Correlation Between Elevated Lipoprotein(a) and Carotid Plaque in Asymptomatic Individuals

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With this acknowledgment, I conclude this thesis with renewed determination to continue striving forward.

Thank you.

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ABSTRACT

Correlation Between Elevated Lipoprotein(a) and Carotid Plaque in Asymptomatic Individuals

Background: Carotid plaque formation is a major global health issue and contributes in pathogenesis of vascular diseases. Lipoprotein(a), similar to low-density lipoprotein, may influence atherogenesis by promoting inflammation and thrombosis. However, the association between lipoprotein(a) levels and presence of carotid plaques has been debated. This study investigated the correlation between these parameters.

Methods: We retrospectively analyzed 4,896 individuals who underwent lipoprotein(a) measurement and carotid ultrasonography at Gangnam Severance Hospital between January 2017 and December 2022. The relationship between lipoprotein(a) levels and the presence of carotid plaques was evaluated using logistic regression analysis adjusted for factors such as age, sex, hypertension (HTN), dyslipidemia, and diabetes mellitus (DM).

Results: Among the 4,896 enrolled participants, those with carotid plaques were older, more likely to be men, and had a higher prevalence of HTN, DM, and dyslipidemia. The analysis showed a significant association between the presence of carotid plaques and a level of lipoprotein(a) ≥50 mg/dL in both univariable (unadjusted odds ratio=1.508, $p<0.001$, 95% confidence interval: 1.192–1.907) and multivariable (adjusted odds ratio=1.335, $p=0.029$, 95% confidence interval: 1.030–1.731) models.

Conclusion: Elevated lipoprotein(a) level emerged as an independent risk factor for carotid plaque formation, emphasizing the need for integrated risk assessment. Targeting lipoprotein(a) could enhance preventive strategies against cerebrovascular events. Therefore, further research is warranted to elucidate this disease's underlying mechanisms and evaluate therapeutic interventions.

Key words : lipoprotein(a); carotid stenosis; carotid ultrasound; dyslipidemias

I. INTRODUCTION

Carotid plaque formation represents a significant global health challenge, while the associated carotid artery atherosclerotic disease is a life-threatening condition.[1] Blood lipid levels are pivotal factors in carotid plaque development. Therefore, maintaining low low-density lipoprotein cholesterol (LDL-C) levels to reduce carotid plaque formation is crucial, and statins are used to achieve this goal. However, despite the successful lowering of LDL-C levels through statin therapy, residual risks have been increasingly recognized. The principal residual risk factor for carotid plaque formation is lipoprotein(a) [Lp(a)], a hepatically synthesized lipoprotein that shares a structural resemblance with LDL. Its formation involves the binding of apolipoprotein(a) to apolipoprotein B100, a constituent of LDL.[2] Lp(a) is considered more atherogenic than LDL due to its heightened ability to permeate arterial walls, inciting inflammatory responses and thrombus formation.[3] Genetic factors predominantly influence Lp(a) levels, while the impact from environmental factors is minimal.[4] In patients with dyslipidemia who experience a reduction in LDL-C levels due to statin therapy, Lp(a) levels resist significant decrease and may even exhibit slight elevation.[5-8]

Several studies have shown a correlation between Lp(a) levels and vascular diseases, such as myocardial infarction, stroke, and peripheral arteriopathy.[9-11] Various types of research, including epidemiological studies, meta-analyses, Mendelian randomization studies, and genome-wide association studies, have shown that elevated Lp(a) level is a risk factor for cerebrovascular and cardiovascular diseases.[12-14] Although evidence suggests that elevated Lp(a) levels contribute to the progression of carotid plaque formation, this remains a topic of debate. Several studies have suggested that high Lp(a) levels are associated with presence of carotid plaques,[15, 16] while other studies have reported no relationship between them.[17-20] Furthermore, one study on asymptomatic Japanese women reported that lower Lp(a) levels are associated with increased carotid intima-media thickness (IMT).[21]

This study aimed to determine the correlation between Lp(a) levels and carotid plaque formation in the general population.

II. SUBJECTS AND METHODS

Study subjects and data collection

We selected healthy participants who underwent both screening Lp(a) measurements and carotid ultrasonography at Gangnam Severance Hospital between January 2017 and December 2022.

