Mini-Review

Lipoprotein(a) and Arterial Stiffness Parameters

Alexander Sorokin^a Kazuhiko Kotani^{b, c}

^aDepartment of Internal Medicine, Kursk State Medical University, Kursk, Russia; ^bDivision of Community and Family Medicine and ^cDepartment of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke, Japan

Key Words

Apolipoprotein(a) · Cardio-ankle vascular index · Lipoprotein(a) · Oxidized lipoprotein(a) · Pulse wave velocity

Abstract

Background: Circulating lipoprotein(a) [Lp(a)] and arterial stiffness are markers associated with the atherosclerotic processes. With regard to cardiovascular outcomes, the relationship between Lp(a) and arterial stiffness has not been sufficiently summarized. The present review focuses on the existing association between Lp(a) and arterial stiffness parameters. **Summary:** This review included human clinical studies that were published between 1980 and 2015. The metrics of arterial stiffness parameters, ‘pulse wave velocity’ (PWV) and ‘cardio-ankle vascular index’ (CAVI), were used for this search, which yielded only 4 cross-sectional studies on this topic. Of these 4 studies, 3 reports were based on the use of PWV, while 1 study was based on the use of CAVI. Three studies (including the study using CAVI) reported that high Lp(a) levels were positively associated with arterial stiffness. **Conclusion:** The present review indicates a positive association between Lp(a) and arterial stiffness, as assessed by PWV and CAVI. To definitively establish these findings, there is a need for further prospective outcome studies that simultaneously measure Lp(a) and the oxidative form of Lp(a) (as a pathological marker) as well as PWV and CAVI.

© 2015 S. Karger AG, Basel

Introduction

Lipoprotein(a) [Lp(a)] consists of a low-density lipoprotein (LDL)-like particle attached to apolipoprotein(a) [apo(a)]. Lp(a) exerts a unique atherothrombotic mode due to its LDL-like property and structural homology with plasminogen [1]. As a specific feature of Lp(a), its blood concentration is genetically determined by the *LPA* gene responsible for the

Kazuhiko Kotani, MD, PhD
Division of Community and Family Medicine, Jichi Medical University
3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498 (Japan)
E-Mail kazukotani@jichi.ac.jp

encoding of apo(a) [1]. The apo(a) isoform size distribution and Lp(a) levels are both recognized as markers of future events of cardiovascular disease (CVD) [2–4].

The structural and physiological changes in the arteries, as expressed by arterial stiffness, are known to be associated with CVD events [5]. Because lipoprotein metabolism is generally considered to be associated with arterial changes, it would be of great interest to know how and to what extent the arterial stiffness conditions are associated with CVD events in relation to Lp(a). With regard to metrics, pulse wave velocity (PWV) is a useful tool to evaluate arterial stiffness by measuring the pulse transit time and the distance travelled between the investigated arterial sites [6]. The PWV level reflects abnormal vascular tone, thickening of the smooth muscle, and alterations in blood viscosity [6]. Thus, PWV is reported to be a marker of future CVD events [7, 8].

Recently, the cardio-ankle vascular index (CAVI) has been used as a new metric of arterial stiffness [9]. The CAVI level differs from standard PWV in that it reflects functional arterial stiffness, without depending on blood pressure (BP) changes during the time of measurement [10, 11]. The aim of the present review is to summarize the possible association between Lp(a) and arterial stiffness as measured by PWV or CAVI.

Review Process

An English language search of PubMed/Medline and the Cochrane Library was conducted to identify reports published between 1980 and 2015. The following terms were used: lipoprotein(a), Lp(a), arterial stiffness, pulse wave velocity, PWV, cardio-ankle vascular index, and CAVI. The Medical Subject Headings (MeSH) key terms included vascular calcification, arteriosclerosis, pulse wave analysis, and cardiovascular disease. Only human clinical studies that focused on the association between Lp(a) and arterial stiffness levels were included in the review. Articles describing original investigations were also included, while editorials and letters were excluded.

For this search, the first step was performed with the combination of the following keywords: lipoprotein(a) or Lp(a), and pulse wave velocity or PWV. At the next step, an alternative definition of the cardio-ankle vascular index or CAVI was used instead of pulse wave velocity or PWV. At the final step, the following keywords were used: lipoprotein(a) or Lp(a), and arterial stiffness.

