Relationship between Lipoprotein(a), Metabolic Syndrome, and Carotid Atherosclerosis in Older Japanese People

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Key Words

Lipoprotein • Carotid intima-media thickness • Metabolic disorder • Aging biology

Abstract

Background: Lipoprotein(a) [Lp(a)] or metabolic syndrome (MS) is individually considered an atherosclerotic factor. Serum Lp(a) may reportedly show the additive effects on atherosclerosis under certain particular pathologies. We do not know the association between serum Lp(a) and carotid artery intima-media thickness (CIMT) with relation to MS in older people. **Objective:** The present study aims at investigating the relationship between Lp(a) and CIMT levels in relation to MS among older subjects. **Methods:** We studied 182 Japanese subjects of ≥ 60 years (mean 72.5 years), free of cardiovascular/cerebrovascular disease. MS was based on the NCEP-ATPIII criteria with a minor modification for Japanese. The CIMT was ultrasonographically measured. **Results:** The CIMT levels were significantly greater in the MS group ($n = 60$, 1.03 ± 0.22 mm) than the non-MS group ($n = 122$, 0.96 ± 0.22 mm). Multivariate analysis, using Lp(a) levels or the product term for interaction between Lp(a) and MS, showed that age significantly and independently correlated to CIMT, along with male gender. **Discussion:** Even when

Lp(a) and MS were simultaneously considered, age was the best determinant of CIMT in this population. The mechanism of our results including weak additive effects of Lp(a) and MS among older subjects may be partly throughout aging.

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Introduction

Lipoprotein(a) [Lp(a)], a macromolecule consisting of a particle of low-density lipoprotein (LDL) linked to apolipoprotein(a), is highly homologous with plasminogen, so the characteristics may contribute to the processes of atherothrombosis. The plasma/serum Lp(a) level is considered an independent risk factor for atherosclerotic events such as cardiovascular and cerebrovascular disease [1], while conflicting data exists [2, 3]. Positive associations between Lp(a) and carotid artery intima-media thickness (CIMT), a well-established surrogate index of coronary/cerebral atherosclerosis, have reported in some [4, 5] but not all [6–8] studies.

Similarly, metabolic syndrome (MS) has recently become considered a risk factor for atherosclerosis and its sequelae such as cardiovascular and cerebrovascular disease [9, 10], and on the other hand, there have been more

recent proposals on non-significance of MS on cardiovascular and cerebrovascular mortality [11, 12]. As well, MS has been shown as a determinant of increased CIMT [13], while there is a report that CIMT is not associated with insulin resistance, which underlies MS [14]. Information about the associations between MS and atherosclerosis in various populations and conditions is eagerly waited for.

Notably, Lp(a) might promote atherosclerosis under the presence of other atherogenic pathologies and conditions. This has been reported in patients with diabetes [4, 15], severe hypercholesterolemia [16], peritoneal dialysis [17], and smoking [4]. Nevertheless, no information is available on whether the atherogenic effects of Lp(a) are enhanced by an interaction with MS. These topics are crucial especially in older people, because of their high prevalence of atherosclerotic disease. Accordingly, the aim of the present study was to examine the relationship between Lp(a) and CIMT levels in relation to MS, with a restriction to older subjects.

Subjects and Methods

A cross-sectional analysis of serum Lp(a) and CIMT levels was conducted among 182 community-dwelling Japanese subjects of ≥ 60 years old (62 men and 120 women with a mean age of 72.5 ± 7.3 [standard deviation (SD)] years) free of manifest cardiovascular and cerebrovascular disease and not on medications which affect blood pressure (BP), blood glucose and lipoprotein. There were no subjects who were on hormone replacement treatment and alcohol abusers/heavy drinkers. 122 subjects without MS (men:women = 40:82; age 73.2 ± 7.6 years) and 60 with MS (men:women = 22:38; age 71.0 ± 6.6 years) were included. The study was approved by the institutional ethics committee and each subject gave informed consent.

In the data collection, current smoking was defined as a smoker. BP values were measured in the upper arm of seated patients using a standard sphygmomanometer. Overnight fasting plasma glucose and serum triglyceride values were enzymatically measured, as well as high-density lipoprotein (HDL) cholesterol and LDL cholesterol values were measured using the homogeneous methods. Lp(a) values were determined using the latex immunoassay method. Based on the NCEP-ATPIII report [18] with a minor modification of obesity for Japanese [13], MS was defined as the presence of at least three of the following five conditions: (1) obesity (identified by body mass index [BMI] of ≥ 25 kg/m²), (2) elevated BP, (3) hypertriglyceridemia, (4) low HDL cholesterol, and (5) elevated glucose.