Data collected from the enrolled participants included sex, age, history of hypertension (HTN), diabetes mellitus (DM), dyslipidemia, smoking, body mass index (BMI), fasting glucose, cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and LDL-C.

Data are summarized as mean values with standard deviations for continuous variables and counts with percentages for categorical variables.

Measurement of Lp(a) levels

Lp(a) levels were assessed using the latex agglutination method, which involved an anti-human Lp(a) monoclonal antibody and a commercial kit from Lp(a) Daiichi Pure Chemicals Co., Ltd.[22] This analysis was performed in conjunction with an autoanalyser (Hitachi 7600-110) to ensure accurate measurements across diverse apo(a) isoforms. The cutoff level for Lp(a) was set at 50 mg/dL.[17]

Carotid artery ultrasound

Carotid artery ultrasound examinations were performed by board-certified radiologists using various ultrasound machines, including the Philips iU22 and Philips EPIQ 5G. Longitudinal images of the bilateral proximal and distal common and internal carotid arteries were acquired separately. Carotid plaque was defined as a focal structure that encroaches into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness, or demonstrated thickness greater than or equal to 1.5 mm.[23, 24]

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26. Logistic regression analysis was used to examine the relationship between Lp(a) levels and presence of carotid plaques. Univariate analysis was conducted for the Lp(a) levels and carotid artery ultrasound results. Multivariate analysis, which included variables such as sex, age, HTN, dyslipidemia, DM, smoking, BMI, glucose, cholesterol, triglycerides, HDL-C, and LDL-C, was also performed.

III. RESULTS

A total of 4,896 participants were selected for the analysis. The mean age was 57.1±10.6 years and 65.7% were men. The prevalence rates of HTN, DM, dyslipidemia, and smoking were 30.9%, 10.7%, 28.2%, and 16.2%, respectively. The mean BMI was 24.8±3.6 kg/m^2. The mean levels of glucose, cholesterol, triglycerides, HDL-C, and LDL-C were 106.2±23.3 mg/dL, 200.8±43.4 mg/dL, 137.4±89.3 mg/dL, 55.3±13.4 mg/dL, and 122.5±36.3 mg/dL, respectively. The mean level of Lp(a) was 15.5±18.1 mg/dL, with 6.0% of participants having Lp(a) levels ≥ 50 mg/dL. Carotid artery plaques were detected in 41.8% of the participants. **(Table 1)**

When comparing participants based on the presence or absence of carotid artery plaque, those with carotid plaques were, on average, older than those without plaques (62.2±9.2 years vs. 53.6±10.2 years, respectively, $p < 0.001$). A higher proportion of men was observed among the participants with plaques than among those without plaques (70.2% vs. 62.5%; $p < 0.001$). Participants with plaques had a higher prevalence of HTN (43.9% vs. 21.5%, $p < 0.001$), DM (16.7% vs. 6.5%, $p < 0.05$), and dyslipidemia (38.0% vs. 21.1%, $p < 0.001$) than those without plaques. There was no significant difference in smoking history between the two groups ($p = 0.353$). In the group with carotid artery plaques, glucose (110.7±26.0 vs. 103.0±20.6, $p < 0.001$) and triglycerides (140.5±87.4 vs. 135.1±90.6, $p = 0.040$) levels were significantly higher, while HDL-C (54.0±12.8 vs. 56.1±13.7, $p < 0.001$) levels were significantly lower. Contrary to the expected outcomes, cholesterol (193.9±46.1 vs. 205.8±40.7, $p < 0.001$) and LDL-C (117.5±38.7 vs. 126.2±34.0, $p < 0.001$) levels were found to be significantly lower in the group with carotid artery plaques. Participants with carotid plaques had significantly higher mean Lp(a) levels compared to those without plaques (16.9±20.1 vs. 14.5±16.5, $p < 0.001$). Furthermore, a greater proportion of individuals with Lp(a) levels ≥ 50 mg/dL were found in the group with carotid plaques than in those without plaques (7.4% vs. 5.1%, $p < 0.001$). **(Table 1)**

