Elevated lipoprotein(a) in the middle-aged Polish population: Preliminary data on the genetic background

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INTRODUCTION

Elevated lipoprotein(a) (Lp[a]), a low-density lipoprotein (LDL)-like lipoprotein containing apolipoprotein (a) homologous to plasminogen, with the molecular weight ranging from 300 to 800 kDa due to a variety of apolipoprotein (a) isoforms, is a well-established genetically determined risk factor for cardiovascular disease (CVD), including coronary artery disease (CAD), myocardial infarction (MI), stroke, and peripheral arterial disease (PAD) [1, 2]. The current guidelines recommend that Lp(a) measurement once in a lifetime should be included in a comprehensive CVD risk evaluation and suggest a global risk underestimation at high or very high Lp(a) concentrations [1, 2]. Little is known about Lp(a) levels in the Polish population except for a small sample (n = 200) from the EUROASPIRE V survey, in which the prevalence of Lp(a) >50 mg/dl was 22.5% in patients without diagnosed CVD but with known risk factors [3].

Given ongoing trials on novel agents substantially reducing Lp(a) by 80% [2], we decided to assess the prevalence of elevated Lp(a) concentration in a middle-aged Polish population and its association with other CVD risk factors.

METHODS

We enrolled consecutive subjects participating in the "Malopolska coronary artery disease prophylactic program for people older than 40 years" from May 2022 to October 2022. The exclusion criteria were age <40 or >65 years, documented CAD or PAD, and a history of MI, stroke, or transient ischemic attack. The study was approved by the local Ethical Committee (OIL/KBL33/2022).

Data about baseline anthropometric and clinical characteristics, previous medical history, lifestyle, and family history of premature CVD were collected. The 10-year risk of the first CVD event was assessed with the Systematic Coronary Risk Evaluation 2 (SCORE2) algorithm. Dyslipidemia was defined as total cholesterol (TC) ≥190 mg/dl, or LDL cholesterol (LDL-C) ≥115 mg/dl, or triglycerides ≥150 mg/dl or statin use. Serum Lp(a) was determined using immunoturbidimetry (Roche Diagnostics, Mannheim, Germany). Elevated Lp(a) was defined as values >50 mg/dl [2]. Lp(a) >100 mg/dl was defined as a very high-risk group [2]. In that case, analysis of the *LPA* gene variant: c.5673A>G (p.Ile1891Met, used nomenclature: p.Ile4399Met, rs3798220), reported as associated with elevated plasma Lp(a) levels [4], was performed with a TaqMan SNP assay (Applied Biosystems, ThermoFisher Scientific, Foster City, CA, US) on the QuantStudio Dx Real-Time PCT Instrument (ThermoFisher Scientific).

Statistical analysis

Statistical analysis was performed with SPSS Statistics software (Version 28.0.1.0, IBM Corp., Armonk, NY, US). Continuous variables were expressed as medians (interquartile range) and categorical variables as numbers (percentage). Normal distribution was assessed

Table 1. Characteristics of the study population according to lipoprotein (a) concentration

	Lipoprotein (a), mg/dl			*P*-value
	<50	50–100	>100	
	n = 656 (82.0%)	n = 101 (12.6%)	n = 43 (5.4%)	
Age, years	49 (44–52)	47 (44–52)	52 (43–56)	0.20
Males	222 (33.8)	31 (30.7)	5 (11.6)[a]	0.001
BMI, kg/m^2	26.4 (24.0–29.8)	27.1 (24.2–31.3)	27.3 (23.9–30.4)	0.41
Current smoking	210 (32.0)	38 (37.6)	14 (32.6)	0.53
Hypertension	167 (25.5)	16 (15.8)	13 (30.2)	0.07
Diabetes mellitus	34 (5.2)	5 (5.0)	2 (4.7)	0.98
Dyslipidemia,	179 (27.3)	28 (27.7)	20 (46.5)[a]	0.025
Family history of premature CVD	282 (43.0)	39 (38.6)	19 (44.2)	0.69
SCORE2	2.40 (1.2–4.0)	2.25 (1.1–4.2)	2.35 (1.1–4.0)	0.97
Fasting glucose, mmol/l	5.2 (4.9–5.5)	5.2 (4.9–5.5)	5.2 (5.0–5.5)	0.80
CRP, mg/l	1.1 (0.6–2.3)	1.2 (0.6–3.0)	1.7 (0.7–3.5)	0.08
Total cholesterol, mmol/l	5.06 (4.52–5.67)	5.22 (4.73–5.82)	5.54 (5.19–6.02)[a]	0.004
LDL-cholesterol, mmol/l	3.23 (2.66–3.74)	3.39 (2.81–3.99)	3.56 (3.11–4.00)[a]	0.015
HDL-cholesterol, mmol/l	1.53 (1.28–1.82)	1.53 (1.27–1.85)	1.64 (1.36–1.99)	0.14
Triglycerides, mmol/l	1.12 (0.83–1.64)	1.16 (0.89–1.51)	1.08 (0.83–1.31)	0.54
Fibrinogen, g/l	2.84 (2.54–3.10)	2.83 (2.52–3.07)	3.10 (2.81–3.46)[a, b]	<0.001

