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Lowering of lipoprotein(a) level under niacin treatment is dependent on apolipoprotein(a) phenotype

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Abstract

Background: Lipoprotein(a) [Lp(a)] is a cardiovascular risk factor; in addition to being a low-density lipoprotein (LDL)-like particle, it contains highly heterogeneous apolipoprotein(a) [apo(a)]. No prior studies have evaluated extended-release (ER) niacin effect on Lp(a) level depending on apo(a) phenotype.

Methods: For this 24-week, prospective, open-label clinical trial we recruited 30 men (mean age 46.2 ± 7.5 years) with Lp(a) levels >20 mg/dL. No participant had previously received lipid lowering therapy, and started ER niacin 500 mg with stepwise dose increasing up to 1.5–2.0 g. Subjects were evaluated for Lp(a), lipids, high-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2 (Lp-PLA2), and fibrinolytic markers (plasminogen activator inhibitor-1, tissue plasminogen activator/plasminogen activator inhibitor-1 complex, plasmin–antiplasmin complex). Patients were divided into two groups with major low- (LMW) or high-molecular weight (HMW) apo(a) isoforms determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis of plasma under reducing conditions followed by immunoblotting.

Results: At baseline, groups were comparable in age, lipid, inflammatory and fibrinolytic biomarkers levels. There was a significant difference in baseline Lp(a) concentrations: 92 ± 29 mg/dL versus 54 ± 46 mg/dL in LMW and HMW apo(a) groups, respectively, $p < 0.01$. During the course of niacin treatment Lp(a) decreased by 28% ($p < 0.003$), Lp-PLA2 by 22% ($p < 0.001$), C-reactive protein by 24% ($p = 0.07$) in LMW apo(a) group, whereas no changes in Lp(a) and biomarkers levels were obtained in HMW apo(a) group.

Conclusion: High-dose ER niacin declines elevated Lp(a) level in male subjects with low- but not high-molecular weight apo(a) phenotype.

Keywords: Lipoprotein(a); Apolipoprotein(a) phenotype; Niacin

1. Introduction

Lipoprotein(a) (Lp(a)) is a cardiovascular risk factor, which, in addition to being a low-density lipoprotein (LDL)-like particle, contains an additional apolipoprotein(a) [apo(a)]. This apolipoprotein shows a high homology with plasminogen and has a tremendous size heterogeneity, which is determined by a copy number variation. This variation is the basis for a repeated number of so called kringle IV type 2 (KIV-2), which results in the apo(a) polymorphism with 11–50 KIV-2 repeats. As previously described, apo(a) isoforms are divided into low- (LMW) and high-molecular weights (HMW) according to their electrophoretic mobility [1]. Lp(a) synthetic rate is higher in subjects with LMW apo(a) isoforms than in those

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with HMW apo(a) isoforms [2] due to the smaller number of KIV-2 repeats. Meta-analysis of 40 studies including 58,334 patients demonstrated that individuals with LMW apo(a) isoforms had 2 times higher risk of coronary heart disease (CHD) and ischemic stroke compared to subjects with HMW apo(a) isoforms [3].

It was shown that the presence of elevated Lp(a) levels can re-stratify the patient to a higher risk group [4]. Despite statin therapy, many patients continue to experience ischemic events, indicating that residual cardiac risk could be linked to hidden and unknown risk factors. Bearing in mind that 1 of 5 people in the general population possesses Lp(a) excess [5], this marker deserves to be evaluated in interventional trials. To date there have been no clear tactics for managing patients with low or moderate risk of cardiovascular disease (CVD) and elevated Lp(a) level. Niacin is the only drug with proven efficacy in lowering Lp(a). In numerous studies niacin has been shown to reduce Lp(a) levels in a dose-dependent manner by up to 30% and as well as cardiovascular events [5,6]. Niacin is effective not only in its influence on Lp(a) but also by diminishing total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), increasing high-density lipoprotein cholesterol (HDL-C) levels and possessing anti-inflammatory potential [7,8]. Precise mechanisms by which niacin affects Lp(a) metabolism still remain unclear. We hypothesized that apo(a) size can predict the niacin response in patients with elevated Lp(a) levels. There have been no previous studies evaluating extended-release (ER) niacin effects on Lp(a) level depending on apo(a) phenotype.

