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Lipoprotein(a) – Structure, Epidemiology, Function and Diagnostics of a Cardiovascular Risk Marker

R. Siekmeier[1,*], H. Scharnagl[2], G.M. Kostner[3], T. Grammer[4], T. Stojakovic[2] and W. März[2,4]

[1]*Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Kurt-Georg-Kiesinger-Allee 3, Bonn, Deutschland;* [2]*Klinisches Institut für Medizinische und Chemische Labordiagnostik, Medizinische Universität Graz, Graz, Österreich;* [3]*Institut für Medizinische Biochemie und Medizinische Molekularbiologie, Medizinische Universität Graz, Graz, Österreich and* [4]*Synlab – Medizinisches Versorgungszentrum für Labordiagnostik Heidelberg, Eppelheim, Deutschland, Germany*

Abstract: Decades after its first description by Berg 1963 lipoprotein(a) (Lp(a)) is an established risk marker of cardiovascular diseases which is independent from other risk markers. The main difference of Lp(a) compared to LDL is the apo(a) residue which is covalently bound to apoB. Apo(a) is a glycoprotein which underlies a large genetic polymorphism. The latter is caused by a variation of the kringle-IV-type-2 repeats of the protein which is characterized by a large structural homology to plasminogen. The Lp(a) plasma concentration in the population is highly skewed and determined to more than 90 % by genetic factors. In healthy subjects the Lp(a)-concentration is correlated to its synthesis and not to its metabolism. Plasma concentrations of Lp(a) are affected by different diseases (e.g. diseases of liver and kidney), hormonal factors (e.g. sexual steroids, glucocorticoids, thyroid hormones), individual and environmental factors (e.g. age, cigarette smoking) as well as pharmaceuticals (e.g. derivatives of nicotinic acid) and therapeutic procedures (lipid apheresis). However, even though a large number of studies on Lp(a) were performed up to now many details of its physiological function and regulation of plasma concentration are not yet understood. In addition, studies showed contradictory results because there were large differences of the included patients, use of not sufficiently validated tests as well as analysis of frozen samples. Aim of our review was to describe function and physiological regulation of Lp(a) as well as factors influencing its plasma concentration.

Key Words: Lipoprotein (a), plasma lipoproteins, atherosclerosis, coronary heart disease.

INTRODUCTION

Lipoprotein (a) (Lp(a)), for the first time described in 1963 by Berg belongs to the lipoproteins with the strongest atherogenic effect [1, 2]. Its importance for the development of various atherosclerotic vasculopathies (coronary heart disease, ischemic stroke, peripheral vasculopathy, abdominal aneurysm), however, was recognised only considerably later [3-6]. With regard to its structure, lipoprotein(a) is a low density lipoprotein (LDL), to whose apolipoprotein B (apoB) another protein, i.e. apolipoprotein(a) (apo(a)) is covalently bound by a disulfide-bridge [7]. The physiological function of Lp(a) is unknown to date, since test persons with very low or not detectable Lp(a) plasma concentrations do not present a specific phenotype. Vice versa, however, numerous studies have shown that elevated Lp(a) plasma concentrations are associated with an increased risk of atherosclerotic diseases (coronary heart disease, peripheral arterial occlusive disease, cerebral stroke) [6, 8-33]. Apo(a) synthesis is performed in the liver, probably followed by extracellular assembly to the apoB moiety of the LDL [34]. The biological half life of Lp(a) is known from kinetic investigations and exceeds the half life of LDL [35, 36]. However, only little is known about the details of Lp(a) catabolism. It is assumed that the kidney has a specific function in Lp(a) catabolism, since the nephrotic syndrome and terminal kidney failure are associated with an elevation of the Lp(a) plasma concentration [37, 38]. One consequence of the poor knowledge of the metabolic paths of Lp(a) is the fact that so far pharmaceutical science has failed to develop drugs that are able to reduce elevated Lp(a) plasma concentrations to the desired extent.

STRUCTURAL CHARACTERISTICS OF Lp(a)

Lp(a) is a complex particle which mainly consists of a LDL molecule, to whose apoB the glycoprotein apo(a) is covalently bound. To a small extent, however, apo(a) has also been detected bound to triglyceride-rich lipoproteins (Very Low Density Lipoproteins; VLDL). Corresponding to the structural similarity to LDL, both particles are very similar to each other with regard to their composition (values in weight percentage; values of LDL in brackets): protein: 30 % (22.5 %), cholesteryl ester: 35.5 % (43 %), free cholesterol: 8.5 % (11 %), phospholipids: 19.5 % (19.5 %), triglycerides: 2 % (3 %) and carbohydrates 4.5 % (1 %) [35, 39]. Apo(a) shows a distinct structural homology to plasminogen, whose gene is also located on chromosome 6 [40, 41]. The kringle repeats of apo(a) present a particularly characteristic

