REVIEW ARTICLE

Lipoprotein(a) – A Potential Cardiovascular Risk Factor and Therapeutic Approaches

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ABSTRACT

Lipoprotein(a), also called as Lp(a), has been shown to be an independent, causal, genetic risk factor for cardiovascular disease and aortic stenosis by genetic and numerous epidemiological studies. High Lp(a) level is an important risk factor for coronary heart disease, cerebrovascular disease, atherosclerosis, thrombosis, and stroke. The physiological functions, the mechanism and sites of Lp(a) catabolism, and pathophysiological details are not well-understood though several mechanisms of Lp(a) participation in atherogenesis have been proposed. The goal of therapy is to bring down elevated Lp(a) levels to below 50 mg/dL. Both statins and estrogens are not used for therapy of elevated Lp(a) levels. Niacin and aspirin are two relatively safe, easily available and inexpensive drugs, which significantly reduce raised Lp(a) levels. A variety of other medications that are in various stages of development are dealt with including miscellaneous agents whose role has not been clinically verified.

Keywords: Lipoprotein(a), atherogenesis, therapeutic approaches

Lipoprotein(a) [also called as Lp(a) or LPA] is a lipoprotein subclass. Lipoprotein is an independent, causal, genetic risk factor for cardiovascular disease (CVD)[1]. Genetic studies and numerous epidemiological studies have also identified Lp(a) as a risk factor for atherosclerotic diseases such as coronary heart disease (CHD) and stroke[2-5]. Lp(a) was discovered in 1963 by Kare Berg[6]. Interestingly, Lp(a) is present only in humans, apes, and old world monkeys.

STRUCTURE

The chemical structure of Lp(a) consists of a low-density lipoprotein (LDL)-like particle and the specific apolipoprotein (a) [apo(a)], which is covalently bound to the apoB-100 of the LDL-like particle via one disulfide bridge[7,8]. Thus, Lp(a) is composed of apoB-100 and apo(a). Lp(a) is a spherical macromolecular complex with a diameter of approximately 25 nm, and density ranging from 1.05 g/mL to 1.12 g/mL[7]. Its concentrations are not significantly affected by dietary or environmental effects. Lp(a) plasma concentrations are highly heritable and mainly controlled by the apo(a) gene (LPA) located on chromosome 6 q 26-27. Probably, LPA gene may be responsible for 91% of the variation in Lp(a) concentration; of these 69% are due to the number of kringle IV (KIV) type 2 repetitions. Lp(a) plasma concentration ranges from <1 mg to >1,000 mg/dL. It is worth mentioning that individuals without Lp(a) or with very low Lp(a) levels seem to be healthy.

Apo(a) proteins vary in size due to a size polymorphism (KIV-2 VNTR), which is caused by a variable number of so called KIV repeats in the LPA gene. This size variation at the gene level is expressed on the protein level as well, resulting in apo(a) proteins with 10 to >50 KIV repeats[8,9]. These variable apo(a) sizes are known as apo(a) isoforms. Generally, there is inverse correlation between the size of the apo(a) isoforms and the Lp(a) plasma concentration[10]. As smaller apo(a) isoforms can be generated more quickly per unit time, hence small isoforms are associated with higher plasma Lp(a) levels. Age and sex have little influence on Lp(a) levels, though racial factor has an important influence on Lp(a) levels. The half-life of Lp(a) in the circulation is about 3 to 4 days. There are 6 different alleles for Lp(a). The protein apo(a) is highly homologous (similar) to

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plasminogen, one of the proteins of the fibrinolytic system, though apo(a) has important differences compared with plasminogen.

SYNTHESIS AND METABOLISM

The synthesis and metabolism of Lp(a) have not been completely clarified and are totally independent from LDL synthesis and metabolism in spite of structural similarities between Lp(a) and LDL. Lp(a) is synthesized in the liver. Apo(a) is expressed by liver cells (hepatocytes). There is no coordination between the synthetic pathways of apo(a) and of apoB-100, as there is no coordination between synthesis of Lp(a) and of plasminogen, its structural analog[7]. Further, Lp(a) levels are not related to lipoprotein lipase activity.

