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ORIGINAL ARTICLE

Relationship between Lipoprotein(a) and Dyslipidemia in the Elderly over 60 Years

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60세 이상 노인에서 혈중 지단백(a)와 이상지질혈증의 관련성

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ABSTRACT

The relationship between lipoprotein(a) and dyslipidemia is not clear. This study was therefore undertaken to investigate the relationship between lipoprotein(a) and dyslipidemia in elderly patients over 60 years. From 2014 to 2020, a total of 2,580 adults aged 60 years or older (73.31±7.24 years, 1,954 males) were enrolled in the study. The patients had checked into a general hospital, and data were obtained for lipoprotein(a), LDL-C, TG, HDL-C, hs-CRP, HbA1c, sex, age, BMI, dyslipidemia diagnosis, and use of lipid-lowering agents. BMI and HbA1c showed no correlation with lipoprotein(a), but hs-CRP (r=0.138), LDL-C (r=0.097), HDL-C (r=-0.089), TG (r=-0.073), and age (r=0.072) were significantly correlated to lipoprotein(a). The partial correlation between lipoprotein(a) and LDL-C, which was adjusted for variables, was significant only in the male gender (r=0.158, $P<0.001$). As the odds ratio of the 4th quartile of lipoprotein(a) (OR=1.376, 95% CI=1.038~1.822) for dyslipidemia was found to be significant in this study when the level of LDL-C, the primary target, could not be reduced even by taking lipid-lowering drugs, we propose that lipoprotein(a) should also be included among the several factors considered as secondary targets. Our results indicate that studies on various lipid factors considering the sex, age, types and use of lipid-lowering agents, are warranted.

INTRODUCTION

Atherosclerosis is a common disease that causes heart attacks and strokes; it is one of the leading causes of death. The known, uncorrectable risk factors for atherosclerosis are age, male sex, and a family history of coronary artery disease, while the correctable risk factors include dyslipidemia, hypertension, diabetes, obesity, smoking, and lack of physical activity [1].

Dyslipidemia refers to disease caused by lipoprotein metabolism disorders, where the lipid levels in the blood are abnormally altered. The factors to consider as diagnostic criteria are low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and total cholesterol. According to the 2018 Guidelines on Cholesterol Management, LDL-C is the primary target for dyslipidemia treatment, while apolipoprotein B (apo B) and non-high density lipoprotein cholesterol (non-HDL cholesterol) are the secondary targets [2].

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Lipoprotein(a) (Lp(a)), a non-HDL cholesterol, is a lipoprotein consisting of apo-lipoprotein(a) and LDL-C that was first reported by Kare Berg from Norway in 1963. In the 1970s, it was reported to be related to ischemic heart disease and cerebrovascular disease [3]. Genetic and epidemiological studies have identified Lp(a) as a risk factor for atherosclerosis and related diseases, such as coronary artery disease and stroke [4]. When a group of patients was classified into quartiles according to Lp(a) level, death rates from coronary artery disease or myocardial infarction risk in the highest group was 1.26 times higher than that of the lowest group, suggesting that Lp(a) is a cardiovascular disease risk factor independent from LDL-C [5].

However, lowering blood Lp(a) levels is not currently a target for therapies since it does not reduce the risk of cardiovascular disease as would be expected from the effects of decreasing LDL-C. This is shown in several large randomized trials that evaluated therapies to lower Lp(a) levels by 20~35% (including niacin, cholesterol ester transfer protein inhibitors, and PCSK9 inhibitors) [6].