*Address correspondence to this author at the Bundesinstitut für Arzneimittel und Medizinprodukte, (BfArM), Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Germany; Tel: 0049/228-207-5360; Fax: 0049/228-207-5300; E-mail: r.siekmeier@bfarm.de

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structure, which have a high similarity to kringle IV (K IV) of plasminogen. Additionally, apo(a) contains a kringle V structure of plasminogen and a protease domain, which cannot be activated, as opposed to the one of plasminogen [2, 40, 41]. At least 30 genetically determined apo(a) isoforms were identified in man, which are the basis for the marked heterogeneity of the molecular size. The individual apo(a) isoforms differ by the number of K IV units in the molecule, i.e. corresponding to a molecular weight of approximately 12.5 kDa per K IV unit [2, 40, 42, 43]. The smallest apo(a) isoform consists of one protease domain, one K V unit and 11 K IV units, while the apo(a) isoform of the highest molecular weight has 52 K IV units. Between the individual K IV units there are highly glycosylated connection units [2].

Lp(a) METABOLISM

Apo(a) is synthesised predominantly, if not exclusively, in the liver. After its synthesis, apo(a) binds with high affinity to apoB on LDL. The binding is then probably completed on the hepato-cellular surface *via* a disulfide-bridge of the Cys4326 of apoB and the only free cysteine group in K IV type 9 (Cys4057) of apo(a) [2, 44]. The synthesis of Lp(a) is thus a two-step process [45]. In a first step, which can be competitively inhibited by lysine analogues, the free sulfhydryl groups of apo(a) and apoB are brought close together. The binding of apo(a) then occurs near the domain of apo B which binds to the LDL receptor, resulting in a reduced affinity of Lp(a) to the LDL receptor. Particles that show a reduced affinity to the LDL receptor, such as particles containing apoB-48 and VLDL are not able to form stable complexes with apo(a) [2]. Thus the largest part of apo(a) is present as apo(a) bound to LDL. Only a small, quantitatively variable part of apo(a) remains as free apo(a) and probably plays an important role in the metabolism of Lp(a) [2, 46]. Investigations into the metabolism have shown that the synthesis rate of Lp(a) is strongly related to its plasma concentration and therefore depends on the apo(a) isoform that determines plasma concentration, while the catabolism rate is only of little significance [36].

The metabolic path of the synthesised Lp(a) is to a large extent unknown. Due to the similarity of the composition of LDL and Lp(a) it was first assumed that Lp(a), like other lipoproteins containing apoB, is degraded *via* the LDL receptor. Thus it could be shown in *in vitro* experiments that the binding of Lp(a) to fibroblasts could be competitively inhibited by addition of LDL, but compared to LDL, Lp(a) only had a small affinity to the LDL receptor. Animal experiments (rat, rabbit, hedgehog) showed that the liver plays an important role in Lp(a) metabolism – followed by the kidney and the spleen [35]. On the other hand, kinetic investigations performed in man, which demonstrated a longer plasma half life for Lp(a) compared to LDL, allowed the conclusion that the LDL receptor practically has no function in the metabolism of Lp(a). The fractional catabolic rates for LDL and Lp(a) are 0.38 and 0.26, respectively, in normal persons and are practically the same as for homozygous patients with a defect of the LDL receptor (0.205 and 0.210, respectively) [35, 36]. This phenomenon was the reason that other metabolic paths are now being discussed for Lp(a). Apo(a) obviously separates from apoB in the blood and as a consequence it comes to a subsequent fragmentation into degradation products of different molecular weight induced by metalloproteinases [2, 47]. As could be shown in experiments in transgenic mice, the resulting degradation products are removed from circulation by different organs and tissues, and only a very small part of them (less than 1 % of apo(a)) is excreted with the urine [2, 47, 48]. Other, receptor-dependent metabolic paths are assumed for the Lp(a) metabolism. Among them are the LDL receptor related protein, megalin, the VLDL receptor and the galactose-specific asialoglycoprotein receptor (ASGPR) [2, 49].

