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What do we know about lipoprotein(a)?

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INTRODUCTION

Lipoprotein(a) [Lp(a)] was discovered in 1963 [1]. Its physiologic role is not known, although it was postulated to participate in wound healing, immunogenicity, and infections (an acute phase protein). Increased Lp(a) levels are considered a risk factor for cardiovascular disease (CVD) based on large prospective studies [2, 3] and metaanalyses [4, 5]. For many years, the interest in Lp(a) was limited due to a lack of randomised clinical trial evidence for risk reduction associated with a decrease in serum Lp(a) level. This was in turn related to the fact that no drug selectively reduces serum Lp(a) level, and drugs that affect serum Lp(a) level also correct other lipid abnormalities. However, the interest in Lp(a) has recently increased and methods of selective Lp(a) level reduction are being searched for.

LIPOPROTEIN(A) STRUCTURE

Lp(a) is a lipoprotein that consists of two elements, a low-density lipoprotein (LDL) and a heterogeneous glycoprotein, apolipoprotein(a) [apo(a)], which is synthesised in the liver. Serum Lp(a) levels correlate closely to apo(a) production. The two components of this lipoprotein are bound by a disulphur bond between two cysteine residues [6]. The gene coding for apo(a) — LPA — is located on the chromosome 6q 22-23, close to the plasminogen gene [7]. Apo(a) is a glycoprotein consisting of domains showing high homology to plasminogen, including a protease kringle V (KV) domain and 10 types of kringle IV (KIV) domain, of which type 2 is present in a variable number of copies, and types 1 and 3 to 10 are present as single copies in all apo(a) isoforms [6–8]. For explanation, the term kringle comes from the shape of a Danish pastry. The number of KIV-2 copies determines Lp(a) molecular mass and level. The lower is the copy number, the higher Lp(a) level and vice versa. Two single nucleotide polymorphisms of the LPA gene, rs 10 455 872 and rs 3 798 220, are associated with a low number of KIV-2 copies and an increased Lp(a) level and CVD risk [9]. Thus, plasma Lp(a) levels are mostly determined genetically in relation to LPA gene variability which results in a variable number of KIV-2 copies.

ABNORMAL LIPOPROTEIN(A) LEVELS

Lp(a) levels vary markedly between subjects and population. In the Copenhagen General Population Study, a typical skewed plasma Lp(a) level distribution was shown, with 80% of the population having levels below 50 mg/dL, and only 20% of the population having levels in the 50–200 mg/dL range [10]. Thus, Lp(a) levels > 50 mg/dL, corresponding to the > 80th percentile, are considered abnormal and a constitute a clinical biomarker of an increased CVD risk. Lowest Lp(a) levels are seen in non-Hispanic whites, higher in Hispanics, and highest in blacks [11]. Of note, however, most studies and metaanalyses indicate an increased CVD risk with Lp(a) levels as low as > 25–30 mg/dL [5].

LIPOPROTEIN(A) AS A RISK FACTOR

Epidemiological evidence confirm an independent association between Lp(a) level and CVD risk, although this relation is weaker that the association between LDL cholesterol (LDL-C) level and CVD risk. The latter is more strongly related to Lp(a) levels in the presence of a high LDL-C level but the risk is observed also in subjects with LDL-C level < 1.8 mmol/L [12]. As elevated Lp(a) level is present since birth, it may potentially contribute to CVD risk already during early life, similarly to other genetic risk factors.

According to an early metaanalysis of 18 prospective studies in the general population that included 4,000 coronary artery disease (CAD) cases, the relative risk (RR) of CAD in the upper tertile of Lp(a) level compared to the lowest tertile was 1.7 (95% confidence interval [CI] 1.4–1.9) [4]. In subsequent metaanalyses, this association was more modest. In a metaanalysis of three prospective studies that included 9,870 CAD cases, RR of CAD in a comparison of extreme thirds of Lp(a) levels was 1.5 (95% Cl 1.3–1.8) [13]. The largest

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metaanalysis, Emerging Risk Factor Collaboration, that included 36 prospective studies with 126,000 participants, showed a continuous, semilogarithmic association of Lp(a) level with CAD without a threshold value [5]. The risk of CAD related to an increase in Lp(a) level by one standard deviation (SD) was 1.13 (95% Cl 1.09–1.18). Among subjects in the upper tertile of Lp(a) level, the incidence of CAD was 5.5 per 1,000 (95% Cl 5.4–5.9), compared to 4.4 per 1000 (95% CI 4.2–4.6) in the lowest tertile. In this study the association between Lp(a) level and CAD risk was not related to LDL-C level, non-high-density lipoprotein cholesterol (HDL-C) level, and other risk factors. In another metaanalysis of patients with a history of CAD, the risk of a cardiovascular event was much higher in the upper tertile of Lp(a) level compared to the lowest tertile (RR 2.37, 95% CI 1.41–3.97, p = 0.001) [14].