Univariate (unadjusted) and multivariate logistic regression analysis were performed using SPSS version 26. Because of the significant correlations among cholesterol, triglycerides, and LDL-C, only the latter was included in the multivariate analysis. A stepwise method was employed to remove variables while selecting the model with the highest receiver operating characteristic (ROC) curve. The univariate logistic regression analysis revealed a significant association between Lp(a) levels ≥ 50 mg/dL and the presence of carotid plaques, with an unadjusted odds ratio (OR) of 1.508 ($p < 0.001$, 95% CI: 1.192–1.907). The multivariate logistic regression analysis was conducted, including

the variables age, sex, HTN, DM, dyslipidemia, smoking, BMI, glucose, HDL-C, LDL-C, and Lp(a) ≥ 50 mg/dL. HDL-C and BMI were removed using a stepwise method. Consequently, the final model included the following variables: age, sex, HTN, DM, dyslipidemia, smoking, glucose, LDL-C, and Lp(a) ≥ 50 mg/dL. Lp(a) levels ≥ 50 mg/dL were significantly associated with the presence of carotid plaques, with an adjusted OR of 1.318 *(p* = 0.038, 95% CI: 1.015–1.711). This indicates a persistent and significant association between Lp(a) levels ≥ 50 mg/dL and the presence of carotid plaques even after adjusting for age, sex, HTN, DM, dyslipidemia, smoking, glucose, LDL-C, and Lp(a) ≥ 50 mg/dL. **(Table 2, Fig. 1)**

Table 1. Demographic and clinical characteristics of the study population categorized by the presence or absence of carotid plaque

	Total (n = 4896) Mean ± 1SD or n (%)	**Carotid plaques (Yes)** (n:2046)	**Carotid plaques (No)** (n:2850)	***p*-value**
Age(years)	57.2±10.6	62.2±9.2	53.6±10.2	< 0.001
Sex: Men(%)	3218(65.7%)	1437(70.2%)	1781(62.5%)	< 0.001
Hypertension(%)	1512(30.9%)	899(43.9%)	613(21.5%)	< 0.001
DM(%)	526(10.7%)	341(16.7%)	185(6.5%)	< 0.001
Dyslipidemia(%)	1380(28.2%)	778(38.0%)	602(21.1%)	< 0.001
Smoking(%)	794(16.2%)	320(15.6%)	474(16.6%)	0.353
BMI(kg/m^2)	24.8±3.6	25.0±3.3	24.7±3.8	0.005
Glucose(mg/dL)	106.2±23.3	110.7±26.0	103.0±20.6	< 0.001
Cholesterol(mg/dL)	200.8±43.4	193.9±46.1	205.8±40.7	< 0.001
Triglycerides(mg/dL)	137.4±89.3	140.5±87.4	135.1±90.6	0.040
HDL-C(mg/dL)	55.3±13.4	54.0±12.8	56.1±13.7	<0.001
LDL-C(mg/dL)	122.5±36.3	117.5±38.7	126.2±34.0	<0.001
Lp(a)(mg/dL)	15.5±18.1	16.9±20.1	14.5±16.5	<0.001
Lp(a)≥50(mg/dL)	296(6.0%)	152(7.4%)	144(5.1%)	<0.001

Continuous variables are represented as mean ± standard deviation, while categorical variables are depicted as counts (n) and percentages (%).

Table 2. The results of unadjusted and adjusted logistic regression analyses

	Unadjusted OR	95% CI		*p*-value	Adjusted OR	95% CI		*p*-value
		Lower limit	Upper limit			Lower limit	Upper limit	
Age	1.097	1.089	1.104	< 0.001	1.094	1.086	1.102	< 0.001
Sex: Men	1.416	1.254	1.599	< 0.001	1.616	1.400	1.866	< 0.001
Hypertension	2.860	2.524	3.241	< 0.001	1.632	1.412	1.886	< 0.001
DM	2.881	2.385	3.48	< 0.001	1.364	1.072	1.737	0.012
Dyslipidemia	2.291	2.018	2.601	< 0.001	1.318	1.128	1.541	0.001
Smoking	0.929	0.796	1.085	0.353	1.286	1.073	1.542	0.006
BMI	1.022	1.006	1.039	0.006				
Glucose	1.016	1.013	1.019	< 0.001	1.006	1.002	1.009	0.001
HDL-C	0.988	0.984	0.992	< 0.001				
LDL-C	0.993	0.992	0.995	< 0.001	1.002	1.000	1.004	0.029
Lp(a) ≥ 50 mg/dL	1.508	1.192	1.907	< 0.001	1.318	1.015	1.711	0.038

Unadjusted odds ratios (OR) and 95% confidence intervals (CI) are presented for each variable. The adjusted OR with their corresponding 95% CIs after controlling for other variables are provided where applicable.

