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# Lipoprotein (a) – An Overview

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## 1. Introduction

Lipoprotein (a) [Lp(a)], first described in 1963 is an inherited cholesterol-rich particle found in a density range of 1.055-1.120 g/ml. The suggestion that Lp(a) might be a risk factor for cardiovascular diseases was first made by Dahlen et al. [1] who found out that individuals with angina pectoris exhibit an “extra pre- $\beta$ -band” in lipid electrophoresis. In whites the concentration of Lp(a) in plasma varies from undetectable up to 200 mg/dl in different individuals but seems to be rather constant in the same person [2]. Chemical and physicochemical properties of Lp(a) in comparison with LDL are summarized in table 1.

Plasma Lp(a) concentrations above 30 mg/dl, as measured in about 20 percent of white people, are associated with an approx. two-fold relative risk of coronary atherosclerosis [3] rising to the range of five-fold when LDL and Lp(a) are both elevated [4]. Interestingly, blacks with high levels of Lp(a) do not experience greatly increased atherosclerotic progression and mortality. In those cases it is assumed that the atherogenicity of Lp(a) must be decreased or counterbalanced by other factors [5].

Till now the site and mechanism of Lp(a) synthesis are quite unclear. Measurements of serum Lp(a) levels of patients suffering from liver disease or from cholestasis who showed significantly lower concentrations than healthy controls gave indications that Lp(a) might be synthesized by the liver [6]. On the other hand there are studies which suggest that apo-a is associated with the postprandial d < 1.006 lipoproteins induced by fat feeding [7] but it is not yet clear however whether apo-a determined in this fraction is really of intestinal origin or whether it originates from free apo-a in serum which might bind to freshly secreted chylomicrons [8]. Because of the chemical similarities between Lp(a) and LDL it is possible that Lp(a) is formed during the metabolic catabolism of chylomicrons, VLDL or LDL. As Lp(a) levels stay nearly constant within one individual and as lipid-rich diet as well as fasting have no influence on Lp(a) concentrations it is assumed that Lp(a) exhibits a

metabolic behaviour completely different from other apo-B containing lipoproteins. Turnover studies in vivo performed with labelled VLDL confirmed these assumptions. Nearly all the activity of labelled VLDL could be detected in LDL whereas only trace amounts could be found in Lp(a) [9] confirming the hypothesis that unlike LDL, Lp(a) probably has no triglyceride-rich lipoproteins as precursors but seems to be secreted directly by the liver [10]. On the other hand the site of catabolism of Lp(a) in humans is unknown so far although the kidney is favoured to be implicated [11].

Despite extensive work on Lp(a) its possible physiological function remains unclear till now.

	LDL	Lp(a)
Hydr. Density [g/ml]	1.034	1.085
Mol. Wt. [ $\times 10^6$ ]	2.4	5.5
Diameter [ $\text{\AA}$ ]	210	250
E. Mobility	$\beta$	pre- $\beta$ 1
Chem. Composition [%]		
Free cholesterol	11	10
Cholesteroleser	40	30
Triglycerides	4	4
Phospholipids	21	20
Protein	22	28
Carbohydrates	2	8

