Physiol. Res. 66 (Suppl. 1): S113-S120, 2017

Inverse Association of Lipoprotein (a) With Markers of Insulin Resistance in Dyslipidemic Subjects

H. VAVERKOVÁ[1], D. KARÁSEK[1], M. HALENKA[1], L. CIBÍČKOVÁ[1], V. KUBÍČKOVÁ[2]

[1]Third Department of Internal Medicine – Nephrology, Rheumatology and Endocrinology, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic, [2]Department of Clinical Biochemistry, University Hospital, Olomouc, Czech Republic

Received November 16, 2016
Accepted December 16, 2016

Summary

Lipoprotein (a) [Lp(a)] is an LDL-like particle that contains an apolipoprotein B100 molecule covalently bound to a plasminogen-like glycoprotein, apolipoprotein (a) [apo(a)]. Epidemiological evidence supports a direct and causal association between Lp(a) levels and coronary risk. On the contrary, a few prospective findings demonstrate inverse association of Lp(a) levels with risk of type 2 diabetes (T2DM). The aim of our study was to evaluate the association of Lp(a) with indicators of insulin resistance (IR) and metabolic syndrome (MS), which precede development of T2DM. We enrolled 607 asymptomatic dyslipidemic subjects (295 men and 312 women, mean age 45.6±14.0 years) into our cross-sectional study. Lp(a) concentrations correlated inversely with TG, AIP, insulin, HOMA, C-peptide, BMI, waist circumference, and number of MS components ($p<0.01$ for all). Subjects with MS had significantly lower Lp(a) concentrations in comparison with those without the presence of this phenotype ($p<0.0001$). Serum concentrations of Lp(a) in the lower (1^{th}-3^{rd}) quartiles of insulin and HOMA were significantly higher than in the 4^{th} quartile of these insulin resistance markers ($p<0.001$). Odds ratios of having increased markers of IR (TG, HOMA) and MS in top quartile of Lp(a) also indicate inverse association of Lp(a) with IR. The results of our study support an inverse association of Lp(a) levels with IR and MS that precedes overt T2DM diagnosis.

Key words

Dyslipidemia • Insulin resistance • Lipoprotein (a) • Metabolic syndrome • Type 2 diabetes mellitus

Corresponding author

H. Vaverková, Third Department of Internal Medicine – Nephrology, Rheumatology and Endocrinology, University Hospital Olomouc, I. P. Pavlova 6, 779 00 Olomouc, Czech Republic. Fax:+420588442526. E-mail: helena.vaverkova@fnol.cz

Introduction

Lipoprotein (a) [Lp(a)] is a plasma lipoprotein consisting of a cholesterol-rich LDL particle with one additional protein – apolipoprotein (a), attached *via* a disulfide bond to apolipoprotein B100 (Utermann 1989). The plasma levels of Lp(a) are under strong genetic control *via* variations in the lipoprotein (a) [LPA] gene, especially the LPA kringle IV 2 repeats, which encode apo(a) and exist in multiple copies (Boerwinkle *et al.* 1992).

The interindividual range of Lp(a) concentrations is very wide from less than 0.1 mg/dl to more than 300 mg/dl. Few people lack Lp(a) in their plasma. The broad range in Lp(a) distribution is known for all populations and is highly skewed towards low levels in most ethnic groups (Kronenberg 2016).

Lp(a) blood concentrations are primarily determined by the apo(a) gene, LPA, (Boerwinkle *et al.* 1992) and are negligibly affected by lifestyle modifications, such as diet and exercise. It is also commonly accepted that plasma Lp(a) levels remain relatively stable over an individual´s lifetime (Marcovina *et al.* 1994, Nordestgaard *et al.* 2010).

Both serum Lp(a) levels (Ergou *et al.* 2009, Danesh *et al.* 2000) and LPA gene variants (Kamstrup *et*

Fax +420 241 062 164, e-mail: physres@fgu.cas.cz, www.biomed.cas.cz/physiolres

al. 2009, Clarke *et al.* 2009) have been reported to be strongly associated with the risk of CVD.

Surprisingly, recent studies found that serum Lp(a) concentrations are inversely associated with T2DM (Mora *et al.* 2010, Kamstrup and Nordestgaard 2013, Ye *et al.* 2014), pre-diabetes, insulin resistance and metabolic syndrome (Ding *et al.* 2015, Sung *et al.* 2013, Marzano *et al.* 2014). The potential reasons for an inverse association between Lp(a) and T2DM are unknown. Some animal studies suggest an effect of insulin in reducing Lp(a) levels (Neele *et al.* 1999). Thus Lp(a) might be another lipoprotein, that is associated with metabolic syndrome characterized by insulin resistance.