According to the analysis of five recent Mendelian randomization studies, the cardiovascular disease prevention resulting from lowering LDL-C has also been observed when Lp(a) was significantly reduced. This finding may explain why the therapeutic agents that reduce Lp(a) did not prevent cardiovascular disease. Moreover, this means that cardiovascular disease prevention can be expected in a high Lp(a)-patient group through a significant reduction in Lp(a). Interest in Lp(a) has decreased as past efforts to use therapeutic agents that lower Lp(a) levels in order to reduce the risk of cardiovascular disease have failed. This is the basis for expecting meaningful results when Lp(a) is significantly lowered. 'AKCEA-APO(a)-LRX(TQJ230)' is an antisense oligonucleotide-based therapeutic agent that lowers Lp(a) levels by up to 80% in a dose-dependent manner in phase 2 clinical trials and which is being prepared for phase 3 clinical trials. Alirocumab (brand name "Praluent") also lowers the risk of major adverse cardiovascular events by 0.6% through a 1 mg/dL reduction in Lp(a) levels, as shown in the recently published ODYSSEY OUTCOME study, suggesting that Lp(a) can serve as an independent therapeutic target.

For patients already receiving lipid-lowering drug therapy, high apo B levels have been shown to be a more accurate marker of myocardial infarction risk than LDL-C [7]. Moreover, in 2019, the European Society of Cardiology and the European Atherosclerosis Society recommend Lp(a) measurement at least once in a lifetime to identify the risk of cardiovascular disease [8].

Elevated Lp(a) levels appear to be an independent risk factor for coronary artery disease, but the importance of Lp(a) for cardiovascular disease decreases with increasing age [9]. It has been reported that elderly people over 60 years old with high levels of LDL-C have longer lifespans than those with low levels of LDL-C, indicating that LDL-C management should be adapted depending on age [10]. In one study, elderly participants (over 65 years old) were divided into Lp(a) quintiles. Men in the highest quintile had a threefold increased risk of death from stroke and vascular disease compared to the lowest, while no such relationship was revealed in women with or without estrogen use [11].

Along with LDL-C, the current cardiovascular disease risk factor and the primary target of dyslipidemia, Lp(a) is also a cardiovascular disease risk factor, but the correlation varies according to age and sex. It has been reported that an independently elevated Lp(a) level is compatible with longevity, given that the Lp(a) values of elderly patients over 75 years were similar to or much higher than those observed in the general population. Thus, it is necessary to determine the correlation between Lp(a) and the related factors of dyslipidemia, which is widely known as a risk factor for cardiovascular disease. Since domestic studies on Lp(a) are currently insufficient, numerous new studies related to Lp(a) are needed. Therefore, the aim of this study is to investigate the relationship between Lp(a) and dyslipidemia in elderly patients over 60 years of age.

MATERIALS AND METHODS

1. Participants

In addition to LDL-C, TG, HDL-C, high sensitivity C-reactive protein (hs-CRP), sex, age, body mass index (BMI), and hemoglobin A1c (HbA1c) were measured simultaneously in 6,519 elderly patients over 60 years old, who had their Lp(a) levels measured at a general hospital located in Gwangju over seven years from January 1, 2014 to December 31, 2020. Those with records of whether they were taking lipid-lowering drugs and whether they had been diagnosed with dyslipidemia were selected as participants in this study. Among them, 2,580 patients were selected for final analysis after excluding 810 patients under 60 years old and 3,129 patients with missing information. This study was approved by the Institutional Review Board of Gwangju Veterans Hospital (Human 2021-6th-No.1).

2. Methods

For the blood test index, TG (Enzymatic Color Test), LDL-C (Liquid Selective Test), and HDL-C (Accelerator Selective Test) were measured by spectrophotometry, as well as Lp(a) levels using the latex immunoturbidimetric method (AU5800, Beckman Coulter Inc., CA, USA), and hs-CRP by nephelometry (Vista500, Siemens Healthineers, Germany). HbA1c was measured using high performance liquid chromatography (HPLC) (G8 HPLC Analyzer, Tosoh Inc., CA, USA). BMI was calculated by dividing each individual's body weight by the square of their height. Those who had been diagnosed with dyslipidemia, those who took lipid-lowering drugs, and those who met one or more of the diagnostic criteria for dyslipidemia (TG≥200 mg/dL, LDL-C≥160 mg/dL, HDL-C<40 mg/dL, total cholesterol≥240 mg/dL) were defined as the dyslipidemia group [12].