An ultrasonograph (SSD-900, Aloka Co., Ltd, Tokyo, Japan) with a 7.5-MHz linear type B-mode probe was used to measure CIMT, as reported previously [19]. The intima-media thickness of the common carotid artery was bilaterally measured in segments free of plaque (plaque was defined as wall thickening of at least $\geq 50\%$ compared to the adjacent thickness) with longitudinal and

Table 1. Clinical characteristics in the group with MS and without MS

Variable	Non-MS group (n = 122)	MS group (n = 60)
Age, years	73.2 $\pm$ 7.6	71.0 $\pm$ 6.6
Men/women	40/82	22/38
Smoking habit ^a , n (%)	6 (4.9)	6 (10.0)
Body mass index, kg/m ²	21.3 $\pm$ 2.7	24.5 $\pm$ 3.0**
Systolic blood pressure, mm Hg	138.3 $\pm$ 16.5	147.0 $\pm$ 14.1**
Diastolic blood pressure, mm Hg	78.7 $\pm$ 7.6	80.4 $\pm$ 7.7
Triglyceride, mmol/l	1.11 $\pm$ 0.57	1.64 $\pm$ 0.73**
HDL cholesterol, mmol/l	1.53 $\pm$ 0.40	1.32 $\pm$ 0.39**
Glucose, mmol/l	5.60 $\pm$ 1.06	6.31 $\pm$ 1.32**
LDL cholesterol, mmol/l	3.07 $\pm$ 0.74	3.29 $\pm$ 0.86
Lp(a), mmol/l	0.60 $\pm$ 0.46	0.62 $\pm$ 0.51
Median Lp(a), mmol/l	0.54	0.49
Lp(a) ≥ 0.78 mmol/l, n (%)	27 (22.1)	14 (23.3)
CIMT, mm	0.96 $\pm$ 0.22	1.03 $\pm$ 0.22*
CIMT ≥ 1.0 mm, n (%)	65 (53.3)	32 (53.3)

MS = Metabolic syndrome; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); CIMT = carotid artery intima-media thickness. Data are expressed as means $\pm$ SD.

^a Smoking habit was defined as a current smoker. A statistical significance level (non-MS vs. MS group): * $p < 0.05$, ** $p < 0.01$.

transverse scans. After three measurements of CIMT were taken at the thickest site and at two other points (10 mm upstream and 10 mm downstream from the thickest site), these averaged levels were used for analyses.

Values are given as mean $\pm$ SD. Mean levels or distribution tendencies between groups were compared using the unpaired t test or χ^2 test. Age, BMI, smoking status, LDL cholesterol, the presence of MS and Lp(a) values as explanatory variables and carotid atherosclerosis (defined as CIMT of ≥ 1.0 mm [13]) as a criterion variable were entered to a multivariate logistic regression model to estimate odds ratios after adjustment for confounders. Lp(a) levels of ≥ 0.78 mmol/l have been considered the threshold to an elevated atherosclerotic disease risk [8], so the presence of Lp(a) of ≥ 0.78 mmol/l was also substituted for Lp(a) values themselves in the same analysis. Subsequently, product term in Lp(a) and MS was used to assess interactions (effect modification) between them in the logistic models. $p < 0.05$ was considered significant.

Results

The studied subjects' clinical characteristics are shown in table 1. The mean Lp(a) level of all subjects was 0.61 ± 0.48 mmol/l. There were no differences in the median

Table 2. Logistic regression analysis for carotid atherosclerosis using the variable of crude Lp(a) values or Lp(a) ≥ 0.78 mmol/l, controlled for possible risk factors

Covariates	Odds ratios (95% CI)	p value
<i>Model 1: using the variable of crude Lp(a) values</i>		
Age	1.10 (1.05–1.16)	<0.0001**
Male gender ^a	2.24 (1.05–4.81)	0.038*
Smoking habit ^b	1.44 (0.32–6.83)	0.613
LDL cholesterol	1.01 (0.99–1.02)	0.305
MS ^b	1.19 (0.61–2.34)	0.607
Lp(a)	1.00 (0.98–1.01)	0.705
<i>Analysis for interaction between MS and crude Lp(a)</i>		
Age	1.10 (1.05–1.15)	<0.0001**
Male gender ^a	2.23 (1.04–4.78)	0.039*
Smoking habit ^b	1.35 (0.29–6.19)	0.701
LDL cholesterol	1.01 (0.99–1.02)	0.400
MS ^b $\times$ Lp(a)	1.01 (0.99–1.03)	0.535
<i>Model 2: using the variable of Lp(a) ≥ 0.78 mmol/l</i>		
Age	1.10 (1.05–1.16)	<0.0001**
Male gender ^a	2.36 (1.09–5.08)	0.029*
Smoking habit ^b	1.18 (0.26–5.42)	0.836
LDL cholesterol	1.00 (0.99–1.02)	0.429
MS ^b	1.21 (0.62–2.39)	0.576
Lp(a) ≥ 0.78 mmol/l ^b	1.64 (0.75–3.56)	0.213
<i>Analysis for interaction between MS and Lp(a) ≥ 0.78 mmol/l</i>		
Age	1.10 (1.05–1.16)	<0.0001**
Male gender ^a	2.17 (1.02–4.66)	0.046*
Smoking habit ^b	1.18 (0.25–5.55)	0.832
LDL cholesterol	1.00 (0.99–1.02)	0.494
MS ^b $\times$ Lp(a) ≥ 0.78 mmol/l ^b	3.02 (0.75–12.19)	0.121

