Lipoprotein(a) and Familial Hypercholesterolemia: A Short Review Including the Laboratory Viewpoint

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Abstract

Lipoprotein(a) (Lp(a)) and low-density lipoprotein cholesterol (LDL-C) are risk factors for cardiovascular disease (CVD). Individuals with familial hypercholesterolemia (FH) have a risk for CVD due to a high LDL-C value. Lp(a) also increases the CVD risk in FH individuals; thus, the Lp(a) value should be carefully managed. The LDL-C value may partly include Lp(a)-cholesterol (Lp(a)-C) in the measurement. Based on the LDL-C value, some individuals are likely misclassified as having FH and/or the status of treatment of FH can be monitored. The present review describes about Lp(a) in FH individuals in terms of the measurement issue of Lp(a) and the related management of FH.

Keywords: Cardiovascular risk; Lp(a)-C; Diagnosis; Therapeutic strategy; Apoprotein(a)

Introduction

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein (LDL)-like particle that binds to apoprotein(a) (apo(a)) via plasminogen-like domains [1]. Lp(a) has an atherosclerotic component of LDL and a thrombotic component due to competitive plasminogen binding [1]. Apo(a) also binds to oxidized phospholipid-rich LDL, which impairs the endothelial function [2]. Thus, Lp(a) shows atherothrombogenic properties, leading to the development of cardiovascular disease (CVD).

Individuals with familial hypercholesterolemia (FH) exhibit a high LDL-cholesterol (LDL-C) value, leading to a high CVD risk [3]. Our meta-analysis has recently shown that a high Lp(a) value plays an important role in CVD in FH individuals [4]. However, we may need to carefully consider the LDL-C value in FH due to a measurement issue of Lp(a), and subsequently, somewhat prudent management of LDL-C in FH

individuals may be required.

Lp(a) in FH Individuals

The Lp(a) values in FH individuals are significantly higher than those in non-FH individuals, regardless of CVD history [5-7]. Here, we summarize the data using available literature (Table 1) [5-7]. Variants of LDL receptor *(LDLR)* cause FH [3]. Although a study reported no difference in Lp(a) values among the causative variants [8], "null" functional *LDLR* variants can induce significantly high Lp(a) values compared to "defective" *LDLR* variants [6] or severe types of *LDLR* variants (D206E, V408M, and D154M) exhibit high Lp(a) values [5]. Lp(a) values in some FH individuals can depend on the genetic factors; that is, a portion of Lp(a) is catabolized by LDLR [9] and then, dysfunctional LDLR due to the genetic variants leads to an increase in Lp(a).

Focusing on the presence of CVD, the Lp(a) values in FH individuals with CVD are also higher than in those without CVD, according to our summary of data using the available literature (Table 2) [6, 10-12]. The increase of Lp(a) in the presence of CVD is thought to be caused by not only genetic factors inflammation involved in the vascular plaque formation [13].

Lp(a) Measurement

Precise measurement of Lp(a) is important in FH individuals. We may know some measurement issues of Lp(a). The mass-based Lp(a) value, expressed in mg/dL, is generally used. This value is often affected by kringle IV type 2 (KIV-2), which is the copy number of apo(a) [1]. The number of KIV-2 varies from 1 to 40 times among individuals, leading to a varied Lp(a) size (2,500 - 3,000 kDa of LDL and 300 - 800 kDa of apo(a)) [1, 14]. The standard assay, which is the method of the Northwest Lipid Metabolism and Diabetes Research Laboratories, measures the molar-based value (expressed in nmol/L) [15].

Several Lp(a) assays detect the KIV-2, and their detection levels are not completely uniform among assays [15]. The smaller the number of KIV-2, the more the KIV-targeted assays underestimate the Lp(a) values [15]. Namely, the number of KIV-2 is inversely correlated with the Lp(a) values [1], thereby underestimating Lp(a) values in individuals with high Lp(a) values [16]. These assays have been widely harmonized [15];

Table 1. Lp(a) Values in FH and Non-FH Individuals

Studies	Gene[a]	FH (-)				FH (+)			
		Subjects (n)	Age (years)	Lp(a) (mg/dL)[b]	LDL-C (mmol/L)[c]	Subjects (n)	Age (years)	Lp(a) (mg/dL)[b]	LDL-C (mmol/L)[c]
Lingenhel et al, 1998 [5]	*LDLR*	57	-	16.3	5.3	103	-	27.7	8.7
Alonso et al, 2014 [6]	*LDLR*	957	40.6	21	3.4	1,960	44.4	23.6	4.8
Tada et al, 2016 [7]	*LDLR*	4,015	58	11.8	2.8	198	42	21.9	5.6
	PCSK9	-	-	-	-	42	52	21.1	6.1

[a]Gene used for diagnosis of FH; [b]Lp(a) expressed as a median value; [c]LDL-C expressed as a mean value. FH: familial hypercholesterolemia; Lp(a): lipoprotein(a); LDL-C: low-density lipoprotein cholesterol; *LDLR*: low-density lipoprotein receptor; *PCSK9*: proprotein convertase subtilisin/kexin type 9.

however, there is a recent study reporting that the Lp(a) values among assays vary up to 5-fold in individuals with few KIV-2 repeats (KIV-2 < 22) [16]. We should select an assay that is correlated with the standard assay of Lp(a) values.