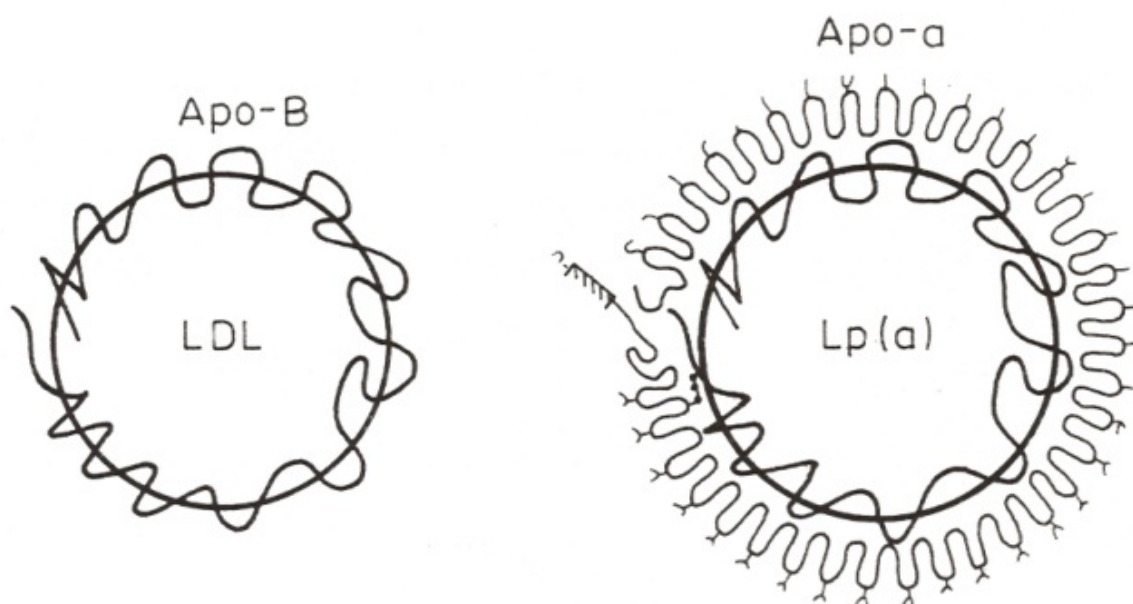
**Table 1.** Chemical and physicochemical properties of LDL and Lp(a)

## 2. Structural arrangement and catabolism of Lp(a)

The major protein component of this LDL-like particle is apolipoprotein B (apo-B-100) which carries an additional protein called apolipoprotein-a [apo-a] linked to apo-B-100 via disulphide bridges (Fig.1) the lipid moiety however being almost indistinguishable from that of LDL [12]. Human apo-a itself consists of multiple so-called kringle repeats, sequences consisting of 80-90 amino acids arranged in a tripleloop tertiary structure and tandemly arrayed resembling kringles IV and V of plasminogen and a protease domain [13]. Copy number variants in the LPA gene on chromosome 6 coding for apo-a are responsible for a variation of plasma Lp(a) levels of up to 1000-fold among individuals. The most influential is the kringle IV-2 size polymorphism [14] while kringle IV types 1 and 3-10 as well as kringle V occur only once in Lp(a) [15]. The number of kringle IV type 2 structure repeats results in a large number of different sized isoforms of apo-a and correlates inversely with the plasma concentration of Lp(a) [16]. Although the exact mechanism responsible for this

inverse correlation has not been elucidated so far an isoform dependent retention and degradation in the endoplasmatic reticulum has been implicated [17].

Contradictory results have been reported about the clearance of Lp(a) and till now it remains unclear whether Lp(a) binds to the B/E receptor via apo-B like LDL or whether it is catabolised independently of the LDL-receptor mediated pathway. Whereas in one study using fibroblasts from normal subjects and from subjects with autosomal dominant hypercholesterolemia the conclusion was reached that Lp(a) enters fibroblasts independently of the LDL-receptor [18] others concluded that Lp(a) is also bound to the LDL-receptor, internalized and degraded but with a degradation capacity of only 25% of that of LDL [19]. Binding studies of native and reduced Lp(a) with different monoclonal antibodies against apolipoprotein B revealed that there was no antibody that failed to react with native Lp(a) but some of the antibodies recognized apoB of Lp(a) to a lesser degree than that of LDL. This favoured the idea that certain regions on apo-B of Lp(a) could be different from those on LDL and led to the assumption that certain domains close to the binding domain of Lp(a) to the B/E-receptor could be covered by apo-a or that apo-a causes conformational changes in the binding region of apo-B thereby constricting the binding of Lp(a) to the LDL-receptor [20] being in agreement with the fact that normal unreduced Lp(a) seemed to be taken up by fibroblasts through B/E-receptor-mediated endocytosis but showed poorer specificity for the receptor than LDL [21].