The mechanism and sites of Lp(a) catabolism are also not well-defined. Moreover, the way cellular uptake occurs is also not well-established[7]. Uptake via LDL receptor is not a major pathway of Lp(a) metabolism[11] and the role of LDL receptor or isoforms size in that process is limited since only a small fraction of Lp(a) binds to hepatoma cells via LDL receptors. Probably, kidneys may play a role in Lp(a) clearance from plasma[12]. Other receptors, such as asialoglycoprotein receptors, megalin receptors and macrophage scavenger receptors may be involved in Lp(a) uptake[13].

METHODOLOGY TO DETERMINE LP(a)

Lp(a) is commonly estimated by determining the apo(a) concentration by using monoclonal anti-apo(a) antibodies. It may be mentioned, there are difficulties in standardizing the methodology to determine Lp(a) for accurate comparison between different studies. Presently, there are a variety of methods for determining Lp(a). A standardized reference material accepted by the World Health Organization (WHO) Expert Committee on Biological Standardization and the International Federation of Clinical Chemistry and Laboratory Medicine has been notified towards standardizing results. Moreover, a test with simple quantitative results may not provide a complete assessment of risk. Therefore, these assays must be validated with reference standard.

Lipoprotein(a) – Lp(a):

- Desirable: <14 mg/dL
- Borderline risk: 14-30 mg/dL
- High risk: 31-50 mg/dL
- Very high risk: >50 mg/dL.

Lp(a) Concentration and Populations

The racial factor has an important influence on Lp(a) levels. There is two- to threefold higher Lp(a) plasma concentration in populations of African descent compared to Asian, Oceanic or European populations[14], but these levels are not related to coronary artery disease (CAD) in Africans.

Physiological Function

The physiological function of Lp(a)/apo(a) is still unknown. The data till date did not show a physiological function for Lp(a) in lipid transportation or metabolism regulation[7]. Its role within the coagulation system seems plausible owing to high similarity between apo(a) and plasminogen[8]. Apo(a) has potent lysine binding domains similar to those on plasminogen and binds to damaged endothelial cells and exposed or injured subendothelial matrix proteins, delivers cholesterol for cell membrane growth. The other functions may be related to recruitment of inflammatory cells through interaction with Mac-1 integrin, angiogenesis, wound healing, innate immunity, and infection.

Pathophysiology

There are 4 major categories of lipid abnormalities in human beings[1]: a) A raised LDL cholesterol, b) a low high-density lipoprotein (HDL) cholesterol, c) elevated triglycerides, and d) elevated Lp(a). Of these, LDL cholesterol, HDL cholesterol and triglyceride levels are modulated by diet. In contrast, Lp(a) plasma levels are mediated largely by the LPA gene locus present on chromosome 6 q 22-23 and is minimally affected by diet[15].

Presently, Lp(a) remains conceptually only a 'pathogenic lipoprotein.' Lp(a) level >50 mg/dL is typically considered to be elevated for clinical biomarkers. Transient increases in Lp(a) levels are noted in the presence of inflammatory processes or tissue damages, such as those occurring with other acute phase proteins (haptoglobin, α_1-antitrypsin, and C-reactive protein)[15]. This can be seen with an episode of acute myocardial infarction, wherein Lp(a) levels are considerably increased in first 24 hours, returning to base values in approximately 30 days. Lp(a) levels are also increased in chronic inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, and acquired immune deficiency syndrome and following heart transplantation, pulmonary arterial hypertension, and chronic renal failure[16]. In contrast, liver diseases and abusive use of steroid hormones decrease Lp(a) levels[16]. The relationship between Lp(a) and diabetes has not

been well-defined. Contrary views have been expressed in type 1 diabetes mellitus. Similarly, conflicting results have been reported for type 2 diabetes as well.

Lp(a) concentrations have a hereditary character, tending to remain constant throughout the life and are not altered by environmental factors. Elevated Lp(a) level is a risk factor for CHD, CVD, atherosclerosis, thrombosis and stroke, though, association between Lp(a) levels and stroke is not as strong as that between Lp(a) and CVD[2].

Several mechanisms have been proposed for Lp(a) participation in atherogenesis. The structure of Lp(a) is similar to plasminogen and tissue plasminogen activator (tPA); it might lead to interference with fibrinolysis cascade since it competes with plasminogen for its binding site, causing reduced fibrinolysis. Lp(a) stimulates secretion of plasminogen activator inhibitor-1 (PAI-1), it leads to thrombogenesis. Lp(a) also carries cholesterol and thus contributes to atherosclerosis[17]. The mechanisms linking thrombogenesis and atherogenesis with plasma lipoproteins via Lp(a) have thrilled the scientific community.