As there are some differences in Lp(a) levels, distribution patterns, and a slightly different association of Lp(a) with risk of CHD in various racial/ethnic groups (Guan *et al.* 2015), it seems reasonable to study patho-physiological associations of this unique lipoprotein in various populations.

We examined the association of Lp(a) with markers of insulin resistance and metabolic syndrome in asymptomatic dyslipidemic Caucasian subjects of European ancestry.

Methods

Study design and subjects

The study was carried out as a cross-sectional study on asymptomatic dyslipidemic subjects who had been examined at the Lipid Center of the 3rd Department of Internal Medicine, University Hospital Olomouc, Czech Republic. All the dyslipidemic subjects filled out a questionnaire on their medical history, especially their cardiovascular status, medication and smoking habits. All the subjects were tested for an underlying cause of secondary hyperlipidemia: diabetes mellitus, hypothyroidism, hepatic or renal impairment, and nephrotic syndrome. Subjects with these diagnoses were not enrolled in the study. Other exclusion criteria were a history of clinically manifest atherosclerosis (coronary artery disease, cerebrovascular ischemic disease, and peripheral arterial disease), hypolipidemic treatment in the previous six weeks, and the clinical presence of acute infectious disease or trauma. Dyslipidemia was defined as total cholesterol >5 mmol/l or triglycerides (TG) >1.5 mmol/l or both. Most authorities recommend TG level ≥1.7 mmol/l for definition of hypertriglyceridemia. The reason why we have chosen the TG level >1.5 mmol/l is justified by the fact that the clinical definition of the most common familial dyslipidemia, the so called familial combined hyperlipidemia, is based (besides other requirements) on concomitant presence of ApoB >1.2 g/l and TG >1.5 mmol/l in several family members (de Graaf *et al.* 2004). Furthermore, small dense LDL start to increase at the TG level >1.5 mmol/l (Campos *et al.* 1992). Nevertheless, in our cohort only 5 subjects had TG levels in the range 1.5-1.7 mmol/l.

Six hundred and seven subjects (295 men and 312 women, mean age 45.6±14.0 years) fulfilled the above-mentioned criteria and were included in the study. The study was reviewed and approved by the Institutional Ethics Committee of the Medical Faculty and University Hospital and informed consent was obtained from all participants.

Anthropometric and laboratory measurements

The body mass index (BMI), waist circumference (WC), systolic (SBP), and diastolic (DBP) blood pressure were determined. The WC was measured in the standing position, at the middle point between the anterior iliac crest and the lower border of the ribs. The auscultatory method of BP measurement with a properly calibrated and validated mercury sphygmomanometer was used. At least three sitting BP measurements were taken at 30-s intervals and the mean of the last two was calculated. Patients treated with antihypertensive drugs or with SBP ≥ 140 or DBP ≥ 90 mm Hg were assumed to be hypertensive.

For a diagnosis of MS we used a harmonized definition (Alberti *et al.* 2009). The presence of any three of five risk factors constitutes a diagnosis of MS: elevated WC (WC ≥102 cm in men and ≥88 cm in women); triglycerides ≥1.7 mmol/l (drug treatment for elevated TG is an alternative indicator – not present in our cohort); reduced HDL-C <1.0 mmol/l in men and <1.3 mmol/l in women (drug treatment for reduced HDL-C is an alternative indicator – not present in our cohort); elevated blood pressure (systolic ≥130 and/or diastolic ≥85 mm Hg or antihypertensive drug treatment in a patient with a history of hypertension), and elevated fasting glucose ≥5.6 mmol/l (drug treatment of elevated glucose is an alternative indicator – not present in our cohort).