In a comprehensive review article, Kostner et al. [6] highlighted a previously reported strong independent association between CAD and the above mentioned LPA gene variants, i.e. rs 10 455 872 and rs 3 798 220 [15], and an association between the rs 3 798 220 variant with angiographically confirmed stenosis or myocardial infarction [16, 17] and small apo(a) isoforms. This was indicated by the metaanalysis of Li et al. [18] which showed that in carriers of one or two smaller rs 3 798 220 alleles, the risk of CAD is 57% higher, and each copy of the rs 10 455 872 allele was associated with an increase in risk by 42%. As was noted by Kostner et al. [6], Erqou et al. [19] in their metaanalysis of 40 studies with more than 58,000 participants showed that the risk of CAD was twice higher in subjects with small apo(a) isoforms compared to those with large isoforms. Smaller apo(a) isoforms are associated with higher Lp(a) levels. It may be thus suspected that the risk of CAD is mostly related to Lp(a) levels and not the presence of both LPA gene variants.

Recently, results of the Bruneck Study have been published [20]. This was a prospective population study that aimed to evaluate whether addition of Lp(a) levels to the categorisation of 15-year risk of a cardiovascular event (< 7.5%, 7.5% to < 15%, 15% to < 30% and ≥ 30%) improves disease predictability. The follow-up period was 15 years and the study included 826 men and women aged 45–84 years who lived in the Italian town of Bruneck. The hazard ratio (HR) of an event was 1.37 per each increase in Lp(a) level by 1 SD (1 SD = 32 mg/dL) and 2.37 for the highest quintile compared to lower quintiles. These estimates were not changed by adjustment for smoking, systolic blood pressure (SBP), HDL-C level, the presence of diabetes, a family history of premature myocardial infarction in parents, and log-transformed high-sensitivity C-reactive protein (hs-CRP) level.

The best improvement of risk category reclassification after adding Lp(a) level was observed in patients with moderate risk (15% to < 30%). In this group, the proportion was 17.1% among subjects with an event and 22% among subjects without an event (total of 39.6%), i.e. among 502 subjects without an event, 82 were correctly reclassified to a lower risk category and 49 to a higher risk category, and among 148 subjects with an event, 17 were correctly reclassified to a lower risk category and 18 to a higher risk category.

No correlation was found between Lp(a) level and age, HDL-C level, SBP, and hs-CRP level. Lp(a) level was strongly correlated to the number of KIV repetitions but in contrast to the previous studies [2, 21], this study did not show an association between either apo(a) isoforms and allele-specific Lp(a) levels and CVD risk. This is also in contradiction to the previous observation in the Bruneck Study, indicating progression of carotid atherosclerosis during a 5-year follow-up in a strong relation to the presence of a low molecular mass apo(a) phenotype and high Lp(a) levels [22]. The authors tried to explain these contradictory results with a higher likelihood of statin treatment during the subsequent 10-year period in patients with low molecular mass isoforms.

The main conclusion of the authors of that study was that an increased Lp(a) level predicted cardiovascular events and improved risk categorisation.