The probable sequence of events is as follows: Lp(a) would interfere with fibrinolytic system thus Lp(a) competes with plasminogen for binding sites of endothelial cells, inhibiting fibrinolysis, and promoting intravascular thrombosis[18]. Additionally, Lp(a) transports the more atherogenic proinflammatory oxidized phospholipids, which attract inflammatory cells to vessel walls[19,20], and leads to smooth muscle cell proliferation[21]. Probably, the major effect of Lp(a) is on advanced plaque development and destabilization rather than thrombosis[1].

An elevated Lp(a) is clearly proatherogenic[22]. The participation of Lp(a) in atherogenesis could be multifaceted. One mechanism of atherogenicity is through the LDL component. However, apo(a) alone and Lp(a) as lipoprotein have additional potential contributions[23], including increasing endothelial cell permeability and expression of adhesion molecules, promoting smooth muscle cell proliferation, enhancing monocyte entry and retention in the vessel wall, macrophage foam cell formation, promoting release of proinflammatory interleukin (IL)-8 levels, and antifibrinolytic effects, as a carrier of proinflammatory and proatherogenic oxidized phospholipids (OxPL)[24]. A study has reported that Lp(a) and OxPL mediate macrophage apoptosis in endoplasmic reticulum. Since, macrophage apoptosis is a key component of plaque vulnerability, these data provide supporting evidence of Lp(a) as a risk factor for the development of advanced, clinically relevant atherosclerotic lesions[1]. Lp(a) levels also predict severity of coronary atherosclerosis in clinically symptomatic patients. A key component of atherogenicity of Lp(a) has been the contribution of OxPL. OxPL are immunogenic and accumulate in atherosclerotic lesions and mediate plaque destabilization. Thus, raised OxPL on apoB are linked with the presence and progression of CAD and peripheral artery disease (PAD) and predict new CVD events in prospective studies[1].

Another proatherogenic mechanism relates to direct deposition of Lp(a) on arterial wall similar to that which happens with LDL and oxidized LDL as Lp(a) is more prone to oxidation than LDL[7]. This might facilitate uptake of macrophages via scavenger receptor[13]. This is the most universal mechanism of atherogenesis. Yet, another proatherogenic mechanism of Lp(a) refers to the inverse correlation between lipoprotein levels and vascular reactivity, wherein increase in Lp(a) plasma levels will induce endothelial dysfunction[25].

A prime feature of atherosclerosis is chronic inflammation and accumulation of proinflammatory substances in the vessel wall, modified and oxidized products of apoB-containing lipoprotein, are key mediators of such proinflammatory responses that contribute to clinical manifestations of CVD. Helgadottir et al[26] has observed the independent residual risk of Lp(a) in mediating CVD is substantial and this can provide an opportunity and a potential target of therapy in reducing the overall risk of CVD even further. Helgadottir et al have suggested that LPA variants rs10455872 and rs3798220, defined as LPA risk score by combining their effects, are associated with angiographically determined earlier onset of CAD ($p = 4.8 \times 10^{12}$), PAD ($p = 2.9 \times 10^{14}$), aortic aneurysm ($p = 6.0 \times 10^{5}$), and ischemic stroke subtype large artery atherosclerosis ($p = 6.7 \times 10^{4}$).

Further, investigators have observed associations between Lp(a) and inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), IL-6, and monocyte chemoattractant protein-1 (MCP-1)[27,28]. In addition to a reduction in fibrinolysis, it may involve platelet aggregation, induction of the expression of adhesion molecules, vascular remodeling via changes in the proliferative and migratory capacity of endothelial cells and resident smooth muscle cells, oxidative modification and formulation of foam cells[7]. In brief, Lp(a) may be atherothrombotic through its LDL moiety, but also through apo(a), including its ability to be retained in vessel well and mediate proinflammatory and proapoptopic effects including those potentiated by its content of OxPL, and antifibrinolytic effects.[1]