Biochemical analyses

Venous blood samples were drawn in the morning after a 12-h fast. Total cholesterol (TC),

triglycerides (TG), and HDL-cholesterol (HDL-C) were determined enzymatically on a Modular SWA analyzer (Roche, Basel, Switzerland) using commercially available kits (Cholesterol SYS 917, Triglycerides GPO-PAP and HDL cholesterol plus, third-generation kits, Roche, Basel, Switzerland). The determination of HDL-C was performed by a direct method without precipitation of lipoproteins containing apoB. LDL-C levels were calculated according to the Friedewald formula (Friedewald *et al.* 1972) in subjects with TG ≤4.5 mmol/l (77 subjects had TG levels >4.5 and LDL-C was not calculated). Therefore, we calculated the non-HDL cholesterol (non-HDL-C = TC – HDL-C). Atherogenic index of plasma (AIP) was calculated as a log (TG/HDL-C) with TG and HDL-C expressed in molar concentrations. This index was proposed by Dobiasova and Frohlich (2001) and Frohlich and Dobiasova (2003). The concentration of apolipoprotein B (ApoB) and apolipoprotein A1 (apoA1) was determined immunoturbidimetrically on a Modular SWA analyzer (TinaQuant Apo A1, TinaQuant Apo B kits, all Roche, Basel, Switzerland). Lipoprotein (a) [Lp(a)] was determined immunoturbidimetrically using a Lipoprotein (a) Tina-Quant TQ kit (Roche, Basel, Switzerland). Glycemia was determined by means of the enzymatic-colorimetric method (Glucose GOD-PAP kit) on a Modular SWA analyzer. Insulin was determined using commercially available kits – Insuline (Immunotech, Marseille, France) using specific antibodies by the IRMA (immunoradiometric assay) method. The result obtained was then used for the calculation of the parameter of insulin resistance HOMA [homeostasis model assessment: fasting glycemia (mmol/l) * fasting insulin (mU/l) / 22.5]. C-peptide was determined using commercially available kits – C-peptide (Immunotech, Marseille, France) using specific antibodies by the IRMA method. Concentrations of insulin and C-peptide were measured in the serum stored at -80 °C.

Statistical analyses

All the values are expressed as means ± SD or as median (interquartile range) for variables with non-normal distribution. The Kolmogorov-Smirnov test was used to test for normal distribution. Variables with a non-normal distribution (Lp(a), TG, insulin, HOMA, C-peptide) were log-transformed to normalize their distribution before statistical analysis. The differences between the groups were analyzed using ANCOVA and adjusted for age and sex, and age, sex, and BMI. Relationships between continuously distributed values were examined by Spearman´s correlation coefficient. Logistic regression analysis was used to determine the odds ratio (OR) and 95 % CIs of having increased markers of insulin resistance (4^{th} quartile) and MS in a top quartile of Lp(a) compared to Lp(a) quartile 1. Statistical analysis was performed using SPSS for Windows version 12.0 (Chicago, Illinois, USA). Due to multiple testing of the data, probability values of $P<0.01$ were considered statistically significant.

Table 1. Clinical and biochemical characteristics of dyslipidemic subjects.

Parameter	Mean ± SD or median (interquartile range)
N (M/F)	607 (295/312)
Age (years)	45.6 ± 14.0
BMI (kg/m^2)	26.3 ± 4.0
Waist (cm)	88.3 ± 12.6
SBP (mm Hg)	129.3 ± 15.5
DBP (mm Hg)	79.7 ± 8.7
TC (mmol/l)	6.73 ± 1.64
*LDL-C (mmol/l)**	4.17 ± 1.28
ApoB (g/l)	1.23 ± 0.32
HDL-C (mmol/l)	1.44 ± 0.45
TG (mmol/l)	1.91 (1.32; 2.98)
AIP log(TG/HDL-C)	0.13 (-0.09; 0.4)
Non-HDL-C (mmol/l)	5.28 ± 1.68
HDL-C (mmol/l)	1.44 ± 0.45
ApoA1 (g/l)	1.57 ± 0.34
ApoB (g/l)	1.23 ± 0.32
Lp(a) (g/l)	0.18 (0.07; 0.56)
Glucose (mmol/l)	5.13 ± 0.82
Insulin (mIU/l)	7.90 (5.40; 11.20)
HOMA	1.75 (1.14; 2.65)
C-peptide (mg/l)	2.28 (1.60; 3.08)
MS (N; %)	199; 32.7 %

Data are means ± SD or medians (interquartile range) for skewed variables, n (number) and % for categorical variables. * LDL-C was calculated in 530 subjects according to Friedewald equation.

Results

The clinical and biochemical characteristics of the whole group are summarized in Table 1.

In the whole group, Lp(a) correlated inversely with TG ($p<0.001$), AIP ($p<0.001$), insulin ($p<0.005$), HOMA ($p<0.005$), BMI ($p<0.001$), waist circumference ($p<0.005$), and number of MS components ($p<0.001$). On the contrary, a positive correlation between Lp(a) and HDL-C ($p<0.05$), and ApoB ($p<0.05$) was found. Negative correlation of Lp(a) with TG and positive correlation with HDL-C indicates that Lp(a) shows an inverse relationship with the atherogenic dyslipidemia characteristically associated with insulin resistance.