3. Statistical analysis

The general characteristics of the subjects were stratified into the non-dyslipidemia group and the dyslipidemia group. Subsequently, an independent sample t-test and chi-square test were performed. Pearson correlation was analyzed to determine the correlations with each variable. Partial correlation analysis was carried out by correcting other variables and investigated by stratifying based on sex to determine the independent correlation of Lp(a) with LDL-C, the primary target for dyslipidemia treatment. Accordingly, multiple logistic regression was analyzed using models 1, 2 to identify the odds ratio of Lp(a) for dyslipidemia. For model 1, age, sex, and BMI were corrected. and for model 2, hs-CRP and HbA1c corrections were further added to model 1 and Lp(a) was divided into quartiles (1st quartile: 0.1~9.5, 2nd quartile: 9.6~17.4, 3rd quartile: 17.5~30.7, 4th quartile: 30.8~171.4). Statistical processing was carried out using the Stata/MP 14.1 program (StataCorp LLC., Texas, USA). The statistical significance level was set to a P-value of less than 0.05.

RESULTS

1. Characteristics of the participants

The total number of participants was 2,580 and their mean age was 73.40±7.27 years, their mean Lp(a) was 23.32±19.93 mg/dL, and their mean LDL-C was 92.29±31.40 mg/dL. The number of men was 1,954 (75.7%), while the number of women was 626 (24.3%). The number of lipid-lowering drug users was 1,485 (57.6%), while the number of non-users was 1,095 (42.4%). The distribution of subjects by medical department was 3,244 (49.8%) for neurology, 2,557 (39.2%) for cardiovascular, 593 (9.1%) for rehabilitation, and 125 (1.9%) for all others (Table 1).

2. Comparison of differences in each variable based on dyslipidemia

The difference between the non- dyslipidemia group and the dyslipidemia group was significant for age, sex, BMI, TG, HDL-C, LDL-C, HbA1c, and administration of lipid-lowering drugs. In contrast, the difference was insignificant for Lp(a) and hs-CRP (Table 2).

3. Correlation between factors

The variables significantly correlated with Lp(a) were hs-CRP (r=0.138), LDL-C (r=0.097), HDL-C (r=−0.089), TG (r=−0.073), and age (r=0.072), while the insignificant variables were BMI and HbA1c (Table 3).

4. Partial correlation between Lp(a) and LDL-C according to sex

A partial correlation between Lp(a) and LDL-C (r=0.144, P<0.001) was found to be significant. When sex is taken into account, this correlation was only significant for men (r=0.158, P<0.001) (Table 4).

5. Factors associated with dyslipidemia

The odds ratio of the 4th quartile of Lp(a) with the presence or absence of dyslipidemia as a dependent variable was significant in model 1 (OR=1.357, 95% CI=1.029~1.790). In model 2, where hs-CRP and HbA1c were additionally corrected for model 1, the 4th quartile of Lp(a) (OR=1.376, 95% CI=1.038~1.822) and HbA1c (OR=1.638, 95% CI=1.436~1.867) were significant, while age and hs-CRP were not. No significant changes in the

Table 1. Characteristics of study subjects (N=2,580)

Parameters	Mean±SD
Age (years)	73.40±7.27
Sex	
Male	1,954 (75.7%)
Female	626 (24.3%)
BMI (kg/m^2)	24.19±5.00
Lp(a) (mg/dL)	23.32±19.93
TG (mg/dL)	138.50±86.23
HDL-C (mg/dL)	43.74±11.48
LDL-C (mg/dL)	92.29±31.40
hs-CRP (mg/L)	7.52±22.27
HbA1c (%)	6.22±1.12
Statin use	
Yes	1,485 (57.6%)
No	1,095 (42.4%)
Department	
Neurology	3,244 (49.8%)
Cardiovascular	2,557 (39.2%)
Rehabilitation	593 (9.1%)
Other	125 (1.9%)

Data are presented as mean±SD or number (%).
Abbreviations: BMI, body mass index; Lp(a), Lipoprotein(a); TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; HbA1c, Hemoglobin A1c; Statin, Intake lipid-lowering agents.