Of note, the density of Lp(a) (1.040 to 1.210 g/mL) overlaps with that of LDL (1.019 to 1.063 g/mL) [17]. Due to the difficulty in separating Lp(a) and LDL fractions, the LDL-C value (by the Friedewald equation or direct assays) partly contains Lp(a)-cholesterol (Lp(a)-C) [18, 19], and the cholesterol content of Lp(a) is distributed from 30 to 45% of the Lp(a) mass [20]. Lp(a) contains other molecules (e.g., apo, 1-alkyl-2-acetylglycerophosphocholine esterase, serum amyloid A) [9], which makes the diversity of the Lp(a) size. The number of KIV-2 contributes 10% of the difference in Lp(a) size, and a low KIV-2 leads to a high cholesterol content [14]. In fact, a low KIV-2 is reported to exhibit 45% of the cholesterol content of Lp(a) [21].

Diagnosis on FH in Regard to Lp(a)

These measurement aspects of Lp(a) can affect clinical practice in FH. A recent study has shown that 8.2% of FH individuals with high Lp(a) values (defined by the Dutch Lipid Clinic Network criteria) were misclassified by inclusion of Lp(a)-C in LDL-C values [22]. For example, a report indicates that 50 mg/dL of Lp(a) contributes 22.5 mg/dL of LDL-C values [14]. In a case of FH with both 50 mg/dL of Lp(a) and 200 mg/dL (5.2 mmol/L) of LDL-C, the LDL-C value was corrected to 178 mg/dL (4.6 mmol/L). The LDL value does not correspond to the diagnostic criteria level of FH. The formula for the corrected LDL-C (mmol/L) is LDL-C (mmol/L) - (Lp(a) (mg/dL) × 0.0116) [14, 23]. The formula will be useful for diagnosing FH individuals with high Lp(a) values.

Thus, Lp(a) should be measured at the first visit in suspected FH individuals, even though the prevalence of people with high Lp(a) is not very high [16, 24, 25]. In individuals with high Lp(a) values and LDL-C values at the borderline level of FH criteria, genetic tests for FH (i.e., *LDLR*) can be performed for a definitive diagnosis of FH.

Treatment of FH in Regard to Lp(a)

The LDL-C value is mainly used in monitoring the status of treatment of FH individuals. 3-hydroxy-3-methyl-glutaryl-co-enzyme A (HMG-CoA) reductase inhibitors, called statins, are the representative oral drugs for cholesterol-lowering therapy [26]. Basically, statins do not markedly change Lp(a) values (0 to +7%) [26], while a few papers describe a slight reduction of Lp(a) by statins (about -5%) [27, 28]. In some FH individuals, the LDL-C values following statin treatment insufficiently reduce to the recommended level in the guidelines [29]. Those individuals need treatments to further reduce LDL-C values. The insufficient reduction of LDL-C value may be, in part, due to the Lp(a)-C contained in LDL-C in individuals with high Lp(a) values.

Niacin or fibrates are not generally used to reduce the LDL-C values in FH individuals, although niacin can reduce the Lp(a) values (-20%) [26] and fibrates have no or little effect on Lp(a) (0 to +10%) [26, 30]. As add-on therapies for FH individuals who do not reach the recommended LDL-C level by statins, Niemann-Pick C1-Like 1 (NPC1L1) inhibitors are used and further reduce LDL-C values [26]. NPC1L1

Table 2. Lp(a) Values in FH Individuals With and Without CVD

Studies	CVD (-)			CVD (+)		
	Subjects (n)	Age (years)	Lp(a) (mg/dL)[a]	Subjects (n)	Age (years)	Lp(a) (mg/dL)[a]
Allard et al, 2014 [10]	221	58	26.3 (10.4 - 60.5)	74	67.7	34.9 (12.2 - 84.1)
Alonso et al, 2014 [6]	1,713	-	21.3 (8.9 - 53.9)	247	-	43.4 (18.2 - 84.3)
Chan et al, 2015 [11]	326	43	39 (34 - 44)	64	57	59 (44 - 75)
Sun et al, 2018 [12]	87	45	21.5 (7.95 - 46.1)	61	49	34.7 (16.2 - 68.1)

[a]Lp(a) expressed as a median (interquartile range). FH: familial hypercholesterolemia; CVD: cardiovascular disease; Lp(a): lipoprotein(a).

inhibitors have no or slightly lowering effect on Lp(a) (-5%) [26, 31]. Recently, as add-on therapies, proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are used and reduce both LDL-C and Lp(a) values (about -30%) [26, 32]. PCSK9 inhibitors may be suitable for FH individuals with high Lp(a) values. The LDL-C value under treatment by PCSK9 inhibitors may be little affected by Lp(a)-C. Thus, the measurements of Lp(a) values are useful for selecting drugs and monitoring the LDL-C values in treatment of FH individuals.

Conclusions

This review summarizes the appearance of high Lp(a) values in FH individuals, the measurement issue of Lp(a) and its effect on LDL-C values, as well as the diagnostic and therapeutic consideration of FH. Even though the clinical relevance of the relationship between Lp(a) and LDL-C in FH remain unclear given the not-very-high prevalence of individuals with high Lp(a) values, understanding of Lp(a) and its measurements can be necessary in practice on FH.

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Conflict of Interest

The authors declared no conflict of interest in this paper.

Author Contributions

MH contributed to the literature review and drafting the paper. KK contributed to the conception and design of the paper and editing the paper. All authors approved the submission of the final version of the paper.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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