The results according to lipoprotein (a) quartiles are summarized in Table 2. Significant differences between quartiles of Lp(a) were found for TG, AIP, BMI, and prevalence of MS. Most prominent differences were found for TG, AIP, and prevalence of MS which persisted after adjustment for age, sex, and BMI.

Table 2. Characteristics of participants according to Lp(a) quartiles.

Parameter	Lp(a) quartile I	Lp(a) quartile II	Lp(a) quartile III	Lp(a) quartile IV	Statical significance
Lipoprotein (a) (g/l)	0.034 (0.012; 0.059)	0.121 (0.098; 0.149)	0.311 (0.238; 0.401)	0.952 (0.745; 1.189)	
Age (years)	44.8 ± 13.4	47.3 ± 13.7	45.3 ± 14.8	45.3 ± 14.0	
BMI (kg/m^2)	27.1 ± 4.4	26.6 ± 4.1	25.6 ±3.7	25.9 ± 3.5	**p<0.01** (I vs. III; I vs. IV)
Waist (cm)	89.9 ± 13.5	89.5 ± 13.4	87.1 ± 12.0	86.5 ± 11.0	p<0.05 (I vs. III; I vs. IV)
SBP (mm Hg)	129.3 ± 15.3	131.5 ± 15.2	128.7 ± 15.4	127.6 ± 15.6	NS
TC (mmol/)	6.87 ± 2.09	6.67 ± 1.54	6.79 ± 1.53	6.66 ± 1.35	NS
LDL-C (mmol/l)	4.06 ± 1.27	4.02 ± 1.17	4.40 ± 1.41	4.23 ± 1.25	NS
Apo B (g/l)	1.20 ± 0.33	1.21 ± 0.29	1.28 ± 0.35	1.24 ± 0.29	NS
HDL-C (mmol/l)	1.38 ± 0.46	1.49 ± 0.47	1.42 ± 0.42	1.49 ± 0.41	NS
TG (mmol/l)	2.32 (1.50; 4.21)	1.85 (1.29; 3.26)	1.74 (1.29; 2.38)	1.77 (1.27; 2.58)	**p<0.001*** (I vs. II; I vs. III; I vs. IV)
AIP log(TG/HDL-C)	0.31 ± 0.47	0.168 ± 0.33	0.132 ± 0.32	0.096 ± 0.33	**p<0.001*** (I vs. II; I vs. III; I vs. IV)
Glucose (mmol/l)	5.23 ± 1.18	5.08 ± 0.64	5.14 ± 0.72	5.04 ± 0.64	NS
Insulin (mIU/l)	8.50 (6.1; 12.2)	8.1 (5.8; 12.2)	7.6 (5.3; 10.3)	7.45 (4.6; 10.1)	p<0.05 (I vs. III; I vs. IV; II vs. III; II vs. IV)
HOMA	1,87 (1.23; 3.00)	1.82 (1.22; 2.74)	1.72 (1.13; 2.42)	1.61 (1.08; 2.29)	p<0.05 (I vs. III; I vs. IV)
C-peptide (mg/l)	2.55 (1.67; 3.44)	2.36 (1.57; 3.10)	2.15 (1.53; 2.92)	2.20 (1.69; 2.90)	NS

Data are means ± SD or medians (interquartile range) for skewed variables. P was calculated using ANCOVA after adjustment for age and sex, persistence of statistical significance after adjustment for age, sex, and BMI is expressed by *. P<0.01 is considered statistical significant (written in bold).

Serum concentrations of Lp(a) (expressed as mean and interquartile range) in the lower (1^{th}-3^{rd}) quartiles of insulin and HOMA were significantly higher (both $p<0.001$) than in the 4^{th} quartile of these insulin resistance markers: for insulin Lp(a) 0.209 (0.083; 0.627) vs. 0.129 (0.059; 0.363); for HOMA Lp(a) 0.213 (0.085; 0.625) vs. 0.126 (0.059; 0.338). Significance persisted after adjustment for age and sex, for HOMA after adjustment for age, sex, and BMI.

Subjects with MS had significantly lower Lp(a) concentrations in comparison with those without the presence of this cardiometabolic risk phenotype: 0.126 (0.059; 0.325) vs. 0.242 (0.089; 0.682), $p<0.0001$. This significance persisted after adjustment for age, sex, and BMI ($p<0.001$).