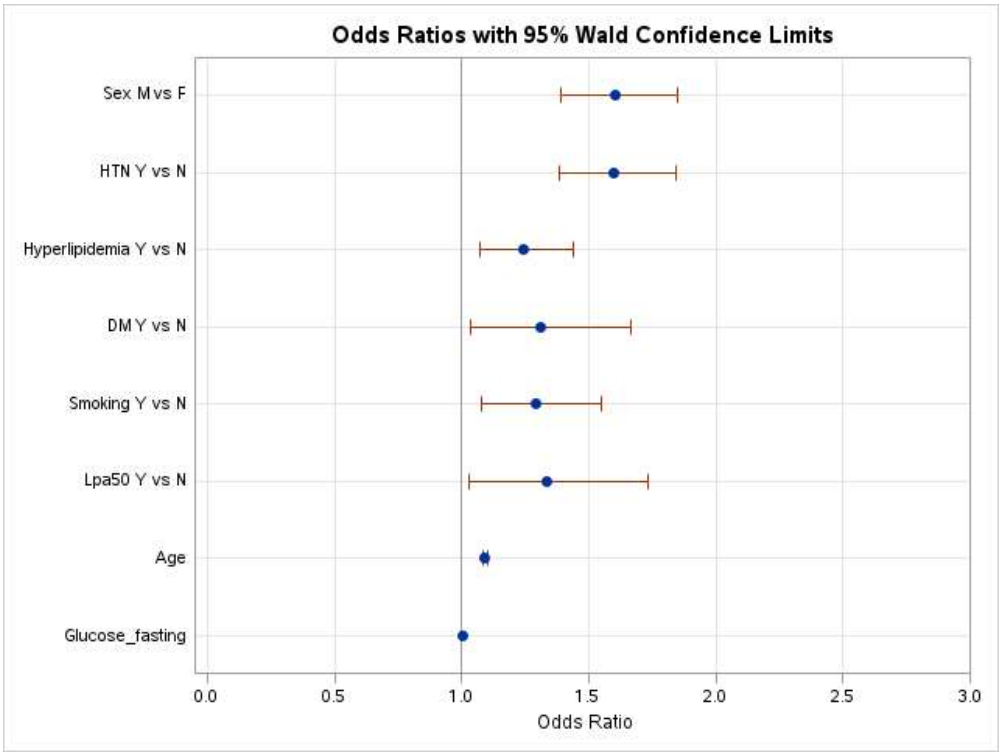

Fig. 1. Odds ratios with 95% Wald confidence intervals for various risk factors.

This figure illustrates the associations between several risk factors and the studied outcome. Odds ratios are depicted as points, with horizontal lines representing 95% Wald confidence intervals.

IV. DISCUSSION

This study aimed to elucidate the association between Lp(a) levels and carotid plaque formation. Despite the widespread use of statins to lower LDL-C levels, further decrease of cerebrovascular risk necessitates the exploration of additional risk factors such as Lp(a). Our study indicates that Lp(a) levels ≥ 50 mg/dL are significantly associated with the presence of carotid artery plaques, reinforcing the hypothesis that Lp(a) is an independent risk factor for carotid plaque formation.

Consistent with previous epidemiological studies and genetic analyses, our data support the hypothesis that Lp(a) levels are closely linked to atherogenesis. This is corroborated by our multivariate logistic regression analysis, which maintained the association of Lp(a) level with carotid plaques even after adjusting for other conventional risk factors such as age, sex, HTN, and dyslipidemia. These findings align with existing evidence on the fact that Lp(a) proinflammatory and prothrombotic properties exacerbate vascular disease pathogenesis.[25, 26]

Nevertheless, in our study, traditional risk factors such as cholesterol and LDL-C levels were lower in participants with carotid plaques. Additionally, univariate logistic regression analysis revealed a significant association between LDL-C and carotid plaque, with an unadjusted odds ratio of 0.993. These findings may be related to the high prevalence of dyslipidemia among patients with carotid plaques. Consequently, these patients are more likely to receive dyslipidemia treatment, which could explain the lower cholesterol and LDL-C levels observed. However, data on dyslipidemia medication use were lacking, which is a limitation in our study.