GENETICS AND PLASMA CONCENTRATION

The plasma concentration of Lp(a) is not evenly distributed in the population, but is highly skewed with regard to frequency, whereby the concentrations among different individuals may differ by a factor of 1000 [35, 50, 51]. Correspondingly the normal values of the Caucasian population show a median of approximately 8 mg/dL to 10 mg/dL, while the mean values are at an approximate level of 16 mg/dL to 18 mg/dL [35, 52]. The concentrations in Black Africans are twice as high as in Caucasians, while the plasma concentrations of Asian individuals are distinctly below that value, although the underlying causes are not finally clarified [2]. The concentrations are determined by genetic factors and are considered subject to only low variations during lifetime [35, 53]. But despite that a continuous rise of Lp(a) plasma concentrations [2] is found mainly in the first weeks after birth and in the course of the later decades in life. There is a distinct inverse correlation between the respective molecular weight of the Lp(a) and of the number of kringle-IV-domains in the apo(a) part of the lipoprotein particle and the individual plasma concentrations, respectively. Thus individuals with a high Lp(a) molecular weight show a low plasma concentration, while individuals with a low Lp(a) molecular weight present high plasma concentrations [34, 54, 55]. The reason for this is the fact that apo(a) isoforms with a high molecular weight are stronger bound and degraded in the rough endoplasmic reticulum, in the Golgi apparatus and in proteasomes than apo(a) isoforms with a low molecular weight [56, 57]. A total of 50 % of the genetic variation of the plasma concentration is determined by the respective number of kringle-IV-domains, while approximately 45 % of the genetic variation of the plasma concentrations are attributable to polymorphisms and mutations of the promoter region (pentanucleotide repeat, TTTTA), to the coding regions (+93 C/T polymorphism) and to other variations of the apo(a) gene [2, 35].

PHYSIOLOGICAL FUNCTIONS OF Lp(a)

Based on the results of the initial investigations by Berg [1], the opinion prevailed for many years, that individuals without detectable Lp(a) plasma concentrations (so-called Lp(a)-negative individuals) did not have any defect. Due to the increasing sensitivity of the analytical procedures used in the detection it could be shown that the plasma concentrations of these individuals were only below 25 mg/dL. Later investigations in individuals with Lp(a) plasma concentrations of < 0.5 mg/dL showed a disproportionately high excretion of apo(a) fragments in the urine of these individuals [2]. Now further investigation results allow the conclusion that apart from its significance as an important agent in the development of atherosclerosis, Lp(a) has even more physiological functions, e.g. in wound healing, angiogenesis and

hemostasis [2, 40, 58]. In the context of pleiotropic actions, however, the favourable action mechanisms are opposed by pathogenetic mechanisms, whereby the importance of Lp(a) in atherogenesis should be particularly mentioned (Table **1**) [14, 16, 17, 40, 58].

Table 1. Pathogenetic Mechanisms by which Elevated Lp(a) Plasma Concentrations Lead to an Accelerated Atherothrombosis [14,16,17,40,58] (Modified According to [17])

Easy oxidisability of Lp(a) and formation of highly atherogenic complexes with LDL in the vessel wall
Increase of oxidation rate, uptake and retention of LDL
Enhancement of lipid uptake by macrophages
Competitive inhibition of plasminogen during the binding to cellular receptors and protein binding sites
Decreased thrombin formation and inhibition of fibrinolysis
Inhibition of t-PA and increased formation of PAI-1
Inactivation of tissue factor pathway inhibitors
Increase of thrombin synthesis
Facilitation of thrombus formation at sites of tissue lesions
Increase of proliferation and migration of smooth vascular muscle cells
Inhibition of transforming growth factor β
Increased expression of intercellular adhesion molecules
Inhibition of the formation of collateral vessels

Lp(a) IN WOUND HEALING

Individual investigations indicate a possible favourable role of Lp(a) in wound healing [39, 58]. After tissue lesions Lp(a) plasma concentrations may increase as a consequence of an acute phase reaction [2, 39, 58], then it comes to an accumulation of Lp(a) at the lesion and subsequently to a proliferation of smooth vascular muscle cells and endothelial cells and to a release of cholesterol into the tissue [58-60]. This led to the theory that a few million years ago, when plasma cholesterol concentrations were assumed to be much lower, Lp(a) could have been a substantial source for the supply of tissues with cholesterol which was to be used in tissue regeneration and repair. This would have been an evolutionary advantage, which later transformed into a risk factor due to altered circumstances [39, 58].

Lp(a) IN ANGIOGENESIS

Lp(a) is also important for the process of angiogenesis and the sprouting of new vessels. This is based on the fact that angiogenesis starts with the remodelling of matrix proteins and the activation of matrix metalloproteinases (MMP). The latter ones are usually synthesised as inactive zymogens and require activation by proteases, this is also accomplished by plasminogen. The marked structural homology of Lp(a) to plasminogen, with a simultaneous lack of protease activity, may indicate that Lp(a) has an antiangiogenetic effect [2]. Accordingly, an antiangiogenetic effect of Lp(a) and apo(a) and its fragments excreted with the urine could be demonstrated in transgenic mice and *in vitro* [61, 62]. In the *in vitro* assay apo(a) did not have any effect on the accumulation of plasminogen activator-inhibitor I (PAI-I) and only little influence on the activation of urokinase, which indicates that for the inhibition of angiogenesis *in vivo* further influences have to be of importance [2, 62]. In another animal experiment it could be shown that apo(a) leads to an inhibition of the angiogenesis-dependent tumour growth in the colon of nude mice [63].