The odds ratios of having increased markers of insulin resistance (TG and HOMA) and MS in the top quartile of Lp(a) also indicate an inverse association of Lp(a) with insulin resistance (Table 3).

Table 3. Odds ratios of having increased markers of insulin resistance (4th quartile), and MS in a top quartile of Lp(a) in comparison with the 1th quartile.

Parameter	Odds ratio (95 % confidence interval)	Significance
TG	0.378 (0.222; 0.645)	**p<0.001**
	0.361 (0.206; 0.632)	**p*<0.001**
Insulin	0.527 (0.307; 0.906)	p<0.05
	0.532 (0.309; 0.918)	p*<0.05
HOMA	0.452 (0.261; 0.782)	**p<0.01**
	0.454 (0.261; 0.789)	**p*<0.01**
C-peptide	0.575 (0.339; 0.976)	p<0.05
	0.577 (0.339; 0.982)	p*<0.05
MS	0.309 (0.184; 0.516)	**p<0.001**
	0.285 (0.167; 0.487)	**p*<0.001**

Lp(a) – lipoprotein (a), TG – triglycerides, HOMA – [homeostasis model assessment: fasting glycemia (mmol/l) * fasting insulin (mU/l) / 22.5], MS: harmonized definition of MS (Alberti *et al.* 2009), p – statistical significance without adjustment, p* – statistical significance after adjustment for age and sex. As multiple testing of the data was performed, only p<0.01 was considered as significant (written in bold).

Discussion

In our study, we observed an inverse association of serum Lp(a) concentrations with markers of insulin resistance (TG, AIP, insulin, HOMA, BMI, waist circumference, and number of MS components), and MS, characteristically associated with insulin resistance. In agreement with this, significant differences were found in TG, AIP, HOMA, BMI, and prevalence of MS between quartiles of Lp(a). Prevalence of MS decreased from the lowest to the top quartile of Lp(a).

This is in agreement with recently published studies. Sung *et al.* (2013) described the inverse association between Lp(a) levels and metabolic syndrome and its components in a large Asian South Korea cohort. Similarly inverse association between serum Lp(a) and type 2 diabetes, prediabetes, and insulin resistance was described in the Chinese population (Ding *et al.* 2015). Marzano *et al.* (2014) described independent inverse association between insulin resistance (according to HOMA) and Lp(a) blood levels in 527 hypertensive patients of the Italian population.

In Czech population, Zlatohlavek *et al.* (2008) evaluated association of Lp(a) with increased risk of atherosclerosis in patients with multiple other risk factors. They demonstrated a significantly elevated Lp(a) levels in patients with coronary heart disease. Nevertheless, they did not evaluate either markers of insulin resistance or metabolic syndrome. Lp(a) levels of 70 T2DM patients of their cohort did not differ from non-diabetics.

An inverse association between Lp(a) and measures of glucose and insulin in a population of Mexican Americans having a high prevalence of non-insulin-dependent diabetes mellitus was even described in 1998 by Rainwater and Haffner (1998). Their glucose-intolerant individuals had significantly lower Lp(a) concentrations and a significant increase of residual apo(a) size. Haffner *et al.* (1995) also observed a positive correlation between insulin sensitivity and Lp(a) levels in normoglycemic men. Until recently, little attention has been paid to this issue as Lp(a) was not a therapeutic target at this time.

Large scale prospective studies and meta-analysis data show that increased Lp(a) levels are a risk factor for CVD (Bennet *et al.* 2008, Kamstrup *et al.* 2008, Ergou *et al.* 2009, Danesh *et al.* 2000). Mendelian randomization analyses in two human genetic association studies provide support for a probable causal role of elevated Lp(a) in the development of cardiovascular disease in the general population (Kamstrup *et al.* 2009, Clarke *et al.* 2009).

Elevated Lp(a) levels may increase the risk of CVD/CHD: i) *via* accelerated atherogenesis as a result of intimal deposition of Lp(a) cholesterol, ii) *via* binding of proinflammatory oxidized phospholipids to Lp(a), iii) *via* prothrombotic/anti-fibrinolytic effects as the apolipoprotein(a) possesses structural homology with both plasminogen and plasmin (but has no fibrinolytic activity), or iiii) *via* all these mechanisms (Kroneberg 2016). The association of Lp(a) with CVD/CHD risk in general population is continuous without a threshold or dependence on LDL- or non-HDL-cholesterol levels (Kamstrup *et al.* 2008).

