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EDITORIAL

Lipoprotein(a)

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Lipoprotein(a) (LP(a))—discovered by Kare Berg [1] in 1963—is of increasing importance in clinical routine as reflected by the ESC/EAS Guidelines for the Management of Dyslipidaemias and the recent AHA Guideline [2, 3]. These guidelines provide detailed recommendations for screening and lipid analyses in the assessment of cardiovascular risk. A consensus paper of the European Society of Cardiology summarizes basic principles, background as well as diagnostic and therapeutic principles [4].

Structure—physiochemical characteristics

LP(a) is a lipid protein complex with a structure compared to that of LDL (low density lipoprotein). Another apoprotein, glycoprotein apoprotein(a) (Apo(a)) is bonded to the apoprotein B-100 (Apo B-100) of the LDL cholesterol via a disulphide bridge [5].

The presence of Apo(a) impairs the bond between Lp(a) and the LDL receptor. An independent Lp(a) receptor has not been identified so far. Corresponding to the LDL cholesterol (LDL-C), the Lp(a) molecule is coated by a layer of simple phospholipids, free cholesterol, and apoproteins. Its core consists of triglycerides and esterified cholesterol [6].

Due to its structural similarity, Lp(a) competes with plasminogen for bindings sites on endothelial cells thus blocking the development of plasmin [7]. This leads to a delay of fibrinolysis. Similar to plasminogen, Apo(a) contains a kringle domain [8].

Kringles are characterized by 2–40 repeats creating at least 30 polymorphous isoforms of Apo(a), which are different in terms of size and mass. Number and qualitative composition of kringle domains determine the atherogeneity of Lp(a). The large isoforms with more kringle repeats seem to be less atherogenous than the smaller ones [9].

Synthesis and metabolism

Apoprotein(a) is synthesized in the liver exclusively [10]. How much Apo(a) is produced by the liver depends on the LPA gene and its amount remains more or less constant during a person's lifetime. As Lp(a) in males rises only to a minor extent with increasing age, this parameter has to be determined only once in a lifetime. In women however, the analysis should be done before and after menopause, as the Lp(a) level might markedly increase during menopause. It is quite unclear where Lp(a) is produced, most probably on the surface of hepatocytes or in plasma.

Catabolism of Lp(a) is independent of a functioning LDL receptor [11]. The kidney seems to have a specific binding capacity for Lp(a) [12]. A reduced glomerular filtration rate (GFR) may lead to an increase in plasma concentration of Lp(a). Other factors are hypothyreosis or an acute phase reaction (e. g. acute myocardial infarction). Oestrogen therapy, pregnancy or aspirin uptake cause a non-significant or relevant reduction [13].

Genetics

Apo(a) is encoded by a gene on chromosome 6q26-27 [14]. Lp(a) plasma concentration is controlled by the Lp(a) gene locus; polymorphisms of the Apo(a) kringle IV-2 repeats are responsible for the differences in plasma level. Of 48 single nucleotide polymorphisms (SNPs) in the Lp(a) gene region, seven SNPs show a significant association with coronary heart disease [15]. The frequently used but slightly arbitrary normal value of <30 mg/dl (1.6 mmol/l) is based on data which show that with an increasing value the car-

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diovascular risk increases without a given threshold value [16]. ESC recommends a threshold value of <50 mg/dl (80th percentile) [4].

Thrombogenous and atherogenous characteristics

In blood coagulation Lp(a) is the opponent of plasminogen—the inactive preliminary enzyme stage of plasmin—which resolves fibrin clots. Lp(a) competes with plasminogen for the binding sites on endothelial cells thus blocking plasmin formation [9]. This leads to a delay in fibrinolysis and to deposits on the vascular wall. High concentrations of Lp(a) cause an increased thrombotic risk due to an inhibition of fibrinolytic mechanisms.