**Figure 1.** Schematic model of Lp(a) in comparison to LDL

### 3. Free apolipoprotein-a in human serum

In the beginning of “Lp(a)-research” this lipoprotein was believed to represent a genetically polymorphic form of LDL [22]. According to this assumption apo-a should distribute

uniformly between all apo-B-containing lipoproteins. Investigation of this problem in more detail revealed that Lp(a) forms a particular lipoprotein class found primarily in the HDL-2 density region [23] but can also be detected in LDL class ( $d = 1.019\text{--}1.063$  g/ml) [24] and even in chylomicrons induced by fat feeding [25]. The fact however that a portion of the Lp(a)-specific antigen can be found in the  $d > 1.21$  g/ml lipoprotein free bottom fraction after ultracentrifugation of plasma [26] led to further investigation of this phenomenon. Apo-a is virtually absent in the VLDL fraction ( $d < 1.006$  g/ml) of freshly drawn fasting human sera while 95% of total Lp(a) can be obtained in the  $d > 1.006$  g/ml bottom fraction. Approximately 5% of the total serum Lp(a) are found in the  $d > 1.125$  g/ml bottom fraction after ultracentrifugation as well as with polyanionic precipitation agents irrespective of the Lp(a) concentration in serum [8]. Due to the lack of Sudan Black staining this bottom Lp(a) is considered as a lipid free “apo-a protein” raising the question whether or not free apo-a can reassociate with LDL to form “native Lp(a)”.

#### 4. Lp(a) and platelet aggregation

One of the physiological roles of platelets involves binding to subendothelial tissue after vascular injury [27]. The adherence of platelets to the exposed connective tissue, preferably collagen, leads to aggregation followed by the release of ADP, 5-hydroxytryptamine and  $\text{Ca}^{2+}$  from their dense granules, causing passing platelets to adhere to the primary clot [28].

There is little doubt that lipoproteins interfere with platelets *in vivo* being reflected by the fact that platelets from hyperlipoproteinemic patients are hyperreactive [29]. This is confirmed by the fact that incubation of platelets with physiological concentrations of atherogenic apoB-containing lipoproteins such as LDL or VLDL results in enhanced platelet aggregability [30] while antiatherogenic lipoproteins such as HDL exert the opposite effect [31]. Concerning Lp(a) it is generally accepted that elevated plasma concentrations of this lipoprotein are connected with premature atherosclerosis [32] but much uncertainty remains about the influence of Lp(a) on platelet activation, a phenomenon that is believed to be involved not only in long-term processes of plaque formation but also in acute events such as stroke and myocardial infarction [33]. Moreover a two-fold increase in the risk of coronary heart disease (CHD) and ischaemic stroke could be demonstrated especially in subjects with small apolipoprotein(a) phenotypes [34] and prospective findings in the Bruneck study have revealed a significant association specifically between small apolipoprotein(a) phenotypes and advanced atherosclerotic disease involving a component of plaque thrombosis [35]. Indeed, Lp(a) is a “sticky” lipoprotein that self-aggregates, attaches to all sorts of surfaces [36], and precipitates not only *in vitro* but possibly *in vivo*. Moreover, Lp(a) binds to proteoglycans and glycosaminoglycans [37] and it has high affinity for fibronectin [38], tetranectin [39], collagen [40], and other connective-tissue structures [41]. Therefore the influence of Lp(a) on platelet aggregation induced with various triggers was investigated measuring serotonin release and thromboxane  $\text{A}_2$  formation during collagen-triggered aggregation as well as adhesion of platelets to collagen in flowing blood