MECHANISMS OF ATHEROGENICITY

Postulated atherogenic mechanisms of Lp(a) include the ability to form foam cells from macrophages in the intima (the LDL component), and a prothrombotic/antifibrinolytic effect by impairing fibrinolysis [apo(a)]. Apo(a) is similar to plasminogen but shows no fibrinolytic activity. Evidence has been reported for both these mechanisms [23, 24]. However, other pathogenic actions of Lp(a) are also known, such as increasing endothelial permeability and expression of adhesion molecules, induction of monocyte chemotaxis, reduced inhibition of tissue factor activity, increased expression of plasminogen activator inhibitor-1 (PAI-1), inducing expression of proinflammatory interleukin-8 in macrophages, and stimulating macrophage apoptosis [7, 23]. All these pathomechanisms are mediated by proinflammatory and proatherogenic oxidated phospholipids (OxPL) associated with apo B 100-containing lipoproteins (OxPL/apo B). It has been recently discovered that oxidation of Lp(a) and OxPL plays an important role in the development of atherosclerosis [25] and most plasma OxPL/apo B is bound to Lp(a) [26]. The case-control EPIC-Norfolk study showed that both Lp(a) and OxPL/apo B were strongly associated with the risk of CAD [27]. OxPL mediate not only atherogenesis but also plaque vulnerability [7, 23] by contributing to macrophage apoptosis [28].

IN WHOM SHOULD WE MEASURE LIPOPROTEIN(A) LEVEL?

Serum Lp(a) level measurements have not been included in risk estimation algorithms and are not generally recommended as a population screening test, although they "may provide useful information to ascribe risk in white patients with CAD or in those with an unexplained family history of early CAD".

This statement was included in the 2012 American Association of Clinical Endocrinologists (AACE) guidelines [29]. The European guidelines on the management of dyslipidaemia recommend measuring Lp(a) level in selected high-risk patients and those with a family history of premature CAD (a class II recommendation, level of evidence C) [30].

A more detailed approach was adopted by the National Lipid Association in 2011 [31]. These American experts divided their recommendations into two groups, referring to initial evaluation and decisions related to further lipid-lowering therapy. Regarding the former issue, Lp(a) level measurements were not recommended for routine use in subjects with a low 10-year coronary heart disease (CHD) event risk (< 5%). In moderate risk subjects (5% to < 20%) or CHD or CHD equivalent, it was recommended to consider Lp(a) level measurements only in selected cases. However, Lp(a) level measurements were considered reasonable in patients with a family history of premature CHD, and also CHD patients with recurrent events despite appropriate lipid-lowering therapy. Regarding already treated subjects, the experts suggested that measuring Lp(a) levels is not necessary in treated low- and moderate-risk patients, as it is not supported by the available evidence, but it may be considered on-treatment before further therapeutic decisions in selected patients (CHD or CHD equivalent, family history of premature CHD, recurrent coronary events). The rationale for measuring Lp(a) levels in the latter group is that aggressive reduction of LDL-C level is beneficial in patients with increased Lp(a) and LDL-C levels, leading to risk reduction.

LIPOPROTEIN(A)-LOWERING THERAPY

As mentioned above, no drug selectively reduces Lp(a) level and there is no evidence that selective Lp(a) level lowering reduces CVD risk. Drugs that reduce Lp(a) level also exert beneficial effects on other lipid parameters. Oestrogens in women also increase HDL-C level, and nicotinic acid reduces Lp(a) level by 20–30% but also lowers LDL-C and triglyceride levels and increases HDL-C level. However, despite positive changes in lipid levels including Lp(a), these drugs did not reduce cardiovascular event rates in randomized clinical trials (niacin when added to a statin) [32–34]. Finally, statins have a minimal effect on Lp(a) level [23, 35].

Acetylsalicylic acid also reduces Lp(a) level by nearly 20% [36]. The highest reduction in risk was shown in rs 3 798 220 gene variant carriers [37]. However, as highlighted by Boffa and Koschinsky [38], acetylsalicylic acid is recommended only in patients with high cardiovascular risk.

Currently, the most effective approach to reduce Lp(a) levels is plasma apheresis, with reductions up to 75% [39]. However, this method removes all lipoproteins containing apo B, and lipid levels return to the pretreatment values by 2 weeks after the procedure. In one long-term study (10-year retrospective follow-up of 160 patients), plasma apheresis compared to drug therapy in patients with very high Lp(a) levels was associated with Lp(a) level reduction by 73% and major cardiac event rate reduction by 86% [40]. However, the latter effect may not be attributed solely to Lp(a) level reduction as other lipoproteins were also beneficially affected, along with reduction of blood viscosity.