Review Results

Our search of the literature only identified 4 articles discussing this topic [11–14]. A summary of these articles is listed in table 1. All articles were reports from Japan [11–14], and all studies used a cross-sectional design [11–14]. Three reports were based on the use of PWV (brachial-ankle type [12, 13] or aortic type [14]), while CAVI was applied in only 1 study [11]. All of the reports included patients with pathologic conditions, such as hypertension [11, 13] and diabetes [12, 14]. The levels of Lp(a) were estimated using two techniques: an enzyme-linked immunosorbent assay [11–13] or the latex agglutination method [14].

We noted that there was basically a positive association between Lp(a) and arterial stiffness levels as measured by PWV and CAVI. Only 1 article, which concerned patients with nonproliferative diabetic retinopathy, did not report a significant association between Lp(a) and PWV [12]. The microvascular pathology of nonproliferative diabetic retinopathy might partly explain this result as PWV is a macrovascular marker and cannot properly reflect microvascular pathologies [12].

Table 1. Summary of the association between Lp(a) and arterial stiffness parameters

Reference, country	Design	Subject disease	Patients	Mean age, years	Mean/median Lp(a), mg/dl	Association with Lp(a)	
						PWV	CAVI
Kotani [11], 2013, Japan	cross-sectional	hypertension (female)	72	64.3	5.0		CAVI = 8.2 (positive association)
Funatsu [12], 2009, Japan	cross-sectional	nonproliferative diabetic retinopathy	106	57.2	18.6	baPWV = 18.5 m/s (insignificant data)	
Morishita [13], 2009, Japan	cross-sectional	hypertension	69	about 65	ND	baPWV; ND (positive association)	
Wakabayashi [14], 2006, Japan	cross-sectional	diabetes	97	71	16.5	aortic PWV = 11.1 m/s (positive association)	

ba = Brachial-ankle; ND = no data described.

Discussion

The present review indicated a positive association between Lp(a) and the arterial stiffness levels as assessed by PWV and CAVI. Lp(a) and arterial stiffness are predictive of CVD events [2–5, 7, 8]; therefore, a high Lp(a) level can be involved in CVD events through an association with arterial stiffness, although more evidence is necessary for establishing the finding. On the other hand, since this relationship has only rarely been summarized up to date, this review is valuable for confirming our existing knowledge.

Lp(a) is known to exert atherothrombotic effects due to its LDL-like property and structural homology with plasminogen [1]. In particular, like LDL, Lp(a) invades the vascular wall, leading to inflammatory and oxidative reactions [15, 16]. Of note, Lp(a) is a cargo carrier for oxidized phospholipids [17], which can promote the progression of atherosclerosis by mediating macrophage apoptosis and foam cell formation, inducing vascular inflammation [18]. Lp(a) also binds to monocyte chemoattractant protein-1, an inflammation-related molecule [19]. Induced monocyte trafficking in the vascular wall activates an inflammatory reaction. These arterial conditions inhibit the process of reverse cholesterol transport and then aggravate lipid accumulation in the arterial wall [20]. Lp(a) also inhibits fibrin clot lysis, leading to vascular thrombotic damage [21]. These findings would account for the positive association that was observed between Lp(a) and arterial stiffness in the present review.

Recently, there have been advances in the measurement of arterial stiffness. The clinical importance of CAVI has been shown in various ethnic populations [22, 23] and in disease conditions including hypertension [24], diabetes [25], coronary disease [26], and stroke [27]. A specific feature of the CAVI metric is its nondependence on BP changes during the time of measurement [9, 10]. Thus, the study results based on CAVI [11] seem to further strengthen the finding of a positive association between Lp(a) and arterial stiffness.

Given the importance of oxidized phospholipids in Lp(a), the measurement of Lp(a)-related markers has been considered [11, 13]. We have developed a measurement for a form of Lp(a) that is modified by oxidation, termed ‘oxidized Lp(a)’ [oxLp(a)] [11]. Although the determination of Lp(a) is predominantly genetic [Lp(a) levels are generally unchanged by common environmental factors] [1, 28], Lp(a) is modified, and, thus, oxLp(a) provides a more relevant reflection of the ongoing pathologic conditions [11]. The accumulation of Lp(a) and

oxLp(a) in plaques has been observed to differ in specific immune expression studies [16], and oxLp(a) has been shown to have a stronger positive correlation with PWV and carotid or coronary atherosclerosis than native Lp(a) [13, 29]. Of interest, the positive correlation between oxLp(a) and CAVI was also stronger than that between Lp(a) and CAVI [11]. The association between oxLp(a) and arterial stiffness, in association with the CVD outcomes, should be further investigated in the future.