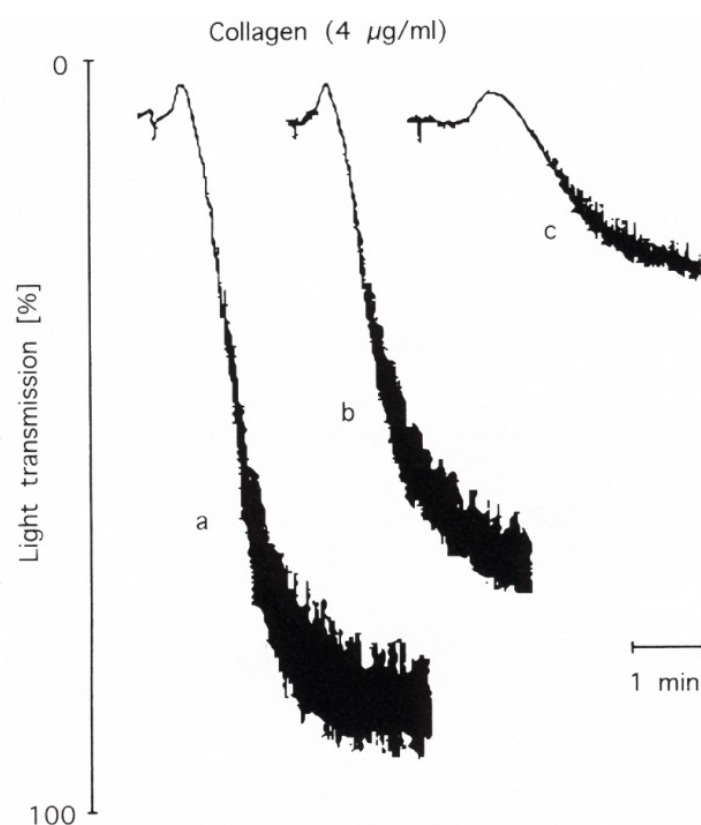
under the influence of Lp(a). As Lp(a) represents an LDL-like particle an elevated platelet reactivity was expected under the influence of this lipoprotein similar to that described for LDL [42].

Unlike LDL, Lp(a) revealed no proaggregatory effects on platelets, contrary collagen-induced platelet aggregation was inhibited by up to 54% and the aggregation rate was attenuated by 47% compared with platelets incubated with Tyrode's solution (Fig. 2), being accompanied by a significant reduction of serotonin release and TXA<sub>2</sub> formation. Furthermore Lp(a) significantly reduced platelet adhesion to collagen by about 20% and the size of platelet aggregates up to 63% especially at high shear rates (Fig. 3) suggesting that Lp(a) exerts antiaggregatory effects at least under well-defined in vitro conditions [43]. If these observations are relevant for the in vivo situation, a variety of potential platelet-collagen binding sites such as GPIa/IIa or GPIV could be covered by Lp(a) the more that binding of Lp(a) to platelets could be demonstrated [44]. As there is conflicting evidence on the role of Lp(a) in thrombosis in vivo and in vitro work has been done to elucidate the mechanisms whereby Lp(a) is influencing platelet aggregation and a variety of mechanisms is suggested how Lp(a) interferes with platelet aggregation and hence fibrin bound clot formation. Lp(a) binds to resting, non-stimulated platelets on the IIb subunit of the fibrinogen (IIb/IIIa) receptor via binding sites distinct from the arginyl-glycyl-aspartyl (RGD) epitope of apo-a [45]. By this way the RGD binding site of Lp(a) could be exposed via conformational change induced by platelet agonist stimulation leading to binding of the RGD epitope of apo-a to the RGD binding site on the IIb protein of the fibrinogen (IIb/IIIa) receptor of the platelet [46] thereby reducing fibrinogen binding to the platelet [47]. Low concentrations of Lp(a) (1-25 mg/100 ml washed platelets) increase intracellular levels of c-AMP of in vitro resting platelets leading to an antiaggregatory condition [48] while at higher in vitro levels of Lp(a) (50-100 mg/100 ml washed platelets) resting platelet intracellular c-AMP levels return to normal [49] which cannot explain the reported progressive Lp(a)-mediated decrease in collagen-induced aggregation [43, 50]. Further investigations strongly support an apo-a mediated, Lp(a) induced reduction of collagen and ADP-stimulated platelet aggregation via diminished production of thromboxane A<sub>2</sub> [43, 51]. Concerning the in vivo situation only one study has been published to date looking at adult human type 2 diabetics all of whom were obese (BMI >30). In this in vivo study of human type 2 diabetics there is a positive correlation between fasting serum concentrations of Lp(a) and bleeding time, a strong correlate of in vivo platelet aggregation [52] favouring the inhibitory effect of Lp(a) on platelet aggregation. On the other hand there are studies reporting an apparent proaggregatory action of Lp(a) possibly mediated by the apo-a subunit. While no effect of recombinant apo-a [r-apo-a] derivatives on primary ADP-induced platelet aggregation was observed weak platelet responses stimulated by the thrombin receptor-activating peptide SFLLRN were significantly enhanced by the r-apo-a derivatives accompanied by a significant enhancement of [<sup>14</sup>C]serotonin release of the dense granules [53]. Further investigations showed that r-apo-a isoforms and Lp(a) do not cause platelet aggregation by themselves but preincubation of platelets with r-apo-a derivatives promotes an aggregation response to otherwise