The structure of Lp(a) contains about 30% of cholesterol and cholesterol ester, in addition atherogenous, proimflammatoray oxidized phospholipids are bonded. This leads to an accumulation of inflammatory cells in the vascular wall with consecutive proliferation of smooth muscle cells. Atherogenesis is thus induced and maintained.

Clinical relevance

Coronary heart disease

The causative role of Lp(a) in the early manifestation of coronary heart disease is becoming more and more evident.

Earlier studies including meta-analyses have shown that an elevated Lp(a) concentration markedly increases the risk for coronary heart disease [17]. In addition, Mendelian randomization has indicated that genetic mutations of Lp(a) in the form of polymorphisms of the Apo(a) kringle IV-2 repeats are associated with a risk of coronary heart disease [18]. Patients with a familial hypercholesterolemia (FH) of a prospective cohort study, where 46,200 individuals of the Copenhagen General Population Study were enrolled, showed the highest risk of developing a coronary heart disease in case of Lp(a) ≥ 50 mg/dL (HR 5.3, 95% CI 3.6–7.6) [19]. In the GENESIS-PRAXY (GENdEr and Sex determinantS of cardiovascular disease) study, 939 young patients admitted for an acute coronary syndrome (ACS) showed an association between high Lp(a) (>50 mg/dl) and high LDL-C (>3.5 mmol/L) so that increased Lp(a) and high LDL-C represent an increased risk for ACS [20].

Aortic valve stenosis

Aortic valve stenosis may be genetically induced as well as result from a lipid disorder and an Lp(a) increase. A large-scale study has proved that an elevated Lp(a) and a corresponding *LP* risk genotype (rs10455872, rs3798220, kringle IV type 2 repeat polymorphism) increase the risk for the development of aortic valve stenosis [21].

Registry data show that the degree of aortic valve stenosis rises with increasing Lp(a) levels [22].

Cerebrovascular and peripheral vascular disease, abdominal aortic aneurysm

Lp(a) is also discussed to be an independent risk factor for cerebrovascular diseases. Particularly in young patients suffering from an apoplectic insult Lp(a) might be a causative factor [23]. Furthermore, Lp(a) seems to be a predictor for an early recurrence [24].

The manifestation of a peripheral arterial occlusive disease is also influenced by Lp(a) concentration and a low molecular (NMW) Apo(a) phenotype [25].

Finally, numerous published reports on increased Lp(a) levels in patients with documented abdominal aortic aneurysms should be mentioned. This might be an evidence for Lp(a)-induced atherosclerotic processes in large vessels [26].

Screening

Presymptomatic patients with an increased cardiovascular risk are identified by the determination of classical risk factors in established scores such as PROCAM, SCORE, ASCVD.

The quality of these scores for risk assessment is not satisfying. The sensitivities of these are <50% and the positive predictive value is at most 30% [27]. The establishment of new risk factors is therefore of high clinical relevance to improve the reliability of prognosis. Considering the genetic determination and hereditary burden Lp(a) might be a candidate.

Therapy

So far lipoprotein apheresis is the only effective available therapeutic option to reduce Lp(a) significantly, with a documented effect on cardiac events [28].

PCSK9 inhibitors reduce LDL cholesterol significantly and Lp(a) by about 25–30% [29]. In case of very high initial values of Lp(a), a favourable influence on athergenous events cannot be expected. A promising approach is the antisense oligonucleotide therapy. Phase 1 and 2 studies have shown reduction rates of Lp(a) of up to 80% with a good tolerability [30]. If these results are reproducible in a phase 3 study and cardiovascular events are reduced, a specific drug therapy of high Lp(a) values might become available for the first time.

The large number of publications during the past years emphasizes the pathophysiological and clinical relevance

of Lp(a). The contributions to this supplement presented at the Lp(a) Update 2018 meeting in Kassel are intended to provide an overview and critical appraisal of cardiovascular risk factors for clinical routine.

Conflict of interest K.P. Mellwig and A. Vogt declare that they have no competing interests.

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