Patients with T2DM have a two- to four-fold higher cardiovascular risk than the non-diabetics (Almdal *et al.* 2004). Surprisingly, Lp(a) probably does not play any role in this high risk. Prospective study of healthy US women (Women´s Health Study [WHS]) revealed inverse association between Lp(a) and the risk of incident T2DM (Mora *et al.* 2010). Moreover, data from Copenhagen City Heart Study and the Copenhagen General Population Study also showed that low concentrations of Lp(a) were associated with a risk of T2DM (Kamstrup and Nordestgaard 2013) and similar findings were observed

in EPIC-Norfolk cohort (Ye *et al.* 2014). However, Mendelian randomization studies, that used genetic variant rs10455872 elevating Lp(a) levels as an instrument, did not support a causal association of Lp(a) with the risk of T2DM (Kamstrup and Nordestgaard 2013, Ye *et al.* 2014). Nevertheless, a causal association for large lipoprotein (a) isoform size with T2DM cannot be excluded (Kamstrup and Nordestgaard 2013). According to Kronenbegr (2016) SNP rs10455872 is an imprecise instrument to support or exclude causality of low Lp(a) levels for T2DM. Better genetic instruments are probably necessary to clarify this issue.

Furthermore, prospective study of two cohorts of T2DM from Nurses´ Health Study and the Health Professional Follow-Up Study support the notion that the effect of Lp(a) on CVD risk among diabetic patients might be different from that in the general population. Qi *et al.* (2012) evaluated relationship between genetic loci influencing Lp(a), plasma Lp(a) levels, and cardiovascular disease risk among diabetic patients and compared it with the observations in the general population. They did not find any significant association between plasma levels of Lp(a) and CVD incidence in T2DM subjects, and consistently, none of the Lp(a) SNPs were associated with CVD risk or mortality in these diabetic cohorts. The genetic effect of Lp(a) on CHD risk showed a significant heterogeneity between the diabetic and general population. Their results suggest that diabetes states may attenuate the relation between Lp(a) and cardiovascular risk.

The potential reasons for an inverse association between Lp(a) and features of insulin resistance and T2DM are unknown. Some human and animal studies suggest an effect of insulin in reducing Lp(a) levels. For example, Rainwater and Hafner (1998) found an inverse correlation of Lp(a) levels with fasting insulin and 2-h glucose concentrations in both diabetic and nondiabetic participants. Neele *et al.* (1999) showed that insulin suppressed apo(a) synthesis by primary cultures of cynomolgus monkey hepatocytes. These data suggest that insulin resistance may be manifested by a lowering of Lp(a) levels that precedes overt T2DM diagnosis. Thus Lp(a) might be another lipoprotein, that is associated with metabolic syndrome characterized by insulin resistance.

A recently published genome-wide study uncovered wide-spread causal effects of Lp(a) on overall lipoprotein metabolism, and especially causal associations between Lp(a) and systemic triglyceride and VLDL metabolism. Lp(a) raising allele rs10455872-G was associated with a smaller diameter of VLDL particles. This allele was also associated with lower concentrations of extra large, large, and medium VLDL particles. Their findings suggest that Lp(a) synthesis affects overall lipoprotein metabolism, and in particular, the synthesis of large VLDL particles in the liver and thereby the triglyceride metabolism in general. Based on these results, they propose that the apoB-containing lipoprotein particle used to form Lp(a) by the covalent attachment of apo(a) may actually also be a poorly lipidated VLDL-type particle. This suggests that circulating Lp(a) particles are likely to be a more heterogeneous group than simply an apo(a) component added to LDL particles (Kettunen *et al.* 2016).

As triglyceride metabolism is closely associated with insulin resistance, this might also explain inverse association of Lp(a) with features of insulin resistance, including metabolic syndrome and T2DM.

Conclusion

Lp(a) levels are inversely associated with features of insulin resistance and metabolic syndrome. The potential reason for this inverse association is not clear. Some human and animal studies suggest an effect of insulin in reducing Lp(a) levels. These data suggest that insulin resistance may be manifested by a lowering of Lp(a) levels that precedes overt diagnosis of T2DM. Thus Lp(a) might be another lipoprotein, that is associated with metabolic syndrome characterized by insulin resistance. Causal association of Lp(a) with systemic triglyceride and VLDL metabolism, as demonstrated recently by the results of genome wide study, might play a role in this association.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

Supported by grant MZ ČR – RVO (FNOL 00098892) – IP 87-54.