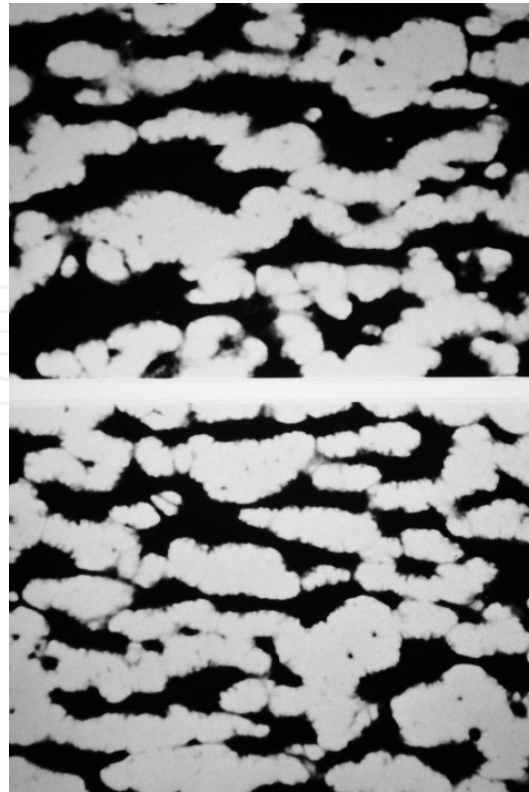


subaggregant doses of thrombin receptor activation peptide (TRAP) and arachidonic acid while inversely platelet stimulation with arachidonic acid enhanced platelet binding of apo-a [54]. In both studies it turned out that the size of r-apo-a determined by the number of KIV type 2 modules seems not to play a crucial role in its proaggregant effect.

Summarizing, *in vitro* studies indicate that Lp(a) induced decreases, increases or no change at all in platelet aggregation [43, 45, 50, 51, 53, 54]. In all cases the mechanisms involved are quite unclear and only speculative. A recent work strongly supports the evidence to suggest that Lp(a) binds to platelets via its arginyl-glycyl-aspartyl (RGD) epitope of the apo(a) but not via apo(a)'s lysine binding region in both strong and weak agonist-stimulated platelets and inhibits the binding of fibrinogen thus reducing aggregation [55]. On the other side there are *in vivo* studies published quite recently suggesting that Lp(a) concentrations greater than 30 mg/dl are a frequent and independent risk factor for venous thrombosis [56] and that high levels of Lp(a) could be a more frequently thrombophilic risk factor in young women [57]. To date disagreement exists about increased arterial thrombosis due to elevated blood levels of Lp(a). The fact that this procedure is a result of collagen-exposed platelets in case of plaque rupture followed by clot formation argues against the proaggregatory nature of Lp(a) and maybe procedures others than platelet activation account for the atherogenic nature of Lp(a).



**Figure 2.** Aggregation curves showing the influence of lipoproteins on collagen-induced platelet aggregation. Gel filtered platelets (200  $\mu$ l;  $2 \times 10^8$ /ml) were incubated for 30 min at 37°C with a) LDL 5 mg/ml, b) Tyrodes's buffer or c) Lp(a) 0.5 mg/ml. Aggregation was triggered with 10  $\mu$ l collagen (final concentration 4  $\mu$ g/ml).