Values are shown as number (percentage) or median (interquartile range) as appropriate
[a]*P* <0.05 between <50 mg/dl and >100 mg/dl. [b]*P* <0.05 between 50–100 mg/dl and >100 mg/dl

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CRP, C-reactive protein, HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCORE2, Systematic Coronary Risk Evaluation 2

using the Shapiro-Wilk test. Differences among the three groups were compared using the ANOVA test with the post-hoc Bonferroni correction when normally distributed or the Kruskal-Wallis test for multiple comparisons of non-normally distributed variables. Categorical variables were analyzed with the chi-square test or Fisher's exact test with a post-hoc z-test for comparison of column proportions with the Bonferroni correction. Associations between nonparametric variables were assessed by the Spearman rank correlation coefficient. All independent variables associated (P <0.2) with Lp(a) in a univariate model and simultaneously not correlated with other independent variables were included in the multivariate linear regression analysis to determine independent predictors of Lp(a) levels. A two-sided P <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

We studied 800 individuals aged 49 (44–53) years (68% women), including 17.8% with Lp(a) >50 mg/dl with a higher proportion of females in this subgroup (Table 1). The prevalence of Lp(a) >50 mg/dl was 18.4% in Germany, which is almost identical to our population while in Finland or Greece, it was 6.0% [5, 6]. Our result is slightly lower than in the study by Ratajczak et al. [3], which evaluated CVD risk factors in subjects aged 18–80 (median, 52 [43–60]) years, while we assessed younger subjects. However, we did not observe a significant correlation between Lp(a) and age in contrast to a previous study in the general population, in which Lp(a) increased slightly with age [2].

Individuals with Lp(a) >100 mg/dl (maximum 237 mg/dl) were more often female and had dyslipidemia compared with those with Lp(a) <50 mg/dl (n = 682, 82.0%). Moreover, TC, LDL-C, and fibrinogen levels were 7.16% (P = 0.008), 9.54% (P = 0.047), and 9.15% (P <0.001), respectively, higher in the Lp(a) >100 mg/dl group compared with < 50 mg/dl. We did not observe any intergroup differences in the prevalence of a family history of premature CVD and the 10-year CVD risk (Table 1).

In multivariable analysis, after adjustment for age, Lp(a) levels were independently associated with female sex, LDL-C, and fibrinogen (Supplementary material, *Table S1*). The associations of Lp(a) with these variables have been reported previously [2, 7]. Higher Lp(a) in women is largely explained by an increase in Lp(a) in the peri- and post-menopausal period, which corresponds to elevated CVD risk in that still undertreated population [2, 8]. We observed higher Lp(a) levels in women aged >52 years as compared to the remainder (10.1 [3.9–45.0] vs. 7.0 [2.9–33.2] mg/dl; P = 0.034). Although the expression, synthesis, and metabolism of Lp(a) and LDL-C are independent, a weak positive correlation of their levels (in the current study, r = 0.11, P = 0.002) has been reported previously [9]. Statin use cannot reduce Lp(a) concentrations, whereas PCSK9 inhibitors lower Lp(a) by 15%–30% [2, 10]. Statins were used by 15.3% (n = 122) participants without any effect on Lp(a), as expected.

A positive association between fibrinogen and Lp(a) in our study (r = 0.135; P <0.001) is consistent with previous studies performed in the general population [7]. This association is of importance since fibrinogen is the key modulator of fibrin clot properties, and elevated Lp(a) has been associated with reduced clot permeability and susceptibility to lysis [11, 12].

Nine patients of 43 subjects with Lp(a) >100 mg/dl were genotyped, and in 4 (44.4%), the heterozygous *LPA* variant (c.5673A>G) was detected. The rs3798220 variant has been reported in 6.5% of apparently healthy Poles and 18.1% of patients with Lp(a) >75 mg/dl worldwide [13]. To our knowledge, this is the first report on genetic assessment of *LPA* variants in Poles with elevated Lp(a). Further research is needed to examine the genetic background of elevated Lp(a) in the Polish population.