Lp(a) as Cardiovascular Risk Factor

A number of cross-sectional studies have confirmed the association between Lp(a) levels and risk of developing CAD, regardless of 2.3 times higher in patients with Lp(a) levels over 50 mg/dL. Riches et al[28] noted risk as twice greater for Lp(a) levels over 20 mg/dL. Rhoads et al[29] and Murai et al[30] confirmed the relationship between Lp(a) and CAD and cerebral infarction. Rhoads et al[29] also noted that with advancing age the risk decreased, and in the age group over 70 years risk became 1.2 times. In the Brazilian population, Maranhao et al[31], have reported a risk of developing CAD 2.3 times greater when Lp(a) levels were over 25 mg/dL. In Korean population with CAD, a raised Lp(a) has been labeled as an independent risk factor[32]. A meta-analysis of 27 prospective studies has clearly identified an independent association between Lp(a) and CAD[5]. A Danish prospective study involving more than 9,000 individuals over 10 years follow-up has observed that very high Lp(a) levels (≥120 mg/dL) increased 3 to 4 times the risk of CAD[33].

Most studies and meta-analyses have shown an increase in CVD risk starting at Lp(a) >25 mg/dL. A majority of prospective studies reported Lp(a) is really an independent risk factor for CVD though conflicting results, ranging from strong positive associations to complete lack of association between Lp(a) and CVD are in the literature. Yet, high Lp(a) levels enhanced the potency as risk factors of both hypercholesterolemia and low HDL cholesterol concentration[34]. High Lp(a) levels predict risk of early atherosclerosis independently of other cardiac risk factors, including LDL. In patients of advanced CVD, Lp(a) indicates a coagulant risk of plaque thrombosis. Elevated Lp(a) levels may augment the CHD risk from increased LDL cholesterol concentrations as has been demonstrated in patients with familial hypercholesterolemia[35]. A consensus paper issued by the European Atherosclerosis Society in 2010 describes Lp(a) as a causal risk factor for CHD and CVD. The possibility that Lp(a) may become functionally altered in patients with CAD has been put forward by Tsironis et al[36] on the basis of mass and specific activity of Lp(a) as mediator of platelet-activating factor acetylhydrolase activity, an enzyme that hydrolyzes oxidized phospholipids. The mean Lp(a) concentrations are markedly high in black individuals, 2 to 3 times greater than in Caucasian and Oriental individuals[14], but these levels are nonpredictive of CVD in black individuals.

Additionally, high Lp(a) is also a risk factor for atherosclerosis in other arterial beds, such as in ischemic cerebral disease where risk gets escalated with Lp(a) levels, over 30 mg/dL. Further, in a 13-year long follow-up in 14,000 participants, a prospective study has shown a higher incidence of ischemic cerebral disease with raised Lp(a) level[37]. Similarly, in another study involving 50,000 individuals, it was also shown that a raised Lp(a) level is associated with ischemic cerebrovascular accidents[5]. In a meta-analysis of 40 prospective studies involving 58,000 individuals, a 2 times increase in the risk for developing CAD and cerebrovascular accident was noted in individuals with smaller apo(a) isoforms, regardless of the Lp(a) concentration, and classical risk factors[38]. In recent years, a number of studies have reported that elevated Lp(a) levels are independently and linearly predictive of future CVD, though the mechanisms linking Lp(a) to atherogenesis are still unclear and that studies proving the therapeutic decrease of Lp(a) reduces the number of events still lack. The influence of Lp(a) levels on carotid intima-media thickness is still controversial. An inverse association in Japanese population has been observed while no relationship between that thickness and Lp(a) levels has been noted in Spaniards.

Regarding implication of gender, it was observed that a raised lipoprotein level leads to more significant risk repercussions in female sex compared to male sex[39]. A more recent Atherosclerosis Risk in Communities (ARIC) study has reported differences in LP(a) concentrations between sexes, which is higher in females[40]. Although most studies have shown no difference between sexes in Lp(a) concentrations. In postmenopausal women, an elevated Lp(a) and triglyceride level are predictive of the presence of CAD. Investigators have observed that predictive utility of Lp(a) is markedly attenuated among women taking hormone replacement therapy and that the relationship of high Lp(a) levels with increased CVD is modified by hormone replacement therapy[41].

Atherogenesis is a common causal factor of abdominal aortic aneurysm and Lp(a) levels are elevated in abdominal aneurysm showing the association between lipoprotein and atherogenesis. Recent events suggest that genetic variation in the LPA locus-mediated by Lp(a) concentration may also predict aortic valve stenosis[42]. This can well explain why heart valve calcification may run in families. A causal relationship between Lp(a) and calcific aortic valve disease has also been demonstrated. Nongenetic risk factors for aortic valve calcification include advanced age, high blood pressure, obesity, high cholesterol levels, and smoking. Development of novel targeted medications in future

might slow the progression of disease. Statins have not been shown to reduce aortic valve calcification.