**Figure 3.** Aggregate formation of fibrillar collagen at a shear rate of 1600/s for a control (top) and under addition of 1 mg/ml Lp(a) (bottom). Aggregates are shown in black.

## 5. Lp(a) and plasminogen

The mechanism by which Lp(a) accelerates atherosclerosis could not yet been clarified. One possible explanation leads via the connection of Lp(a) to the fibrinolytic system as in 1987 it was found out that Lp(a) and plasminogen are immunochemically related [58] leading to speculations whether Lp(a) might interfere with fibrinolysis. Through partial amino acid sequencing it could be shown for the first time that apo-a has a striking homology of about 70% to plasminogen, the precursor of the proteolytic enzyme plasmin which dissolves fibrin clots [58]. This could be confirmed in our own studies demonstrating that polyclonal antisera from rabbit, sheep and horse as well as three monoclonal antibodies from mouse raised against apo-a reacted with plasminogen on immunoblots and similar to plasminogen, Lp(a) bound selectively but with somewhat lower affinity to lysine-Sepharose [59]. Plasminogen, a protein of 791 amino acids and a molecular weight of about 92 000 D is a plasma serine protease zymogen that consists of five cysteine-rich sequences of 80-114 amino acids each, called kringles, followed by a trypsin like protease domain [60]. The highly glycosylated apo-a exists in various polymorphic forms with molecular weights higher, lower or equal to apoprotein B ( $M_r \approx 550\,000$  D) [61] which are covalently linked to apoprotein B via disulfide bridges [62]. It contains a hydrophobic signal sequence for secretion followed by up to >50 copies of kringle IV of plasminogen predicting the risk for coronary heart disease in the way that apo-a alleles with a low kringle IV copy number (<22) and high Lp(a) plasma concentration are significantly more frequent in the CHD group



( $p < 0.001$ ) [63]. Additionally one kringle V as well as protease domains of plasminogen are found in apo-a [58]. Later on cDNA sequencing revealed that human apolipoprotein(a) is homologous to plasminogen but despite the fact that apo-a contains a protease domain it does not act fibrinolytically like plasminogen because the arginine at the cleavage site for tissue plasminogen activator in plasminogen is changed to serine in apo-a [64].

Nevertheless Lp(a) might interfere with the fibrinolytic system in different ways due to its similarity to plasminogen as it may inhibit the binding of plasminogen to its receptor on endothelial cells thereby preventing generation of plasmin and increasing the thrombotic risk [65, 66]. Furthermore it could be demonstrated that Lp(a) accumulates in atherosclerotic lesions maybe via adherence to fibrinogen or fibrin incorporated in atherosclerotic plaques thereby inhibiting fibrinolysis [66]. Another mechanism by which Lp(a) is thought to attenuate fibrinolysis involves direct competition with plasminogen for fibrinogen or fibrin binding sites thus reducing the efficiency of plasminogen activation [67]. Fibrinolysis is initiated by binding of plasminogen to lysine residues on fibrin thereby initiating activation of plasmin and amplifying fibrinolytic processes [68]. Like plasminogen Lp(a) also binds to lysine residues [69] but without catalytical activity leading to interference with or inhibition of fibrinolysis resulting in hypofibrinolysis and accumulation of cholesterol included in the LDL-like component of Lp(a) [66]. The fact that low molecular weight isoforms of apo-a are associated with greater inhibition of fibrinolysis [70, 71] confirms the hypothesis that subjects with small apo-a phenotypes have a two-fold risk of CHD and stroke compared with those with larger isoforms of apo-a [34]. In contrast Knapp et al. [72] observed that the rate of plasmin formation was inversely related to Lp(a) but inhibition of plasmin generation increased with the size of apo-a using a standardized in vitro fibrinolysis model. From the fact that the inhibitory effect of free apo-a was much stronger than that of the complete Lp(a) particle they conclude that the apo-a component is responsible for the observed reduction of plasmin formation maybe due to the availability of additional lysine binding sites in the unbound apo-a which was formerly reported by Scanu et al. [73]. On the other hand there are also data showing that the plasma concentration of Lp(a) is inversely related to plasmin formation but that this relationship is not influenced by the size of apo-a isoforms [74]. Above all there are other reports explaining the inhibitory effect of Lp(a) on fibrinolysis not only by competition of Lp(a) with plasminogen for the binding sites on fibrin, endothelial cells and monocytes but also by reduction of tissue plasminogen activator or streptokinase-induced fibrinolytic activity [75, 76, 77].