Limitations and Perspectives

There are several limitations associated with the studies that we reviewed. The search criteria yielded a limited number of human clinical studies, and the selected studies were conducted with a relatively small sample size. These studies were based on the cross-sectional design; that is, there were no longer-term prospective cohort studies with CVD outcomes. As arterial stiffness is affected by multiple CVD-related factors, the multivariate adjustment must be made to show the results. Although the adjustment was used in most of the studies [11, 12, 14], the adjusted factors might not always be perfect (i.e., age and systolic BP [11]; not described in detail [12]; age, gender, diabetic retinopathy, and lipid-lowering drug use [14]). Moreover, while there are known differences in the sizes of apo(a) isoforms and CAVI levels of different ethnic groups [22, 23, 30], there have been no interethnic studies on this topic. Additionally, there are no specific pharmacological interventions available to achieve the independent lowering of Lp(a), although promising therapies, such as proprotein convertase subtilisin/kexin type 9 and cholesteryl ester transfer protein inhibitors, which can reduce the Lp(a) level [31, 32], have recently emerged. To date, there are no intervention studies determining the specific effects of the lowering of Lp(a) on the arterial stiffness parameters. These limitations should be addressed in future studies.

Conclusions

In summary, from the findings of the present review, a high Lp(a) level could be found to be associated with arterial stiffness as assessed by PWV and CAVI. To establish the finding definitively, prospective outcome studies are further needed, which simultaneously measure Lp(a) and the oxidative form of Lp(a) (as a pathological marker) as well as PWV and CAVI.

Disclosure Statement

The founding played no relevant role in the design and presentation of the review work.

References

- 1 Utermann G: Genetic architecture and evolution of the lipoprotein(a) trait. *Curr Opin Lipidol* 1999;10:133–141.
- 2 Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG: Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;301:2331–2339.
- 3 Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M: Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;361:2518–2528.
- 4 IBC 50K CAD Consortium: Large-scale gene-centric analysis identifies novel variants for coronary artery disease. *PLoS Genet* 2011;7:e1002260.