Data show the results of multivariate logistic regression analysis. Carotid atherosclerosis is defined as carotid artery intima-media thickness of ≥ 1.0 mm. CI = Confidence interval; LDL = low-density lipoprotein; MS = metabolic syndrome.

^a Female: 0, male: 1; ^b absence: 0, presence: 1. Age (per 1 year), LDL cholesterol (per 0.26 mmol/l), Lp(a) (per 0.26 mmol/l in Model 1): continuous variable.

A statistical significance level: * $p < 0.05$, ** $p < 0.01$.

and mean Lp(a) levels as well as frequency distributions of Lp(a) of ≥ 0.78 mmol/l between groups with versus without MS, respectively. The mean CIMT level of all subjects was 0.97 ± 0.22 mm, and the levels were slightly but significantly higher in the group with MS than that without MS. The prevalence of carotid atherosclerosis, defined by CIMT levels of ≥ 1.0 mm, was similar between groups with and without MS.

Logistic regression analysis using crude Lp(a) values demonstrated age to be significantly associated with

CIMT, along with male gender (table 2: model 1). When the product term for interaction between Lp(a) values and MS was used, we did not detect the effect modification by the interaction. Logistic analysis using the presence of Lp(a) of ≥ 0.78 mmol/l demonstrated age and male gender to be significantly associated with CIMT (table 2: model 2). When the product term for interaction between Lp(a) of ≥ 0.78 mmol/l and MS was used, the term seemed to have more enhanced effects on CIMT than a sole variable, but the effect modification remained insignificant.

Discussion

In our study, it was unlikely that both Lp(a) levels and MS showed remarkable interactions on CIMT, even if both Lp(a) and MS are considered atherosclerotic risk factors. In this situation, age was identified as the strongest contributor to CIMT, and male gender ranked second. Our study results might expand the fact that age is one of the strongest independent risk factors of carotid atherosclerosis [20] even in the aged population. Moreover, an association between CIMT and male gender was thought to agree with previous findings of a greater CIMT in men than women [6, 14].

In our simple tests, the presence of MS was associated with a higher CIMT level (which was likely consistent to earlier reports [13]), and Lp(a) was not associated with CIMT (which likely supported earlier reports [6–8]). Subsequently, however, multivariate analyses could not confirm any independent association between CIMT and both Lp(a) and MS alone, in addition to no clear effect modification by interaction of Lp(a) and MS on CIMT (this effect modification is a primary focus in our study). Although the detailed mechanism on more influence of age, than Lp(a) and MS, on CIMT remains unclear, Lp(a) and other major atherosclerotic risk factors have been suggested to be less powerful in predicting atherosclerotic risk throughout aging [6]. Furthermore, among earlier reports examining the relationship between MS and atherosclerotic disease [9–12], no associations are observed particularly in rural Japanese populations, consisting of older subjects [11, 12]: these report results may have some concern with the present study results. Additionally, other reasons for the inconsistency in the association between studies including ours might be differences in the study design and population. Our study including no subjects with any vascular events and medications (maybe recruiting the subjects with relative-

ly moderate degree of pathophysiology of MS, i.e. hypertension) can induce diminished effects on CIMT (this is given care when generalizing the results).

This study also had potential limitations such as a cross-sectional design and relatively small sample size. Although insignificant in our study population, the possibility that the interaction between high Lp(a) status (the levels of ≥ 0.78 mmol/l) and MS had some enhanced effects on CIMT should be reconsidered as a future issue of sample collection. Further studies with a prospective design and larger sample size are required.

In summary, our study has disclosed that age is the best determinant of CIMT, even when both Lp(a) and MS

are considered atherosclerotic risk factors, in older Japanese people. High Lp(a) levels and MS had additive but insignificant effects on CIMT in this population. The mechanism of our results may partly be throughout aging. Deeper understanding of vascular biology on aging and anti-aging strategy will be a future important challenge. Our theory calls for more studies.

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