Finally it should be stated that elevated Lp(a) plasma concentrations are found in individuals over eighty years and in tumour patients, as opposed to healthy individuals. These increases indicate that individuals with higher Lp(a) concentrations, provided they do not develop atherosclerosis, may have a certain protection against tumour diseases or that Lp(a) may have a certain function in tumour defence [2, 39]. Likewise, the plasminogen fragments have an antiantiangiogenetic effect due to their homologous structure [39]. In summary it can be said, however, that the possible relationships between an antiangiogenetic effect of Lp(a) and a possible protection against tumour formation are only insufficiently known and require extensive further experimental investigation.

Lp(a) IN HEMOSTASIS

Due to the marked structural homology between the apo(a) part and plasminogen, which both belong to the so-called plasminogen group [41], a relationship between the coagulation system and Lp(a) was assumed quite early [64]. Lp(a) is able to competitively inhibit the binding of plasminogen to fibrinogen and fibrin, and to inhibit the fibrin-dependent activation of plasminogen to plasmin *via* the tissue plasminogen activator [64-66], whereby apo(a) isoforms of low molecular weight have a higher affinity to fibrin than apo(a) isoforms of higher molecular weight [65]. Like other compounds containing sulfhydryl groups, homocysteine enhances the binding of Lp(a) to fibrin [67]. During fibrinolysis, physiological importance of which lies in the dissolution of fibrin deposits and in the restoration of an injured vascular endothelium [68], the binding of plasminogen to lysine residues results in plasmin activation and subsequently in the enhancement of the following fibrinolytic processes [69-74]. Lp(a) binding also involves lysine [65] with the consequence, that due to the lack of catalytic activity it comes to hypofibrinolysis and, due to the LDL-component of the Lp(a), to an accumulation of cholesterol [2, 40, 41, 58, 65, 75-77]. Moreover, Lp(a) stimulates the synthesis of plasminogen activator-inhibitor I (PAI-I) in endothelial cells or of PAI-II in monocytes [2, 78]. The thus induced decrease of plasmin activity is not only important for the fibrinolytic system, since plasmin is also required for the activation of transforming growth factor-β1 (TGF- β1) which plays an important role in the proliferation and migration of the smooth vascular muscle cells within the atherosclerotic process [79]. Another relationship, which also favours the formation of thromboses, between Lp(a) and the fibrinolytic system is found in its property, to bind to the Tissue Factor Pathway Inhibitor (TFPI), a regulator of the tissue factor (TF)-mediated coagulation, expressed in activated monocytes, endothelial cells and thrombocytes [58, 80-84], and to

subsequently inactivate this factor [85]. But in addition to the mentioned prothrombotic properties Lp(a) also has anti-thrombotic properties. Thus Lp(a) binds with high affinity and specificity to the platelet activating factor acetylhydrolase. This does not only result in the inhibition of PAF, one of the strongest trigger factors of thrombocyte aggregation, but also in the hydrolysis of the short-chain phospholipids that develop during the process of lipid oxidation [2, 86-88]. Additionally, Lp(a) also leads to the inhibition of the collagen-induced thrombocyte aggregation and to the inhibition of serotonin and thromboxan secretion [2, 89]. In summary it shows that *via* various mechanisms Lp(a) possesses both prothrombotic and antithrombotic properties, which may be an explanation for the contradictory trial results achieved in different patient cohorts, since the properties of Lp(a) find different expression [2].

Several studies demonstrate a role of Lp(a) as an important risk marker, partly independent of other risk markers, for the occurrence of an acute coronary syndrome and spontaneous, partly recurring, ischemic strokes and of venous thromboses and thromboembolism in children and adults [58, 90-96], while other investigations did not establish any relationship between the occurrence of thrombotic events or thromboembolism and the existence of an elevated Lp(a) plasma concentration [97-99]. Moreover, elevated Lp(a) plasma concentrations were measured in a number of studies performed in patients with early-stage or terminal kidney diseases and autoimmune diseases (antiphospholipid syndrome, systemic sclerosis, chronic thromboembolic pulmonary hypertension, rheumatoid arthritis and systemic lupus erythematosus), which fact supports the involvement of Lp(a) in the increased occurrence of thromboembolic events [100-109].