- 5 Vlachopoulos C, Aznaouridis K, Stefanadis C: Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;55:1318–1327.
- 6 Safar ME: Arterial aging – hemodynamic changes and therapeutic options. *Nat Rev Cardiol* 2010;7:442–449.
- 7 Nilsson PM, Khalili P, Franklin SS: Blood pressure and pulse wave velocity as metrics for evaluating pathologic ageing of the cardiovascular system. *Blood Press* 2014;23:17–30.
- 8 Liao J, Farmer J: Arterial stiffness as a risk factor for coronary artery disease. *Curr Atheroscler Rep* 2014;16:387.
- 9 Shirai K, Hiruta N, Song M, Kurosu T, Suzuki J, Tomaru T, Miyashita Y, Saiki A, Takahashi M, Suzuki K, Takata M: Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: theory, evidence and perspectives. *J Atheroscler Thromb* 2011;18:924–938.
- 10 Kotani K, Miyamoto M, Taniguchi N: Clinical significance of the cardio-ankle vascular index (CAVI) in hypertension. *Curr Hypertens Rev* 2010;6:251–253.
- 11 Kotani K, Yamada S, Yamada T, Kario K, Taniguchi N: Oxidized lipoprotein(a) and cardio-ankle vascular index (CAVI) in hypertensive subjects. *Heart Vessels* 2013;28:461–466.
- 12 Funatsu H, Shimizu E, Noma H, Mimura T, Hori S: Association between serum lipoprotein(a) level and progression of non-proliferative diabetic retinopathy in type 2 diabetes. *Acta Ophthalmol* 2009;87:501–505.
- 13 Morishita R, Ishii J, Kusumi Y, Yamada S, Komai N, Ohishi M, Nomura M, Hishida H, Niihashi M, Mitsumata M: Association of serum oxidized lipoprotein(a) concentration with coronary artery disease: potential role of oxidized lipoprotein(a) in the vascular wall. *J Atheroscler Thromb* 2009;16:410–418.
- 14 Wakabayashi I, Masuda H: Lipoprotein(a) as a determinant of arterial stiffness in elderly patients with type 2 diabetes mellitus. *Clin Chim Acta* 2006;373:127–131.
- 15 Hulsmans M, Holvoet P: The vicious circle between oxidative stress and inflammation in atherosclerosis. *J Cell Mol Med* 2010;14:70–78.
- 16 Umahara T, Uchiyama T, Yamada S, Hashimoto T, Akimoto J, Haraoka J, Iwamoto T: Differential expression of oxidized/native lipoprotein(a) and plasminogen in human carotid and cerebral artery plaques. *Atherosclerosis* 2011;215:392–398.
- 17 Taleb A, Witztum JL, Tsimikas S: Oxidized phospholipids on apoB-100-containing lipoproteins: a biomarker predicting cardiovascular disease and cardiovascular events. *Biomark Med* 2011;5:673–694.
- 18 Koschinsky M, Boffa M: Lipoprotein(a) as a therapeutic target in cardiovascular disease. *Expert Opin Ther Targets* 2014;18:747–757.
- 19 Wiesner P, Tafelmeier M, Chittka D, Choi SH, Zhang L, Byun YS, Almazan F, Yang X, Iqbal N, Chowdhury P, Maisel A, Witztum JL, Handel TM, Tsimikas S, Miller YI: MCP-1 binds to oxidized LDL and is carried by lipoprotein(a) in human plasma. *J Lipid Res* 2013;54:1877–1883.
- 20 McGillicuddy FC, de la Llera Moya M, Hinkle CC, Joshi MR, Chiquoine EH, Billheimer JT, Rothblat GH, Reilly MP: Inflammation impairs reverse cholesterol transport in vivo. *Circulation* 2009;119:1135–1145.
- 21 Undas A, Stepien E, Tracz W, Szczeklik A: Lipoprotein(a) as a modifier of fibrin clot permeability and susceptibility to lysis. *J Thromb Haemost* 2006;4:973–975.
- 22 Sorokin A, Kotani K, Bushueva O, Taniguchi N, Lazarenko V: The cardio-ankle vascular index and ankle-brachial index in young Russians. *J Atheroscler Thromb* 2015;22:211–218.
- 23 Uurtuya S, Taniguchi N, Kotani K, Yamada T, Kawano M, Khurelbataar N, Itoh K, Lkhagvasuren T: Comparative study of the cardio-ankle vascular index and ankle-brachial index between young Japanese and Mongolian subjects. *Hypertens Res* 2009;32:140–144.
- 24 Wang H, Liu J, Zhao H, Zhao X, Li L, Shi H, Zhan S, Liu J: Relationship between cardio-ankle vascular index and plasma lipids in hypertension subjects. *J Hum Hypertens* 2015;29:105–108.
- 25 Gomez-Marcos MA, Recio-Rodriguez JI, Patino-Alonso MC, Agudo-Conde C, Gomez-Sanchez L, Gomez-Sanchez M, Rodriguez-Sanchez E, Maderuelo-Fernandez JA, Garcia-Ortiz L: Cardio-ankle vascular index is associated with cardiovascular target organ damage and vascular structure and function in patients with diabetes or metabolic syndrome, LOD-DIABETES study: a case series report. *Cardiovasc Diabetol* 2015;14:7.
- 26 Otsuka K, Fukuda S, Shimada K, Suzuki K, Nakanishi K, Yoshiyama M, Yoshikawa J: Serial assessment of arterial stiffness by cardio-ankle vascular index for prediction of future cardiovascular events in patients with coronary artery disease. *Hypertens Res* 2014;37:1014–1020.
- 27 Saji N, Kimura K, Yagita Y, Kawarai T, Shimizu H, Kita Y: Comparison of arteriosclerotic indicators in patients with ischemic stroke: ankle-brachial index, brachial-ankle pulse wave velocity and cardio-ankle vascular index. *Hypertens Res* 2015;38:323–328.
- 28 Kostner KM, Kostner GM: Factors affecting plasma lipoprotein(a) levels: role of hormones and other nongenetic factors. *Semin Vasc Med* 2004;4:211–214.
- 29 Kotani K, Yamada S, Yamada T, Taniguchi N, Sakurabayashi I: The relationship between oxidized lipoprotein(a) and carotid atherosclerosis in asymptomatic subjects: a comparison with native lipoprotein(a). *Lipids Health Dis* 2011;10:174.
- 30 Rowland CM, Pullinger CR, Luke MM, Shiffman D, Green L, Movsesyan I, Devlin JJ, Malloy MJ, Kane JP, Undas A: Lipoprotein(a), LPA Ile4399Met, and fibrin clot properties. *Thromb Res* 2014;133:863–867.
- 31 Bochem AE, Kuivenhoven JA, Stroes ES: The promise of cholesteryl ester transfer protein (CETP) inhibition in the treatment of cardiovascular disease. *Curr Pharm Des* 2013;19:3143–3149.
- 32 Jacobson TA: Lipoprotein(a), cardiovascular disease, and contemporary management. *Mayo Clin Proc* 2013;88:1294–1311.