High Lp(a) levels predict risk of early atherosclerosis independently of other cardiac risk factors, including LDL and that Lp(a) concentrations also associate significantly with the severity of coronary atherosclerosis. In addition, Lp(a) appears to be an independent risk factor in both primary and secondary settings though there is a paucity of information on the predictive value of Lp(a) in patients with stable CVD[43]. The authors observed that Lp(a) represents a significant risk factor for recurrent events. In patients of advanced CVD, Lp(a) indicates a coagulant risk of plaque thrombosis. In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, baseline Lp(a) was associated with future CVD and CHD. The authors observed that baseline Lp(a) concentration was associated with total CHD events ($p < 0.001$), total CVD events ($p = 0.002$) and coronary events ($p = 0.03$). For events after 1 year, an increase in Lp(a) at 1 year was associated with adverse outcomes for total CHD events and total CVD events ($p = 0.002$ each). It was demonstrated that a rising Lp(a) level is associated with cardiovascular events[43].

THERAPEUTIC APPROACHES FOR ELEVATED LP(a) LEVELS

The European Atherosclerosis Society currently recommends that patients with a moderate or high risk of cardiovascular risk having one of the following risk factors such as premature CVD, familial hypercholesterolemia, family history of premature CVD, family history of elevated Lp(a), recurrent CVD despite statin treatment, ≥3% 10-year risk of fatal CVD according to the European guidelines, ≥10% 10-year risk of fatal and or nonfatal CVD according to US guidelines should be screened for their Lp(a) levels[2].

If the Lp(a) levels are raised, treatment should be started with a goal of bringing the level below 50 mg/dL. In addition, the patient's other cardiovascular risk factors (including LDL levels) should be optimally managed[2]. Besides Lp(a) plasma concentration, the apo(a) isoforms might be an important risk parameter as well. Moreover, a better understanding of the basic mechanism of production and metabolism of Lp(a) and apo(a) is important to correlate the effect of future therapeutic agents. Major gaps in clinical medicine are: Lowering Lp(a) levels leads to clinical benefit have not been documented; in majority of studies, Lp(a) levels were lowered in conjunction with changes in other lipoprotein thus complexing the outcomes and the underlying mechanisms of Lp(a)-lowering of these agents are not fully clarified[1].

EFFECTS OF DRUGS ON LP(a) CONCENTRATION

There is no specifically targeted definitive therapy to decrease Lp(a) levels and specific and effective agents do not exist without affecting other lipoproteins. Traditional lipid-lowering agents such as statins or fibrates do not consistently decrease Lp(a) concentrations. Statins either have no effect or increase Lp(a) levels, sometimes significantly. The use of atorvastatin at a dose of 20 mg/day for 24 weeks caused no effect on Lp(a) levels. In a double-blind study with placebo, using doses of 10 or 40 mg/day of atorvastatin for 12 weeks, the Lp(a) concentration had significantly decreased[44]. A meta-analysis published in 2012, suggests that atorvastatin may lower Lp(a) levels[45]. In respect to lovastatin, simvastatin, and gemfibrozil, the latter has shown greater efficacy in reducing Lp(a)[46]. Ezetimibe decreases Lp(a) levels approximately 29%[47]; however, ezetimibe is commonly used with simvastatin, which does not have any additive effect to that of ezetimibe in regard to Lp(a) levels.

Presently, more commonly simple treatment which is relatively safe and independent for raised Lp(a) levels is niacin and aspirin.

Niacin

High dose niacin 1-3 g/day generally in an extended-release form is preferred. The Lp(a) levels are reduced by 20%-30%[48], while 4 g/day of niacin leads to 38% reduction in Lp(a) levels though at lower dose 1 g/day niacin has not shown that effectiveness. High dose niacin is widely used in the treatment of dyslipidemia because in addition to reducing LDL cholesterol levels, it increases HDL cholesterol levels and decreases Lp(a) levels[49]. The European Atherosclerosis Society Consensus Panel have suggested use of niacin for Lp(a) and CVD risk reduction. Further, extended-release niacin has also reduced Lp(a) levels in diabetic patients with dyslipidemia. Etofibrate, a hybrid drug combining niacin and clofibrate, at a dose of 1 g/day decreases Lp(a) levels by 26% in type II dyslipidemic patients[50]. Patients with type IIa and IIb hyperlipidemia being treated with neomycin alone have seen a decrease in Lp(a) concentration by 24%, while the neomycin-niacin association in high doses has resulted in a 45% reduction[51].