Lp(a) IN ATHEROSCLEROSIS

The importance of Lp(a) in the formation and progression of atherosclerotic vascular diseases could be demonstrated in numerous animal experiments. Thus evidence was supplied that in transgenic, hyperlipidemic and Lp(a) expressing Watanabe rabbits, Lp(a) leads to enhanced atherosclerosis with development of calcifications [110-112]. Under the influence of Lp(a), the binding of Lp(a) to glycoproteins, e.g. laminin, results - *via* its apo(a)-part [113-115] - both in an increased invasion of inflammatory cells [116, 117] and in an activation of smooth vascular muscle cells with an increased formation of alkaline phosphatase and subsequent calcifications [111, 112] in the vascular wall. The inhibition of TGF-1β activation is another mechanism *via* which Lp(a) contributes to the development of atherosclerotic vasculopathies. TGF-1β is subject to proteolytic activation by plasmin and its active form leads to an inhibition of the proliferation and migration of smooth muscle cells, which play a central role in the formation and progression of atherosclerotic vascular diseases [79, 118-120]. If TGF-1β fails to be activated, e.g. due to Lp(a) accumulation in the vascular wall, it is associated with an increased proliferation and migration of the smooth vascular muscle cells and the formation of atherosclerotic lesions [79, 118, 121, 122].

In man, Lp(a) is an important risk marker which is independent of other risk markers. Its importance, partly also under consideration of the molecular weight and other genetic polymorphisms, could be demonstrated by a high number of epidemiological and clinical studies investigating the formation and progression of atherosclerosis, myocardial infarction, and stroke and also by meta-analyses [6, 8-33]. The simultaneous presence of other risk markers, e.g. hypercholesterolemia, hyperfibrinogenemia or reduced HDL-cholesterol, will lead to an even stronger increase of the total risk for the occurrence of cardiovascular diseases due to Lp(a) [11, 13, 31]. However, there are other studies that could not find evidence for the role of Lp(a) as a risk marker for cardiovascular diseases, e.g. the Physicians Health Study [2, 123]. Possible causes for such negative results may be performance of analyses with samples that were stored for too long and the use of insufficiently validated test kits, but also the investigation of smaller study populations, which are subject to an increased influence of the skewed distribution of the Lp(a) plasma concentration in the population (< 0.1 mg/dL up to >300mg/dL) [2].

INFLUENCE OF DISEASES ON Lp(a) PLASMA CONCENTRATION

Predominantly, the Lp(a) plasma concentration is considered genetically determined [35, 53]. But a number of factors may lead to an increase or decrease of the plasma concentration. In the following, some of these factors will be discussed in detail. Cholestatic liver diseases, particularly those that are characterised by high concentrations of lipoprotein X, are associated with reduced Lp(a) concentrations. In these cases it is assumed that a lack of normal LDL is the cause for this phenomenon, which leads to an impairment of the assembly of LDL and apo(a) [2].

Many studies have investigated the influence of chronic kidney diseases on the concentration and metabolism of plasma lipoproteins. Elevated Lp(a) plasma concentrations were found in patients with diabetic microscopic albuminuria [17], nephrotic syndrome [17, 105, 109], nephropathy [17] and kidney failure of different etiology and stages [17, 26, 104, 105, 107, 108]. The high number of those studies shows that Lp(a) plays an important part as a risk marker for the development of cardiovascular diseases in patients with kidney diseases [17, 26, 104].

On account of the interleukin-6 (IL-6) dependent regulation of Lp(a) synthesis, Lp(a) can to a certain extent be regarded as an acute phase protein [2], with the consequence, that inflammatory stimulants may be associated with a particularly marked elevation of the Lp(a) plasma concentration [124, 125].

HORMONAL INFLUENCE ON THE Lp(a) PLASMA CONCENTRATION

Several hormonal factors, that are either attributable to the respective underlying diseases or to therapeutic administration, lead to alterations of the Lp(a) plasma concentration, which are partly opposed to the alterations of the other plasma proteins. Thus patients with disturbed thyroid function present marked alterations of the fat metabolism [2, 35, 126] if compared to euthyroid patients. Hypothyroidism is associated with an increase of Lp(a) concentrations, while vice versa, hyperthyroidism is accompanied by a decrease of Lp(a). Manifest diseases show more marked alterations than

subclinical stages. The same applies under administration of a therapy. Thus triiodothyronine (T_3) or thyroxine (T_4) substitution results in a decrease of Lp(a) plasma concentration, while the administration of a thyroid inhibitor is associated with an increase. In both cases the therapeutic alterations are all the more marked, the more distinct the manifestations of the underlying hormonal disturbance are [2, 35, 126].