References

ALBERTI KG, ECKEL RH, GRUNDY SM, ZIMMET PZ, CLEEMAN JI, DONATO KA, FRUCHART JC, JAMES WP, LORIA CM, SMITH SC JR, ET AL.: Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* **120**: 1640-1645, 2009.

ALMDAL T, SCHARLING H, JENSEN JS, VESTERGAARD H: The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Arch Intern Med* **164**: 1422-1426, 2004.

BENNET A, DI ANGELANTONIO E, ERQOU S, EIRIKSDOTTIR G, SIGURDSSON G, WOODWARD M, RUMLEY A, LOWE GD, DANESH J, GUDNASON V: Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. *Arch Intern Med* **168**: 598-608, 2008.

BOERWINKLE E, LEFFERT CC, LIN J, LACKNER C, CHIESA G, HOBBS HH: Apolipoprotein(a) gene accounts for greater than 90 % of the variation in plasma lipoprotein(a) concentrations. *J Clin Invest* **90**: 52-60, 1992.

CAMPOS H, BLIJLEVENS E, MCNAMARA JR, ORDOVAS JM, POSNER BM, WILSON PW, CASTELLI WP, SCHAEFER EJ: LDL particle size distribution. Results from the Framingham Offspring Study. *Arterioscler Thromb* **12**: 1410-1419, 1992.

CLARKE R, PEDEN JF, HOPEWELL JC, KYRIAKOU T, GOEL A, HEATH SC, PARISH S, BARLERA S, FRANZOSI MG, RUST S, BENNETT D, SILVEIRA A, MALARSTIG A, GREEN FR, LATHROP M, GIGANTE B, LEANDER K, DE FAIRE U, SEEDORF U, HAMSTEN A, COLLINS R, WATKINS H, FARRALL M; PROCARDIS CONSORTIUM: Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* **361**: 2518-2528, 2009.

DANESH J, COLLINS R, PETO R: Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. *Circulation* **102**: 1082-1085, 2000.

DE GRAAF J, VAN DER VLEUTEN G, STALENHOEF AF: Diagnostic criteria in relation to the pathogenesis of familial combined hyperlipidemia. *Semin Vasc Med* **4**: 229-240, 2004.

DING L, SONG A, DAI M, XU M, SUN W, XU B, SUN J, WANG T, XU Y, LU J, WANG W, BI Y, NING G: Serum lipoprotein (a) concentrations are inversely associated with T2D, prediabetes, and insulin resistance in a middle-aged and elderly Chinese population. *J Lipid Res* **56**: 920-926, 2015.

DOBIASOVA M, FROHLICH J: The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER HDL). *Clin Biochem* **34**: 583-588, 2001.

ERQOU S, KAPTOGE S, PERRY PL, DI ANGELANTONIO E, THOMPSON A, WHITE IR, MARCOVINA SM, COLLINS R, THOMPSON SG, DANESH J; EMERGING RISK FACTORS COLLABORATION: Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* **302**: 412-423, 2009.

FRIEDEWALD WT, LEVY RJ, FREDRICKSON DS: Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* **18**: 499-502, 1972.

FROHLICH J, DOBIASOVA M: Fractional esterification rate of cholesterol and ratio of triglycerides to HDL-cholesterol are powerful predictors of positive findings on coronary angiography. *Clin Chem* **49**: 1873-1880, 2003.

GUAN W, CAO J, STEFFEN BT, POST WS, STEIN JH, TATTERSALL MC, KAUFMAN JD, MCCONNELL JP, HOEFNER DM, WARNICK R, TSAI MY: Race is a key variable in assigning lipoprotein(a) cutoff values for coronary heart disease risk assessment: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol* **35**: 996-1001, 2015.

HAFFNER SM, KARHAPAA P, RAINWATER DL, MYKKANEN L, ALDRETE G JR, LAAKSO M: Insulin sensitivity and Lp(a) concentrations in normoglycemic men. *Diabetes Care* **18**: 193-199, 1995.

KAMSTRUP PR, NORDESTGAARD BG: Lipoprotein(a) concetrations, isoform size, and risk of type 2 diabetes: a Mendelian randomisation study. *Lancet Diabetes Endocrinol* **1**: 220-227, 2013.

KAMSTRUP PR, BENN M, TYBJAERG-HANSEN A, NORDESTGAARD BG: Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation* **117**: 176-184, 2008.