It may be mentioned that high doses of niacin are associated with adverse effects, such as migraine, flushing, diarrhea, vomiting, tachycardia, and liver toxicity, though, administration of aspirin 30 minutes prior to niacin can relieve some of these adverse effects.

Aspirin

Another commonly used cheap drug, aspirin may be beneficial. Japanese patients with elevated Lp(a) levels (>300 mg/dL) have shown a 20% reduction in Lp(a) levels even with low doses of aspirin (81 mg/day)[52]. Women with high Lp(a) levels and an apo(a) polymorphic allele seem to have benefited more from treatment with aspirin than those who lack that allele[53]. Thus, aspirin has been found useful only in patients that carry the apolipoprotein(a) gene minor allele variant (rs3798220)[53].

Estrogen Replacement

Estrogens lower Lp(a) up to 30%; although estrogen replacement therapy in postmenopausal women has beneficial effects on Lp(a) and other plasma lipids, yet it is studded with controversies regarding increased risk of certain malignant neoplasias and thromboembolic accidents. At present, estrogen is not indicated for treatment of elevated Lp(a). Tamoxifene and raloxifene have not been shown to reduce levels. The precise underlying mechanisms of Lp(a)-lowering of these agents are not fully defined. A variety of agents belonging to different chemical groups are in various stages of development or undergoing clinical trials that may reduce Lp(a) concentrations and in future may open the doors to new avenues of therapy include:

L-carnitine

It is a combination of L-lysine and ascorbate; it may also reduce LPA levels[54]. A more effective treatment is the Linus Pauling protocol, 6-18 g/day ascorbic acid, 6 g/day L-lysine and 2 g/day L-proline. This protocol may reduce Lp(a) two- to fivefold over a few months.

Thyromimetics

The development of selective thyromimetics having specific liver selectivity (affinity to THRβ isoforms) provide an opportunity for the treatment of dyslipidemia, obesity or for weight loss, nonalcoholic fatty liver disease and may play a role in decreasing Lp(a) levels[55].

- *Sobetirome,* a selective thyromimetic compound reduced LDL cholesterol by 41% at 100 μg/day and in primates caused increase in oxygen consumption, reduction in body weight and minimal effects on skeletal mass. The agent reduces fat mass without increasing food intake and controls dyslipidemia, without causing deleterious effects on heart or bone mass[55].
- *KB-141* is another THRβ agonist, which is 10 times more selective for stimulating metabolic rate and 30 times more selective for cholesterol-lowering than for increase in heart rate[55]. KB-141 has been shown to cause weight reduction as well as reduction of cholesterol and Lp(a)[56].
- *Eprotirome:* It is also a THRβ selective compound, causes 40% reduction in total and LDL cholesterol after 14 days treatment probably owing to an increase in bile acid synthesis[55]. In humans, data from a clinical trial of 98 hyperlipidemic patients revealed eprotirome to cause 25% reduction in LDL, apoB, along with 37% decrease in Lp(a) at 100 μg/day after 16 weeks. At 200 μg/day, there was 45% decrease in Lp(a). Triglycerides also decreased significantly. No cardiac, bone or muscle effects were observed, though mild transient elevation in liver enzymes was seen. Moreover, selective thyromimetics may have additive LDL cholesterol-lowering when used in combination with statins in animal models.

Cholesteryl Ester Transfer Protein Inhibitors

These agents reduce risk of atherosclerosis by improving plasma lipid levels. They substantially increase HDL, lower LDL and reverse the transport of cholesterol. A few of these agents namely torcetrapib, dalcetrapib, evacetrapib have failed in clinical trials. However, anacetrapib and TA-8995 had shown encouraging phase II clinical trials results[57]. Cholesteryl ester transfer protein (CETP) inhibitors inhibit CETP, which normally transfer cholesterol from HDL cholesterol to very LDL (VLDL) or LDL. Inhibition of this process results in higher HDL levels and reduces LDL levels. CETP inhibitors do not reduce rates of mortality, heart attack or stroke in patients already taking statins.