Animal experiments performed in transgenic mice showed a regulation of the apo(a) gene by sexual steroids. Testosterone leads to down-regulation [127]. While endogenous testosterone does not have a relevant effect on the Lp(a) plasma concentration [128], the supplementation of testosterone or other androgenic substances (e.g. nandronlone acetate, stanozolol, dehydroepiandrosterone) is associated with a suppression of the Lp(a) plasma concentration [128-131]. Vice versa, an orchidectomy will result in an increase of Lp(a) due to the low testosterone levels [130]. The administration of gonadotropin releasing hormone agonists and antagonists, which act *via* the inhibition of testosterone synthesis [132-135] has a similar effect. The same applies to the administration of antiandrogens, e.g. of the 5α-reductase inhibitor finasteride, which may also result in an elevation of Lp(a) [136].

The female sexual steroids also have an influence on various parameters of the fat metabolism [137, 138]. While in premenopausal women with normal menstrual cycles, we observe no or only little alteration of Lp(a) [139-142], the stimulation with follicle-stimulating hormone (FSH) in the luteal phase will result in a temporary increase [140, 142]. Once the women have reached the postmenopausal stage (due to physiological, pharmacological or surgical reasons), the associated hormonal alterations also result in a distinct elevation of Lp(a) [143-148]. A hormone replacement therapy with estrogen as a monotherapy or in combination with progesterone leads to a decrease of Lp(a) in these patients, which is particularly marked in those women whose pretherapy Lp(a) concentrations were elevated [143, 144, 147, 148]. In postmenopausal women with breast cancer the frequently administered estrogen receptor-modifying substances such as tamoxifen and toremifene [149, 150], but not aromatase inhibitors, such as letrozole [151] also lead to a decrease of Lp(a).

The influence of a number of additional hormones on Lp(a) plasma concentrations is also discussed. The administration of corticotropin or its analogues (e.g. synacthene) leads to a distinct decrease of Lp(a) [2, 152-154], both in healthy individuals and in patients with terminal renal failure and hemodialysis and in patients after kidney transplantation. With regard to diabetes mellitus there exists a whole range of partly contradictory publications. Insulin does not directly influence the Lp(a) plasma concentration [35]. A comparison with healthy individuals shows that the Lp(a) in patients with type 1 diabetes mellitus show hardly any alterations, which means that an improvement of the metabolic control is not associated with an alteration of Lp(a) [2, 35]. Contrary to that patients with type 2 diabetes mellitus show more frequently an increase of Lp(a) compared to healthy individuals, which may be secondarily induced, since the patients studied excrete fewer apo(a) fragments with the urine than healthy individuals due to a concomitant limitation of the renal function [2, 155].

INFLUENCE OF NUTRITION AND LIFE-STYLE ON Lp(a) PLASMA CONCENTRATIONS

Many studies have investigated the influence of alcohol on the Lp(a) plasma concentration. The chronic consumption of ethanol results in a marked decrease of the Lp(a) concentration which is dose-dependent and has no relationship with the size polymorphism of apo(a) [2, 156, 157]. Vice versa the Lp(a) concentration rises again after termination or reduction of alcohol consumption [158-160]. The mechanism of action is not completely known. It is discussed that it involves insulin-like growth factor (IGF)-binding protein [2, 159].

Furthermore there are investigations that observed an influence of different nutritional styles on Lp(a) concentrations. Trans-fatty acids such as elaidic acid, which is found in deep-fried food, obviously lead to a 25 % - 50 % increase of Lp(a) concentration, which is particularly marked in individuals with initially elevated Lp(a) concentrations [17, 161, 162]. Vice versa several studies also discuss that mono- or poly-unsaturated fatty acids or fat-modified foods may have a lowering and protective effect on Lp(a) plasma concentrations [17, 163-165].

Several studies and overviews describe decreased Lp(a) plasma concentrations in smokers as compared to non-smokers [2, 166-168]. Vice versa such an influence could not be established in other studies that were performed partly with monozygotic twins [169-171].

Finally a possible effect of exercise on Lp(a) concentrations should be mentioned. While some studies could not observe an alteration of the Lp(a) concentration [172-174], older studies showed a slight increase without further clinical relevance [170, 175].

THERAPEUTIC MODIFICATION OF Lp(a)

A large number of studies investigated the influence of therapy forms on Lp(a) plasma concentrations. The administration of niacin or nicotinic acid may produce a distinct decrease of Lp(a), with simultaneous favourable influence on other parameters of the lipid metabolism. Moreover it is possible, to combine nicotinic acid with other substances, such as gemfibrozil and inhibitors of hydroxymethyl-CoA-reductase (statins) [2, 176-179].

Although fibrates (to include gemfibrozil) *in vitro* decrease the mRNA for Lp(a) [180], rather controversial results have been obtained *in vivo* for the effect of these drugs on Lp(a) plasma concentrations [2].