2. Materials and methods

From September, 2011, to March, 2012, in this prospective, open-label study we selected 30 consecutive patients from the database of the Atherosclerosis Department of Russian Cardiology Research and Production Center (Moscow, Russia). The study protocol was approved by the Review Board of the Institute of Clinical Cardiology named after A.L. Myasnikov. Subjects with 10 year risk of fatal cardiovascular events of 1–5% (as assessed by SCORE chart for high-risk population), Lp(a) ≥20 mg/dL and known apo(a) isoforms were eligible to this study. We did not include those with TG > 4.5 mmol/L, creatine kinase (CK) > 3 upper limit of normal (ULN), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 ULN, total bilirubin >2 ULN, creatinine clearance ≤60 mL/min, thyroid-stimulating hormone >1.5 ULN or <1.0 ULN, gout, active peptic ulcer, lipid-lowering medication during last month prior to screening. Under the lifestyle modification LDL-C concentration should be maintained less than 4.8 mmol/L. All patients provided written informed consent.

At baseline, standard evaluation was performed assessing the presence of atherosclerosis risk factors, medical history and physical condition. Monotherapy with ER niacin was initiated from 500 mg with weekly stepwise dose increasing by 500 mg up to 1.5–2.0 g as a goal. Blood samples were taken at baseline, 6 and 24 weeks of the treatment period. TC, TG, HDL-C, high-sensitivity C-reactive protein (hsCRP) were measured in the serum with analyzer "Architect-C 8000" (Abbott, USA). LDL-C was calculated by Friedewald formula and its modification: $LDL\text{-}C_{corr} = TC - HDL\text{-}C - TG/2.2{-}0.3 \times Lp(a)/38.7$ (mmol/L). Concentration of lipoprotein-associated phospholipase A2 (Lp-PLA2) was determined by "PLAC® Test ELISA kit" (diaDexus Inc, USA). Fibrinolytic markers were measured by enzyme-linked immunosorbent assay (ELISA) with commercially available kits: plasminogen activator inhibitor-1 (PAI-1) by "Actibind PAI-1 ELISA", plasmin–antiplasmin complex (PAP) by "PAP Complex ELISA", tissue-type plasminogen activator/plasminogen activator inhibitor-1 (t-PA/PAI-1) by "t-PA/PAI-1 Complex ELISA" ("Technoclone", Austria).

Lp(a) concentration was estimated by ELISA using monospecific polyclonal sheep anti-human-apo(a) antibodies as previously reported [9]. Apo(a) phenotyping was performed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis of plasma under reducing conditions followed by immunoblotting with the use of affinity-purified antibodies against Lp(a). The sensitivity of this method allows determination of apo(a) bands if plasma Lp(a) concentration is >4 mg/dL. Apo(a) isoforms were defined according to their electrophoretic mobility compared to apolipoproteinB-100 and were designated as F, B or S1–S4 [1]. All patients were divided into two groups according to major apo(a) isoform – with low molecular weight apo(a) phenotype (LMW, containing major band apo(a) F, B, S1 or S2) and high molecular weight apo(a) phenotype (HMW, containing major band S3 or S4).

STATISTICA software (version 10.0, StatSoft, Inc., USA) was used to perform statistical analysis. Variables with normal distribution were represented as means ± standard deviation, while those with abnormal distribution were expressed as median (25–75% quartiles). Comparisons of changes from the baseline were performed with Student's *t*-test and Mann–Whitney test and between two groups were done with Student's *t*-test or Wilcoxon test for continuous parameters and Fisher's exact test for categorical variables. Statistical significance was accepted when $p < 0.05$.

3. Results

We divided 30 male subjects (mean age 47 ± 7 years, range 30–60 years) into two groups according to predominant apo(a) phenotype. Almost half of the participants had hyperlipidemia and one third were hypertensive, 17% ($n = 5$) had positive CHD family history and four persons continued to smoke. Lp(a) level was almost twice higher in patients with LMW apo(a) isoforms as compared to those with HMW apo(a) isoforms (Table 1).