A novel contribution to the understanding of Lp(a)/apo-a-mediated inhibition of plasminogen activation comes from results showing the ability of the apo(a) component of Lp(a) to inhibit the key positive feedback step of plasmin-mediated conversion of Glu-plasminogen to Lys-plasminogen an essential step for fibrin clot lysis [78]. Interestingly, with the exception of the smallest naturally-occurring isoform of apo(a), isoform size was found not to contribute to the inhibitory capacity of apo(a).

In summary, the proposed mechanisms modulating the antifibrinolytic effects of elevated Lp(a) levels in vitro are manifold and emphasize the prothrombotic effects of this lipoprotein particle. The in vivo situation however seems to be much more complex the

more that there is a strong positive correlation reported between bleeding time and fasting serum concentrations of Lp(a) [52].

## 6. Lp(a) and lipid lowering drugs

High levels of Lp(a) are strongly associated with atherosclerosis as revealed by numerous studies [4, 79, 80, 81, 82]. As plasma Lp(a) concentrations above 30 mg/dl, as measured in about 20 percent of white people, are associated with an approx. two-fold relative risk of coronary atherosclerosis [3] rising to the range of five-fold when LDL and Lp(a) are both elevated [4] reduction of plasma Lp(a) concentration is recommended. Dietary interventions do not seem to be effective in lowering Lp(a) plasma levels [9, 83] or even lead to an increase of Lp(a) in plasma, alone [84] or at least when combined with exercise [85]. The same phenomenon could be observed in case of exercise where cross-sectional data suggest that a lifestyle of moderate to intense exercise training does not exert a significant impact on the Lp(a) level [86, 87]. Therefore pharmacological reduction of plasma levels of Lp(a) would be desirable.

Innumerable investigations however indicate that the plasma concentration of Lp(a) is resistant to drug therapy in most cases. As Lp(a) resembles LDL especially with regard to the lipid content (Tab.1) medications reducing LDL-cholesterol should be suitable for lowering Lp(a) as well. Bile acid resins such as cholestyramine which actually cause a significant reduction of LDL-cholesterol as well as of apo-B have no effect on Lp(a) levels [88, 89]. Therapies with bezafibrate or clofibrate [90, 91] showed that there is no role for fibrates in the treatment of elevated Lp(a) concentrations and estrogens also do not seem to significantly affect Lp(a) [92, 93].

Stanozolol, an anabolic steroid used in the treatment of postmenopausal osteoporosis, showed a significant reduction of Lp(a) by about 65% after six weeks therapy but five weeks after the drug was discontinued Lp(a) was near pretreatment levels [94]. Although drastic reductions of Lp(a) up to 40-50% are reported in another study [95] these compounds seem to be unsuitable for the routine treatment due to their harmful side effects [96].

Statins, also known as HMG-CoA-reductase inhibitors are another group of lipid lowering drugs which could be interesting with regard to Lp(a). These drugs have proven to be extremely effective in lowering plasma LDL and apo-B levels presumably through inhibition of intracellular cholesterol synthesis concomitant with an increase of the LDL receptors in the liver [97]. Although Lp(a) and LDL are very similar especially concerning the content of cholesterol, inhibitors of HMG-CoA-reductase, the regulating enzyme of cholesterol biosynthesis, show no influence [98, 99], only modest reduction of about 10% [100, 101] or even an increase of serum Lp(a) levels [102]. Altogether the limited magnitude of decrease of Lp(a) by HMG-CoA-reductase inhibitors confirms the assumption that the LDL-receptor does not seem to play a major role in Lp(a) clearance from plasma [103].