Table 2. Comparison of differences in each variable based on dyslipidemia (N=2,580)

Parameters	Dyslipidemia		P-value
	No (N=533)	Yes (N=2,047)	
Age (years)	74.17±7.75	73.20±7.12	0.006
Sex			<0.001
Male	369 (69.2)	1,585 (77.4)	
Female	164 (30.8)	462 (22.6)	
BMI (kg/m^2)	23.36±5.41	24.41±4.87	<0.001
Lp(a) (mg/dL)	22.10±19.08	23.63±20.14	0.113
TG (mg/dL)	98.77±38.32	148.84±92.04	<0.001
HDL-C (mg/dL)	51.91±10.09	41.62±10.85	<0.001
LDL-C (mg/dL)	97.59±24.26	90.91±32.88	<0.001
hs-CRP (mg/L)	7.9±23.96	7.42±21.81	0.658
HbA1c (%)	5.88±0.86	6.31±1.16	<0.001
Statin use			<0.001
Yes	0 (0)	1,485 (72.6)	
No	533 (100)	562 (27.4)	

P-values were calculated by t-test or chi-square test.
Data are presented as mean±SD or number (%).
Abbreviations: See Table 1.

Table 3. Correlation of each variable (N=2,580)

Parameters	1	2	3	4	5	6	7	8
1. Lp(a)	1							
2. Age	0.072**	1						
3. BMI	−0.014	−0.172**	1					
4. hs-CRP	0.138**	0.199**	−0.047*	1				
5. TG	−0.073**	−0.192**	0.141**	−0.049*	1			
6. HDL-C	−0.089**	−0.008	−0.075**	−0.184**	−0.187**	1		
7. LDL-C	0.097**	−0.070**	−0.008	−0.021	0.269**	0.142**	1	
8. HbA1c	−0.029	−0.108**	0.096**	−0.021	0.147**	−0.068**	−0.014	1

Data were calculated by Pearson's correlation coefficient.
*P<0.05, **P<0.01.
Abbreviations: See Table 1.

odds ratio or significance of Lp(a) were found between model 1 and model 2, but the odds ratio and coefficient of determination were slightly increased (Table 5).

DISCUSSION

Lp(a) contributes to the arteriosclerosis process as follows. The structure of apolipoprotein(a) is similar to that of plasminogen and tissue plasminogen activator, enabling competition with plasminogen for binding sites to induce decreased fibrinolysis. Moreover, Lp(a) stimulates the secretion of endothelial plasminogen activator inhibitor-1 to induce thrombogenesis [13, 14]. The half-life of Lp(a) is approximately 3~4 days [15], but absorption through the LDL-C receptor is not a major pathway of Lp(a) metabolism. The mechanism and site of catabolism are little known [1, 16] but the role of the kidneys in blood Lp(a) clearance has been confirmed [2].

Table 4. Partial correlations of Lp(a) with LDL-C by sex (N=2,580)

Parameters	r	*P*
Total	0.144	<0.001
Male (N=1,954)	0.158	<0.001
Female (N=626)	0.065	0.104

P-values were calculated by partial-correlation analysis adjusting for age, BMI, TG, HDL-C, hs-CRP, HbA1c.
Abbreviations: See Table 1.

When troponin-I was added to the institutional inspection items as a continuous variable related to cardiovascular disease, the total number of participants was reduced by 80%, thus, hs-CRP, which has a relatively high test frequency, was added. For hs-CRP less than 2 mg/L, no significant risk of cardiovascular disease was observed at any Lp(a) level, however, when accompanied by an increase in Lp(a) above 2 mg/L, a significant cardiovascular risk was found [17].