Lipid apheresis is an effective method for which a number of approaches are available, but due to its invasiveness and the necessity of a frequent repetition (at least every two weeks) it is more or less regarded as *ultima ratio*. The procedures that are primarily developed for the removal of LDL allow a reduction of Lp(a) plasma concentrations by up to 80 %, depending on the volume of blood or plasma that is treated [2, 181-183].

By contrast, the different statins, if administered as monotherapy, do not only fail to achieve a decrease of Lp(a), but partly may even lead to an increase. Only a small number of studies observed a decrease of Lp(a) under the administration of statins [2, 35, 184-188]. Analogously, this applies to

substances which inhibit intestinal cholesterol absorption (e.g. resins) and which may be combined with other antilipemics, particularly with statins, to enhance the cholesterol-lowering effect [184-186].

Apart from these substances long established in the therapy of dyslipidemia there are other pharmaceuticals, only recently introduced into therapy and new compounds still in the phase of development [189]. Substances specifically targeting the peroxisome proliferator-activated receptor (PPAR) [189] are particularly important in this context. This group includes thiazolidindiones (e.g. pioglitazone, rosiglitazone, troglitazone). Studies in type 2 diabetics were able to show a favourable influence of these substances on the glycometabolic control and lipid metabolism, and additionally a decrease of the Lp(a) plasma concentrations under the therapy [190, 191].

Various studies investigated the influence of fatty acids, particularly fish oil, and ω3- and ω6-fatty acids on Lp(a) plasma concentrations. The results obtained in these studies are altogether quite controversial and stating either an increase of Lp(a), denying any influence or even observing a decrease [2, 163, 165, 192].

Finally there are also individual studies with partly controversial results, which indicate a possible favourable influence originating from other compounds such as carnitine [2, 193-196], coenzyme Q_{10} [197, 198] or aspirin [199, 200].

ANALYTICS OF Lp(a)

A considerable number of studies investigating the cardiovascular risk factor Lp(a) shows controversial results, whereby the contradictions may be a consequence of both the study design and the analytical methods used for that purpose (Table **2**) [17, 201, 202]. The following paragraphs will discuss the analytical causes for the variability.

In the past, the Lp(a) concentrations were often determined with analytical procedures that allow only a very limited comparability of the results. At present the Lp(a) value is determined by electrophoresis, electroimmunodiffusion, electroimmunoassays, radioimmunoassays, immunoradiometric assays, immunoturbidimetric assays and enzyme-linked immunoassays (ELISAs) [16, 17]. The electrophoretic methods have the advantage that they are not dependent on the polymorphism of Lp(a) [17, 203, 204]. Although larger studies could show the value of these methods, they have the disadvantage that with a specificity of 95 % their sensitivity with regard to the detection of Lp(a) concentrations > 30 mg/dL is only 51 %, which limits their use in scientific investigations [17, 205].

The heterogeneity of apo(a) with regard to size constitutes an analytical problem in so far, as the antibodies used by most manufacturers are specific for the K IV type 2 epitope [17, 201]. Depending on the molecular weight this results in a variable immune reactivity with overestimation of concentrations in cases of high or underrating in cases of low molecular weights of apo(a). As a consequence of a use of these antibodies studies may have had controversial results with regard to the relationship between Lp(a) and vascular diseases [17, 201].

Based on experiences from the past, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) developed an international reference material (IFCC SRM 2B) with a defined amount of Lp(a) and a monoclonal antibody against an epitope in K IV type 9, which occurs only once per apo(a) molecule and thus delivers results that are not dependent on the molecular weight [17, 206]. ELISAs on the basis of this reference material are independent of the apo(a) isoform and could in the future serve as gold standard for Lp(a), which is already recognised by the National Heart, Lung and Blood Institute (NHLBI) and the World Health Organization (WHO) as “First WHO/IFCC International Reagent for Lipoprotein(a) for Immunoassay”. The availability of this standard would enable the manufacturers to minimise the inaccuracy and between batch variability of the antibodies and to improve the comparability of the Lp(a) assays in scientific investigations [17, 206, 207].

The additional determination of the molecular weight of apo(a) or of the isoform would further improve the risk assessment, but is not yet available in a suitable form for clinical routine use. On account of the inverse relationship between molecular weight and concentration, the exact determination of the Lp(a) plasma concentrations appears suitable, for the time being, to determine the individual risk [17].