KAMSTRUP PR, TYBJAERG-HANSEN A, STEFFENSEN R, NORDESTGAARD BG: Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* **301**: 2331-2339, 2009.

KETTUNEN J, DEMIRKAN A, WÜRTZ P, DRAISMA HH, HALLER T, RAWAL R, VAARHORST A, KANGAS AJ, LYYTIKÄINEN LP, PIRINEN M, POOL R, SARIN AP, SOININEN P, TUKIAINEN T, WANG Q, ET AL.: Genome-wide study for circulating metabolites identifies 62 loci and reveals novel systemic effects of LPA. *Nat Commun* **7**: 11122, 2016.

KRONENBERG F: Human genetics and the causal role of lipoprotein(a) for various diseases. *Cardiovasc Drugs Ther* **30**: 87-100, 2016.

MARCOVINA SM, GAUR VP, ALBERS JJ: Biological variability of cholesterol, triglyceride, low- and high-density lipoprotein cholesterol, lipoprotein(a), and apolipoproteins A-I and B. *Clin Chem* **40**: 574-578, 1994.

MARZANO L, COLUSSI G, DEL TORRE M, SECHI LA, CATENA C: Relationships of plasma lipoprotein(a) levels with insulin resistance in hypertensive patients. *Metabolism* **63**: 1439-1446, 2014.

MORA S, KAMSTRUP PR, RIFAI N, NORDESTGAARD BG, BURING JE, RIDKER PM: Lipoprotein(a) and risk of type 2 diabetes. *Clin Chem* **56**: 1252-1260, 2010.

NEELE DM, DE WIT EC, PRINCEN HM: Insulin supresses apolipoprotein(a) synthesis by primary cultures of cynomolgus monkey hepatocytes. *Diabetologia* **42**: 41-44, 1999.

NORDESTGAARD BG, CHAPMAN MJ, RAY K, BORÉN J, ANDREOTTI F, WATTS GF, GINSBERG H, AMARENCO P, CATAPANO A, DESCAMPS OS, FISHER E, KOVANEN PT, KUIVENHOVEN JA, LESNIK P, MASANA L, REINER Z, TASKINEN MR, TOKGÖZOGLU L, TYBJÆRG-HANSEN A; EUROPEAN ATHEROSCLEROSIS SOCIETY CONSENSUS PANEL: Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J* **31**: 2844-2853, 2010.

QI Q, WORKALEMAHU T, ZHANG C, HU FB, QI L: Genetic variants, plasma lipoprotein(a) levels, and risk of cardiovascular morbidity and mortality among two prospective cohorts of type 2 diabetes. *Eur Heart J* **33**: 325-334, 2012.

RAINWATER DL, HAFFNER SM: Insulin and 2-hour glucose levels are inversely related to Lp(a) concentrations controlled for LPA genotype. *Arterioscler Thromb Vasc Biol* **18**: 1335-1341, 1998.

SNIDERMAN AD, CASTRO CABEZAS M, RIBALTA J, CARMENA R, DE BRUIN TW, DE GRAAF J, ERKELENS DW, HUMPHRIES SE, MASANA L, REAL JT, TALMUD PJ, TASKINEN MR: A proposal to redefine familial combined hyperlipidemia – third worshopon FCHL held in Barcelona from 3 to 5 May 2001, during the scientific sessions of the European Society for Clinical Investigation. *Eur J Clin Invest* **32**: 71-73, 2002.

SUNG KC, WILD SH, BYRNE CD: Lipoprotein (a), metabolic syndrome and coronary calcium score in a large occupational cohort. *Nutr Metab Cardiovasc Dis* **23**: 1239-1246, 2013.

UTERMANN G: The mysteries of lipoprotein (a). *Science* **246**: 904-910, 1989.

YE Z, HAYCOCK PC, GURDASANI D, POMILLA C, BOEKHOLDT M, TSIMIKAS S, KHAW KT, WAREHAM NJ, SANDHU MS, FOROUHI NG: The association between circulating lipoprotein(a) and type 2 diabetes: is it causal? *Diabetes* **63**: 332-342, 2014.

ZLATOHLÁVEK L, ZÍDKOVÁ K, VRABLÍK M, HAAS T, PRUSÍKOVÁ M, SVOBODOVÁ H, ČEŠKA R: Lipoprotein(a) and its position among other risk factors of atherosclerosis. *Physiol Res* **57**: 777-783, 2008.