Although it was not significant in the comparison of differences in each variable based on dyslipidemia, the mean value of hs-CRP, which is well known as an indicator of cardiovascular disease, was found to be lower in the dyslipidemia group than in the non-dyslipidemia group. In the non-dyslipidemia group in this study, the number of lipid-lowering drug users was 0, and a previous study reported an increase in hs-CRP in the placebo user group along with a decrease in the lipid-lowering user group.

In the partial correlation analysis between Lp(a) and LDL-C by sex, the correlation coefficient increased significantly in men, but it was insignificant in women. A previous study found that an increased Lp(a) value was an independent risk factor for coronary arterial heart disease in men but not conclusive in women [18]. During pregnancy, the level of estrogen in the blood increases, and at the end of pregnancy, it reaches about

Table 5. Factors associated with dyslipidemia (N=2,580)

Variables	Model 1 (R^2=0.020)		Model 2 (R^2=0.047)	
	OR	*P*	OR	*P*
Age (years)	0.992 (0.979~1.005)	0.235	0.996 (0.982~1.010)	0.547
Sex				
Men	1		1	
Women	0.648 (0.523~0.802)	<0.001	0.638 (0.514~0.793)	<0.001
BMI	1.078 (1.046~1.111)	<0.001	1.062 (1.030~1.095)	<0.001
Lp(a)				
1st Quartile	1		1	
2nd Quartile	1.065 (0.816~1.391)	0.643	1.053 (0.803~1.381)	0.709
3rd Quartile	1.203 (0.918~1.577)	0.181	1.221 (0.928~1.608)	0.154
4th Quartile	1.357 (1.029~1.790)	0.031	1.376 (1.038~1.822)	0.026
hs-CRP			1.000 (0.995~1.004)	0.880
HbA1c			1.638 (1.436~1.867)	<0.001

P-values were calculated by multiple logistic regression.
Abbreviations: See Table 1.

100 times that of during non-pregnancy, but this level decreases rapidly after delivery. In addition, testosterone is known to decrease Lp(a) levels [19]. Although estrogen-related drugs are currently not used to treat elevated Lp(a) [20], tamoxifen has been reported to decrease Lp(a) levels, unlike raloxifene [21]. It is commonly thought that sex hormones are important regulators of plasma lipid kinetics and are responsible for sexual dimorphism in the plasma lipid profile. It has become clear that normal physiological alterations in the hormonal milieu (i.e. due to menopause or throughout the menstrual cycle) do not significantly affect plasma lipid homeostasis. But the underlying physiological modulators of plasma lipid metabolism responsible for the differences between men and women remain to be elucidated [22].

Lp(a) exhibits a relatively smaller change compared to other factors due to external influences and it is known to have a significant genetic influence. As such, it is not yet a diagnostic criterion for dyslipidemia and it is the only type of lipoprotein whose metabolic process is still unknown. In addition, since lowering Lp(a) did not significantly reduce the risk of cardiovascular disease, Lp(a) is not a primary target for cardiovascular disease therapy. Although Lp(a) has an inverse correlation with TG in the lipid profile, it plays a synergistic role with familial hypercholesterolemia in predicting the early onset and severity of coronary artery disease [23]. As such, although the relationship between Lp(a) and familial hypercholesterolemia has been consistently reported, the effect of Lp(a) on lipid profile is very complex.

The odds ratio of Lp(a) was not significant in the logistic regression analysis with the factors related to dyslipidemia, but it was significant in Model 2 and Model 3, which were corrected for TG, LDL-C, and HDL-C (Table 5). Although Lp(a) was considered to be a genetically fixed level, according to a given condition, Lp(a) seems to be correlated with lipid factors as in the correlation between Lp(a) and other variables.

