0.62	0.001
HDL-C (mg/dl)	62.26 ± 0.57	46.02 ± 0.42	52.2 ± 0.58	0.12
LDL-C (mg/dl)	73.86 ± 0.35	122.2 ± 0.92	109.05 ± 0.41	0.001
Lp (a) (mg/dl)	23.48 ± 7.48	18.9 ± 7.72	23.5 ± 7.76	0.30

*By ANOVA

*TC: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, Lp(a): Lipoprotein(a).

Table-2: Frequency of dyslipidaemia in the study groups.

	Healthy individuals % (n)*	Hyperlipidaemics without statins % (n)*	Hyperlipidaemics with statins % (n)*
Hypercholesterolaemia (TC)	Zero (0)	90% (27)	53% (16)
Hypertriglyceridaemia (TG)	Zero (0)	76% (23)	26% (8)
LDL-Hypercholesterolaemia (LDL-C)	6% (2)	73% (22)	53% (16)
HDL-Hypocholesterolaemia (HDL-C)	23% (7)	36% (11)	36% (11)
Hyperlipoproteinaemia (a) Lp(a)	90 (27)	70% (21)	90% (27)

*n= number of patients

TC: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, Lp(a): Lipoprotein(a).

Table-3: Correlation of Lp (a) with hyperlipidaemia and body mass index (BMI).

Independent Parameter	Dependant Parameter	Healthy individuals **(r-value)	Hyperlipidaemics without statin **(r-value)	Hyperlipidaemics with statin **(r-value)
Lp (a)	TC	0.32	- 0.16	- 0.126
	TG	- 0.101	- 0.172	-0.10
	LDL-C	0.189	0.007	0.241
	HDL- C	0.158	- 0.072	- 0.285
	BMI	- 0.247	- 0.397	- 0. 138

** By Pearson correlation

TC: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, Lp(a): Lipoprotein(a).

significantly different from group II (p=0.09), but not with group III (p=1.58). LDL level in group II was significantly different from group III (p=0.02). Lp(a) level in group 1 was not significantly different from group II (p=0.58), and it was also not significantly different between group II and group III (p=0.53). The Lp(a) level in group III was not significantly different from group I (p=0.99). Hyperlipoproteinaemia(a) was found in 27(90%) subjects in both group I and group III, while hypercholesterolaemia was found in 27(90%) subjects in group II (Table-2).

Lp(a) showed weak negative correlation with BMI, TC, TG and HDL across all the three groups, but had a weak positive correlation with LDL (Table-3).

Discussion

Although more than five decades have passed since the discovery of Lp(a) and the establishment of its independent pathological role in atherosclerotic CVDs, measurement of Lp(a) levels has still not made its way into conventional lipid profile done to evaluate CVD risk. The current study aimed at establishing some baseline data with respect to Lp(a) and its relationship with other variables of lipid profile and with statin therapy.

BMI was found to be raised in both groups II and III. A cross-sectional study in Pakistan also showed overweight and obesity in hyperlipidaemic patients.[13]

Mean TC, TG and LDL were significant in the current study. A comparative study in India on haemodialysis patients and healthy individuals indicated significant mean LDL and TC, although the levels in the current study were not as high as in the Indian population.[14] In American adults, mean TC, LDL, TG and HDL were found to be higher more than in the current study.[15] A study done in Germany showed increased TC and TG.[16] In Pakistan, hyperlipidaemia in 11.2% was reported where only TG was raised.[17] A study in Karachi reported raised levels of TC, TG and LDL.[18]

According to the current study, mean Lp(a) concentration across all the groups was 21.98±1.23 which was within the borderline risk (14-30mg/dl) category. A study in California reported Lp(a) concentrations twice than normal in people of African descent (26-45.7mg/dl) compared to Europeans (8-13mg/dl), and also found that among Asians, the Indians had elevated Lp(a) levels (8-33 mg/dl).[19] The African level was quite high in comparison with the Chinese population which may be because the Chinese have the largest isoform sizes, and, hence, lowest Lp(a) concentrations.[20] Lp(a) level in the current study indicated that it was independent of lipid profile levels and statin treatment.

When Lp(a) values were compared in each group with other variables in the current study, there was very weak correlation between the lipid profile and Lp(a). In some of the parameters, the correlation was positive and in others it was negative. The important thing was that LDL had a positive relationship with Lp(a), while the rest of the parameters had a negative correlation. A study on patients with recent myocardial infarction found raised Lp(a) levels independent of other parameters of the lipid profile.[21] A study compared Lp(a) levels in healthy subjects and diabetics, and found a positive correlation of Lp(a) with TC and LDL.[22]

In the current study, 90% individuals had hyperlipoproteinaemia(a) in group I and 90% in group III despite taking statins. Patients taking atorvastatin in one study showed decrease in Lp(a) levels by 18.73% while those taking simvastatin only showed 3.15% reduction, and rosuvastatin showed elevation in Lp(a) levels by 8.58%.[23] Another study reported 18-55% reduction in LDL by statins, 7-30% decrease in TG and an increase in HDL by 5-10%.[24] According to a literature review, statins can decrease LDL levels by 25-60%.[25] Meta-analysis of 12 statin-related trials showed a mean 8.5-19.6% increase rather than decrease in Lp(a) levels.[14] In another meta-analysis, risk of cardiovascular events increased to 43% in patients taking statins, a 12% increase from those who were not taking statins, having Lp(a) $\geq$50mg/dl in both groups, putting a controversial dimension to statin therapy.[14] A study showed that TG, TC and LDL levels dropped more with rosuvastatin.[26]

The current study demonstrated that Lp(a) levels were independent of lipid profile levels and that they were unresponsive to statin therapy. It is novel in the manner that no such study has been done to assess the relationship of Lp(a) with TC, TG, HDL and LDL in the absence of complications of dyslipidaemia. The current study, to the best of our knowledge, is the first to assess effects of statins on Lp(a) concentration in the local population in the absence of co-morbids.

In terms of limitations, due to time constraint and novelty of the topic, it was not possible to study the genetic factor behind Lp(a) concentrations in the local population or to monitor dose-related response to specific statins.

Conclusion

Lp(a) levels were found to be independent of other parameters of lipid profile, and statins failed to alter Lp(a) levels. Lp(a) is a better diagnostic and prognostic tool for hyperlipidaemia in relation to CVDs.

Disclaimer: The text is based based on MPhil thesis.

Conflict of Interest: None.

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