Table 2. Causes for Contradictory Results in Studies Investigating Lp(a) [17,201,202]

Analysis
Different analytical methods with/without relationship to apo(a) isoforms
Lacking standardisation of methods
Different degree of degradation of Lp(a) with a distinct decrease of concentrations with smaller apo(a)isoforms
Underrating of the concentration of smaller apo(a) isoforms with simultaneous overrating of larger apo(a) isoforms
Study cohorts and study design
Small number of samples
Different age of investigated individuals and inclusion of older individuals
Different study end points
Ethnic differences
Different sex
Length of follow-up period
Stringency of exclusion criteria
Application of different statistical methods for data evaluation

Finally it also has to be considered that the quality of the results obtained for Lp(a) depends to a considerable extent on the quality of the sample. In the meantime it is an established fact that the prolonged storage of plasma samples results in an enhanced degradation of the smaller Lp(a) isoforms, while larger isoforms do not degrade to such an extent, which will lead to false negative results. It is assumed that the storage of samples over several years or storage under suboptimal conditions leads to a decrease of Lp(a) con-

centrations by 25 % or up to 50 % [17, 208-210]. Thus the negative results of many studies that were unable to show a relationship between Lp(a) concentration and vascular diseases, are at least partly the consequence of the analysis of frozen samples, while on the other hand those studies that analysed suitable biological material, established a distinct relationship between Lp(a) and vascular events [17, 201]. This applies all the more, since it seems that small apo(a) isoforms have a greater importance as risk markers than larger isoforms [17].

Several investigations indicate that, as opposed to other risk markers, the Lp(a) plasma concentration dependent risk for the occurrence of cardiovascular diseases does not rise continuously [17, 201]. In the case of plasma concentrations above the 80th percentile one can assume the presence of an increased individual risk [17]. The reported cut-off values, however, show considerable differences. Many studies that analysed frozen samples with methods dependent on apo(a) isoforms, described cut-off values for Lp(a) of >30 mg/dL up to 40 mg/dL. The analysis of fresh samples showed an increase of the risk already at concentrations of >20 mg/dL in the white population. Under consideration of the ethnic differences applying to Lp(a), however, higher cut-off values would have to be determined for black individuals and lower ones for Asian individuals, which are at present only available to a small extent. This means that for the time being the 80th percentile could be regarded as suitable cut-off, above which the cardiovascular risk is substantially increased [17, 201].

In most laboratories the Lp(a) assay is performed by reporting the mass. Occasionally, assays and results are expressed as Lp(a)-protein or Lp(a)-cholesterol. Unless further specified, the Lp(a) mass is usually determined. Under consideration of the composition of the particle, the statement of 20 mg/dL Lp(a) corresponds to values of 7 mg/dL Lp(a)-protein or Lp(a)-cholesterol [17]. The NHLBI recommends to stop using data for total Lp(a), and to use nmol/L units instead, which consider the number of particles. The NHLBI also recommends performing the analysis with International Reference Material [17, 206, 207]. In white individuals, values above 75 nmol/L are regarded as a cut-off value for the presence of an increased risk [17, 207]. Methods should be applied that are not dependent on the apo(a) isoform [17, 201]. If methods are used that are not independent of the apo(a) isoform, then Lp(a) values >50 nmol/L should be subjected to another analysis using a method independent of the isoform [17, 207].

RECOMMENDATIONS CONCERNING THE DETERMINATION OF THE Lp(a) PLASMA CONCENTRATION

Although the third report of the American National Cholesterol Education Program recognises the importance of the Lp(a) plasma concentration as cardiovascular risk marker, it does not recommend its determination within the framework of general routine analyses [17, 211]. The determination of Lp(a) concentration, however, is recommended in patients with a positive familial history of a cardiovascular disease or in patients with manifest genetically determined dyslipidemia [17, 211]. However, considering the fact that Lp(a) is a factor that is to a large extent independent of the remaining risk markers for atherosclerotic and thromboembolic diseases, the quantitative determination should be considered even in the other patient and risk groups listed in Table **3** [17].

Table 3. Patient- and Risk Groups where an Assay of the Lp(a) Plasma Concentration is Recommended (According to [17])

Individuals with a positive familial history of vascular diseases, in particular with premature death
Patients with a personal history of a premature heart disease, a stroke or a peripheral vasculopathy, independent of other risk markers
Patients with remaining stenosis after coronary angioplasty, vascular stent implantation or bypass-surgery
Patients and individuals with so-called statin resistance
Adopted individuals
Individuals with an otherwise inexplicable expression of heart disease, including those patients with a rapid progression documented by angiography, a complex morphology of the lesion and a total or persistent occlusion of one or more coronary arteries
Individuals with thrombus formation in the left atrium
Women with repeated abortions

In addition, it is the opinion of the authors that measurement of Lp(a) concentration is also indicated in individuals who are at an only slightly increased risk (risk for the incidence of a severe coronary event between 10 % and 20 % in 10 years according to the current methods for risk stratification) in which decisions for or against pharmacological interventions (e.g. treatment with antilipemics or antihypertensives) are difficult to make.

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