Nicotinic acid, also known as niacin has been shown to lower not only plasma total cholesterol, LDL-cholesterol and triglycerides thereby increasing HDL-cholesterol [104] but

also Lp(a) in a dose-dependent manner up to 40% [105]. A more pronounced effect could be observed in a combination therapy with niacin and neomycin showing a reduction of LDL-cholesterol by 48% and of Lp(a) by 45% respectively [106]. In a recently published study niacin was applied in combination with omega-3-fatty acids and the Mediterranean diet. The average reduction of Lp(a) after 12 weeks combination therapy was reported to be about 23%. Additionally a significant association with increasing baseline levels of Lp(a) was observed [107].

Diets rich in fish oils containing considerable amounts of omega-3 polyunsaturated fatty acids are recommended to have beneficial effects on plasma lipids thereby lowering the risk of vascular complications [108, 109]. In a study investigating the influence of dietary fish oils on plasma Lp(a) levels a decrease of triglycerides could be observed after six weeks dietary supplementation while total cholesterol, LDL- and HDL-cholesterol as well as Lp(a) remained unchanged [110]. Furthermore collagen- and thrombin-stimulated platelet aggregation and TXB<sub>2</sub>-formation in platelets decreased by approx. 45% irrespective of the plasma concentration of Lp(a) [111]. This is in agreement with many other studies showing that fish oils only seem to be able to reduce Lp(a) in combination with other therapies [107] or moderate exercise [112] but not when used alone [113, 114, 115].

Summarizing it can be shown that increased Lp(a) levels are minimally if at all influenced by drug treatment or drugs reducing Lp(a) to a greater extent like nicotinic acid are not widely used due to undesirable side effects. From previous turnover studies it could be demonstrated that plasma Lp(a) levels correlate with its rate of biosynthesis rather than with the fractional catabolic rate [116, 117] and therefore attempts to reduce Lp(a) should focus on an interference with apo-a biosynthesis. This is supported by the fact that adenovirus-mediated apo-a-antisense RNA expression efficiently inhibits apo-a synthesis in vitro in stably transfected liver cells but also in vivo in transduced mice expressing recombinant human apo-a [118]. In a recently published study it was found that patients suffering from biliary obstructions have very low plasma Lp(a) levels that rise substantially after surgical intervention. Consistent with this, common bile duct ligation in mice transgenic for human apo-a lowered plasma concentrations and hepatic expression of apo-a. Treatment of transgenic mice with cholic acid led to farnesoid X receptor (FXR) activation followed by markedly reduced plasma concentrations and hepatic expression of human apo-a [119]. From that it is concluded that transcription of the apo-a gene is under strong control of the farnesoid X receptor which may have important implications in the development of Lp(a)-lowering medications.

## 7. Conclusion

High levels of Lp(a) are strongly associated with atherosclerosis. About 10-15% of the white population exhibit plasma Lp(a) concentrations above the atherogenic cut-off value of approx. 30 mg/dl. Therefore the European Atherosclerosis Society recommended screening for Lp(a) in a consensus report, in which the desirable cut-off was set at less than 50 mg/dl [82]. On the other hand it is very well known that Lp(a) is an inherited atherogenic plasma

component determined to more than 90% by genetic factors a fact that aggravates the influence on plasma levels of this lipoprotein. So far there are only speculations about the mechanism by which Lp(a) accelerates atherosclerosis and the exact mechanism could not yet be clarified. Its prothrombotic effects may be ascribed to impaired fibrinolysis by inhibition of plasminogen activation rather than to amplification of platelet aggregation which is shown to be reduced by Lp(a) in most cases. At present dietary interventions or drug therapies seem to be only minimal if at all successful concerning reduction of plasma Lp(a). Up to now it was assumed that the atherogenicity of high Lp(a) levels in blacks must be decreased by other factors [5]. However data published recently show that associations between Lp(a) levels and cardiovascular disease are at least as strong in blacks compared with whites [120] and emphasize the recommendation that factors such as total cholesterol, LDL-cholesterol, smoking, diabetes mellitus or overweight that can still increase the atherosclerotic risk of Lp(a) should be kept under observation.

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