These results underscore the need for a paradigm shift in cerebrovascular risk assessment and disease management. Currently, statin therapy is the cornerstone of dyslipidemia treatment; however, it has little effect on Lp(a) levels. Therefore, our study further emphasizes the need for targeted therapies such as proprotein convertase subtilisin-kexin 9 (PCSK9) inhibitors or antisense oligonucleotides to reduce Lp(a) levels.[27-30]

Our study has several strengths, including a large sample size and incorporation of a comprehensive set of cerebrovascular risk factors. However, there are several limitations. First, the cross-sectional nature of the study prevented the establishment of a causal relationship between Lp(a) levels and carotid plaques. Second, data on the use of lipid-lowering medications, particularly statins, were lacking. Given the high prevalence of dyslipidemia in the group with carotid plaques, it is likely that a substantial proportion of participants were receiving statin therapy, which could have influenced Lp(a) levels. Third, our data did not include information on plaque characteristics.

Differences in plaque composition between the groups may have influenced the results. Fourth, most participants were from a single ethnic group undergoing health screening, which may have limited the generalizability of our findings.

V. Conclusion

Our analysis provides further evidence on the significant role of Lp(a) in the pathogenesis of carotid plaques. However, prospective studies are required to evaluate the effectiveness of Lp(a)-lowering therapies on reducing carotid plaque formation and incidence of cerebrovascular events. Furthermore, our findings support the inclusion of Lp(a) level assessments in the routine evaluation of atherosclerotic cerebrovascular disease risk.

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Abstract in Korean

건강검진 수검자에서 높은 지질단백(a) 수치와 경동맥 플라크의 상관관계

배경: 경동맥 플라크 형성은 전 세계적인 건강 문제로, 혈관 질환의 병태생리에 기여한다. 저밀도 지단백과 유사한 지질단백(a)은 염증과 혈전증을 촉진하여 죽상경화증에 영향을 미칠 수 있다. 그러나 지질단백(a) 수치와 경동맥 플라크 존재 간의 연관성에 대해서는 논란이 있다. 본 연구는 이들 간의 상관관계를 조사하고자 하였다.

방법: 본 연구에서는 2017년 1월부터 2022년 12월까지 강남세브란스병원에서 지질단백(a) 측정 및 경동맥 초음파 검사를 시행한 4,896명의 건강검진 수검자를 후향적으로 분석하였다. 지질단백(a) 수치와 경동맥 플라크의 존재 간의 관계를 연령, 성별, 고혈압, 이상지질혈증, 당뇨병 등과 같은 요인을 보정한 다중 로지스틱 회귀 분석을 사용하여 평가하였다.

결과: 4,896명의 수검자 중 경동맥 플라크를 가진 수검자들은 나이가 더 많고, 남성이며, 고혈압, 당뇨병, 이상지질혈증의 유병률이 더 높았다. 분석 결과, 지질단백(a) 수치가 ≥ 50 mg/dl인 경우 경동맥 플라크의 존재와 유의한 연관성이 확인되었다. 단순 로지스틱 분석에서는 오즈비 1.508, $p < 0.001$, 95% 신뢰구간: 1.192–1.907로 나타났고, 다중 로지스틱 분석에서는 오즈비 1.335, $p = 0.029$, 95% 신뢰구간: 1.030–1.731로 나타났다.

결론: 본 연구에서 높은 지질단백(a) 수치는 경동맥 플라크 형성의 독립적인 위험인자로 확인되었다. 지질단백(a)을 타겟으로 치료하는 것은 뇌혈관 질환의 예방 전략에 도움이 될 수 있다. 추후 고지질단백(a)과 경동맥 플라크에 기전을 규명하고 치료적 개입을 위한 추가 연구가 필요하다.

핵심되는 말 : 지질단백(a); 경동맥 플라크; 경동맥 초음파; 이상지질혈증