Emerging new LDL-C-lowering therapies also result in a reduction of Lp(a) level. These include mipomersen (in subcutaneous injections), proprotein convertase subtilisin/kexin type 9 (PCSK 9) inhibitors (in subcutaneous injections), and lomitapide (oral drug). Mipomersen is an antisense oligonucleotide with reduces hepatic apo B synthesis, leading to reduced levels of all apo B-containing lipoproteins, including Lp(a). The drug does not reduce apo(a) mRNA and apo(a) levels, which suggests that Lp(a) level reduction is due to reduced apo B availability to form Lp(a) particles [41]. Available studies indicate that mipomersen reduces Lp(a) levels by 21–39% [42]. PCSK 9 inhibitors increase LDL receptor activity by reducing their lysosomal degradation in the liver, with subsequent receptor return to the cell membrane and their increased expression thereby. These drugs reduce Lp(a) levels by 15–44% [43–45]. The mechanism of this effect is not known but it is unlikely to occur via LDL receptors as they do not mediate Lp(a) catabolism.

Lomitapide, which is an inhibitor of microsomal triglyceride transfer protein (MTP) in hepatic microsomes and thus inhibits hepatic synthesis and release of triglyceride-containing very-low-density lipoproteins (VLDL), reduces plasma levels of not only VLDL and LDL which are formed from VLDL, but also Lp(a) [46]. The mechanism of this reduction is unclear, and lopitamide has not been approved in Europe due to serious hepatotoxicity resulting in significant increases in aminotransferase activity.

Another drug that significantly reduces Lp(a) levels (by 38.8%) is anacetrapib [47], a cholesteryl ester transfer protein inhibitor. Anacetrapib reduces cholesteryl ester transfer from HDL particles, resulting in an increase in HDL-C level and a reduction in LDL-C level. The mechanism of Lp(a) level reduction is again unclear.

Among emerging new therapies to reduce excessive LDL-C levels (mostly in familial hypercholesterolaemia), only mipomersen has been approved for the treatment of homozygous familial hypercholesterolaemia. Reduction in Lp(a) levels by these drugs is a secondary effect and it is unclear whether they will be ever approved for the treatment of increased Lp(a) levels. They show, first of all, the beneficial effects on the levels of other lipoproteins (mostly LDL, and also triglycerides in case of the MTP inhibitor) which renders it impossible to ascertain risk reduction attributable to Lp(a) level reduction.

Currently, specific Lp(a)-lowering therapies are searched for. An example of such therapy is an antisense oligonucleotide

targeted at KIV-2 copies. It has reduced plasma apo(a) mRNA and apo(a) levels in transgenic mice by 85%, with little effect on other lipoproteins [48].

The European guidelines on the management of dyslipidaemia include no recommendations regarding Lp(a)-lowering therapies [30]. According to American experts from the National Lipid Association, no evidence is available to justify drug treatment to reduce level of this lipoprotein, although there are theoretical grounds to believe that reducing Lp(a) level might be beneficial [31]. Specifically, event rate reduction in treated patients has not been shown to be related to a change in Lp(a) level. Experts indicate, however, that retrospective studies suggest large risk reduction associated with aggressive LDL-C level reduction in patients with elevation of both Lp(a) and LDL-C levels, and thus more intensive LDL-C reduction to lower target values has been recommended.

We hope that our review will contribute to better understanding of the current views of the role of Lp(a) in atherogenesis. This issue, along with the management of familial hypercholesterolaemia [49, 50] and severe hypertriglyceridaemia [51, 52] and changing views on the importance of HDL-C level in the development and prevention of atherosclerosis [53, 54], is one of the hot topics in lipidology.

CONCLUSIONS

1. Increased Lp(a) level is a genetically determined, independent risk factor for CVD.
2. Abnormal Lp(a) levels are usually defined as > 50 mg/dL, although risk increases above values as low as 25–30 mg/dL.
3. Due to lacking clinical trial evidence, target Lp(a) level has not been established.
4. There are no drugs that would specifically lower Lp(a) levels. Drugs that lower plasma Lp(a) also exert beneficial effects on the levels of other lipoproteins.
5. It is recommended to consider Lp(a) level measurements in patients with a family history of premature CAD and those with recurrent coronary events despite adequate lipid-lowering therapy.
6. Intensification of the therapy to reduce LDL-C level is currently recommended in patients with increased Lp(a) levels as this approach reduces risk when levels of both lipoproteins are increased.

Conflict of interest: *none declared*

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