Although not shown in the table, the odds ratio of Lp(a) with the presence or absence of dyslipidemia as a dependent variable was marginally significant (P=0.050) in model 1 (OR=1.005, 95% CI=1.000~1.010). As the odds ratio of the 4th quartile of Lp(a) (OR=1.376, 95% CI=1.038~1.822) for dyslipidemia was found to be significant in this study, when the level of LDL-C, the primary target, could not be reduced even by taking lipid-lowering drugs, the Lp(a) should also be included among several factors to be considered as secondary targets. As previously mentioned, the European Atherosclerosis Society recommended in 2019 measuring Lp(a) at least once in a lifetime in clinical practice to identify an individual's risk of cardiovascular disease.

The lipid-lowering drugs that are usually prescribed have been reported to have an insignificant effect on Lp(a) levels, and although a meta-analysis published in 2012 suggested that atorvastatin might be helpful, most previous studies agree that several statin family drugs should be taken in combination [24]. It is clear that numerous studies are needed in relation to the change of various lipid factors according to the use and type of lipid-lowering drugs administered.

The limitations of this study are as follows. As a cross-sectional study using secondary data, it is insufficient to accurately understand a causal relationship, and because it was based on hospital blood test data, many variables, such as eating habits, smoking, physical activities, and sleeping time, could not be included [25]. Moreover, due to the age characteristics of the elderly subjects of this institution, it was impossible to determine when they may have started taking lipid-lowering drugs at other institutions. Since Lp(a) was not included in the general checkup items, healthy adults without a diagnosis could not be obtained as a control group.

If you look at the descriptive statistics of HbA1c and hs-CRP, the standard deviation is quite large, so the possibility of a patient with severe inflammation or a pre-diabetic patient is high. This was due to some very high numerical results because the 'average' was taken as the 'representative'. There were 614 (23.8%) patients with HbA1c greater than 6.5% for diabetes, and 699

(27.1%) patients with high-risk (>3.0 mg/dL) hs-CRP levels according to the American Heart Association. The highest value of HbA1c was 16.5%, and the highest value of hs-CRP was 197.35 mg/dL.

In addition to LDL-C, Lp(a) is also a known risk factor for cardiovascular disease, but patients' responses to different lipid-lowering drugs vary. Research trends show that non-HDL cholesterol is also receiving attention [26], but there are few studies on Lp(a) currently in the Republic of Korea. Therefore, numerous studies related to Lp(a) are needed.

요 약

Lp(a)와 이상지질혈증의 관계가 명확하지 않아, 본 연구는 60세 이상 노인 환자를 대상으로 Lp(a)와 이상지질혈증의 관계를 조사하고자 하였다. 2014년 1월 1일부터 2020년 12월 31일까지 7년간 한 종합병원을 내원한 60세 이상 노인 중 나이, 성별, BMI, Lp(a), LDL-C, TG, HDL-C, hs-CRP, HbA1c, 지질강하제 복용 여부, 이상지질혈증 의사진단여부 등의 기록이 있는 2,580명을 최종 분석대상자로 선정하였다. Lp(a)와의 상관성은 hs-CRP (r=0.138), LDL-C (r=0.097), HDL-C (r=-0.089), TG (r=-0.073), 나이(r=0.072) 등이 유의하였으며, BMI, HbA1c는 유의하지 않았다. 변수들을 보정한 Lp(a)와 LDL-C의 편상관관계는 남성그룹에서만 유의하였다(r=0.158, P<0.001). 본 연구에서 이상지질혈증에 대한 Lp(a)의 4사분위의 교차비(교차비=1.376, 95% 신뢰구간=1.038~1.822)가 유의하게 나타남으로써 지질강하제 복용으로도 1차 표적인 LDL-C 수준을 낮추지 못했을 때, 2차적으로 고려해봐야 할 여러 요소 중 Lp(a)도 포함되어야 한다고 판단된다.

성별, 연령, 지질강하제 복용 여부 등에 따른 다양한 지질인자들에 대한 연구들이 필요하다고 사료된다.

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