Antisense Oligonucleotides to ApoB

Mipomersen, a second-generation antisense oligonucleotide injectable drug approved by the Food and Drug Administration (FDA) to be used in homozygous familial hypercholesterolemia in January 2013, might be a promise to decrease Lp(a) levels[58]. Mipomersen is a polynucleotide of 20 bases that is complementary in sequence to a segment of human apoB-100 mRNA. It specifically binds to apoB-100 mRNA, blocking the translation of the gene product[58]. A reduction in the synthesis of apoB-100 decreases the hepatic production of VLDL, consequently decreasing circulating levels of atherogenic VLDL remnants, intermediate-density lipoprotein (IDL), LDL, and Lp(a) particles[58]. Thus,

mipomersen reduces all apoB-containing atherogenic lipoproteins and that it consistently and effectively reduces Lp(a) levels in patients with a variety of lipid abnormalities and cardiovascular risk. It has been demonstrated that a specific antisense oligonucleotide directed to KIV-11 repeats lowers apo(a) mRNA and apo(a) plasma levels by 85% in apo(a) transgenic mice, with minor effects on other lipoproteins. Mipomersen's mode of action differs from traditional enzymes or protein-targeting drugs such as statins. It has no dependency on cytochrome P450 metabolism, hence minimal interaction with statins, ezetimibe, bile acids binding resins or other lipid-lowering medications with which it might be combined. Lp(a) levels are decreased in conjunction with changes in other lipoproteins. However, the safety of its use has not been well-established.

Farnesoid X Receptor Agonists

Farnesoid X receptor (FXR, also referred to as NR1H4) is a member of the nuclear receptor superfamily of ligand-regulated transcription factors that plays critical role in the regulation of bile acid, triglyceride, and cholesterol homeostasis. However, its impact on cholesterol homeostasis is less clear. Bile acids, the end-product of cholesterol catabolism, are physiological ligand for FXR. Activation of FXR leads to down-regulation of CYP7A1, the rate limiting enzyme in bile acid synthesis, resulting in reduced cholesterol catabolism. WAY-362450 is a potent synthetic FXR agonist, which decreases serum triglyceride levels with efficacy comparable to fenofibrate. It also reduced serum cholesterol levels via reductions in LDL cholesterol, VLDL cholesterol and HDL cholesterol lipoprotein fractions, and may be of clinical utility in the treatment of mixed dyslipidemia. Synthetic FXR ligands have been demonstrated to regulate apolipoprotein CII (apoCII) and apolipoprotein CIII (apoCIII), cofactors involved in lipoprotein lipase (LPL)-mediated lipolysis and down modulate sterol regulatory element-binding protein 1c (SREBP-1c), the master regulator of the triglyceride synthetic pathway. Evans et al[59] demonstrated that orally active FXR ligand WAY-362450 potently lowers serum triglyceride levels and VLDL cholesterol in multiple rodent models of dyslipidemia along with consistent-lowering of circulating serum cholesterol levels. The mechanism of action of WAY-362450 is probably through modulation of genes involved in both lipolysis and lipogenesis.

Anti-proprotein convertase, subtilisin/Kexin type 9 (anti-PCSK-9) inhibitors, monoclonal antibodies, protein responsible for degrading LDL receptor; and anti-tocilizumab antibody, that can block IL-6-signaling are still in experimental phase. In severe cases, such as familial hypercholesterolemia or treatment-resistant hypercholesterolemia lipid apheresis may lead to dramatic reductions in Lp(a) levels in more than 50% of patients.

Miscellaneous Agents

- **Methotrexate:** An immunosuppressive and anti-inflammatory drug used in the treatment of rheumatoid arthritis, may also reduce Lp(a) levels[60].
- ***Gingko biloba*** may be beneficial, but has not been clinically verified. Coenzyme Q-10, pine-bark extract and pharmacological amounts of fish oil supplements may be helpful to lower the levels of Lp(a) but none of these are clinically proven.

Interactions

Lp(a) has been shown to interact with calnexin, fibronectin, and fibrinogen beta chain.

CONCLUSION

New novel, targeted therapeutic agents that can specifically and definitely reduce Lp(a) plasma concentrations are still being sought. In general, in the absence of well-tolerated drugs that effectively decrease Lp(a) concentrations, levels over 25-30 mg/dL should lead to a more strict control of other risk factors for CAD. However, the presumption that lowering Lp(a) levels leads to clinical benefits such as decreased risk of CVD needs confirmation.

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