Our study has limitations. Firstly, the size of the study population was limited, though it was the largest study sample in the Polish population. Secondly, clinical characteristics of the study participants were typical of screening programs; therefore, the findings could not be likely extrapolated to younger or older individuals as well as to those with CVD or the whole Polish population.

In conclusion, this study shows a relatively high (17.8%) prevalence of hyperlipoproteinemia(a) in a large Polish middle-aged population without evident CVD. In the upcoming era of new drugs with a potent Lp(a) lowering effect (e.g. pelacarsen) [2, 4], screening for elevated Lp(a) in high CVD-risk countries, including Poland [14], should be encouraged. Now, in individuals with high Lp(a), free of CVD, the management of modifiable risk factors as well as screening for high Lp(a) in families of the "index" subject should be implemented.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

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REFERENCES

1. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42(34): 3227–3337, doi: 10.1093/eurheartj/ehab484, indexed in Pubmed: 34458905.
2. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J. 2022; 43(39): 3925–3946, doi: 10.1093/eurheartj/ehac361, indexed in Pubmed: 36036785.
3. Ratajczak J, Kubica A, Michalski P, et al. Determinants of lipid parameters in patients without diagnosed cardiovascular disease-results of the Polish arm of the EUROASPIRE V survey. J Clin Med. 2023; 12(7), doi: 10.3390/jcm12072738, indexed in Pubmed: 37048821.
4. Boffa MB, Koschinsky ML. Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? J Lipid Res. 2016; 57(5): 745–757, doi: 10.1194/jlr.R060582, indexed in Pubmed: 26647358.
5. van Buuren F, Horstkotte D, Knabbe C, et al. Incidence of elevated lipoprotein (a) levels in a large cohort of patients with cardiovascular disease. Clin Res Cardiol Suppl. 2017; 12(Suppl 1): 55–59, doi: 10.1007/s11789-017-0087-y, indexed in Pubmed: 28229283.
6. Raitakari O, Kivelä A, Pahkala K, et al. Long-term tracking and population characteristics of lipoprotein (a) in the Cardiovascular Risk in Young Finns Study. Atherosclerosis. 2022; 356: 18–27, doi: 10.1016/j.atherosclerosis.2022.07.009, indexed in Pubmed: 35961208.
7. Slunga L, Asplund K, Johnson O, et al. Lipoprotein(a) in a randomly selected 25-64 year old population: the Northern Sweden Monica Study. J Clin Epidemiol. 1993; 46: 617–624.
8. Duda-Pyszny D, Trzeciak P, Desperak P, et al. Comparison of clinical characteristics, in-hospital course, and 12-month prognosis in women and men with chronic coronary syndromes. Kardiol Pol. 2021; 79(4): 393–400, doi: 10.33963/KP.15749, indexed in Pubmed: 33463985.
9. Varvel S, McConnell JP, Tsimikas S. Prevalence of elevated Lp(a) mass levels and patient thresholds in 532 359 patients in the United States. Arterioscler Thromb Vasc Biol. 2016; 36(11): 2239–2245, doi: 10.1161/ATVBAHA.116.308011, indexed in Pubmed: 27659098.
10. Atar D, Langslet G, Tonstad S. Do we need new lipid-lowering agents in the era of PCSK9 inhibitors? Recent advances. Kardiol Pol. 2022; 80(7-8): 741–749, doi: 10.33963/KP.a2022.0117, indexed in Pubmed: 35521719.
11. Ząbczyk M, Ariëns RAS, Undas A. Fibrin clot properties in cardiovascular disease: from basic mechanisms to clinical practice. Cardiovasc Res. 2023; 119(1): 94–111, doi: 10.1093/cvr/cvad017, indexed in Pubmed: 36662542.
12. Kopytek M, Ząbczyk M, Mazur P, et al. Oxidized phospholipids associated with lipoprotein(a) contribute to hypofibrinolysis in severe aortic stenosis. Pol Arch Intern Med. 2022; 132(11), doi: 10.20452/pamw.16372, indexed in Pubmed: 36384266.
13. Karwatowska-Prokopczuk E, Clouet-Foraison N, Xia S, et al. Prevalence and influence of LPA gene variants and isoform size on the Lp(a)-lowering effect of pelacarsen. Atherosclerosis. 2021; 324: 102–108, doi: 10.1016/j.atherosclerosis.2021.03.036, indexed in Pubmed: 33872986.
14. Pająk A, Jankowski P, Zdrojewski T. The burden of cardiovascular disease risk factors: A current problem. Kardiol Pol. 2022; 80(1): 5–15, doi: 10.33963/KP.a2022.0018, indexed in Pubmed: 35137945.