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Effect of Nicotinic acid/Laropiprant in the lipoprotein(a) concentration with regard to baseline lipoprotein(a) concentration and *LPA* genotype ☆

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ABSTRACT

Background. Lipoprotein(a) [Lp(a)] is a lipoprotein in which apolipoproteinB-100 is linked to apolipoprotein(a) [apo(a)]. Significant variation in Lp(a) concentration is specific to *LPA* gene, which codes for apo(a). Nicotinic acid (NA) is used for treatment of dyslipidemias, and the lowering effect of NA on Lp(a) has been previously reported.

Objective. To evaluate the Lp(a) lowering effect of 1 g/20 mg and 2 g/40 mg day of Nicotinic acid/Laropiprant in subjects with different baseline Lp(a) concentrations and depending on the *LPA* genotype.

Methods. In an open-label, 10-week study, 1 g/20 mg day of NA/Laropiprant for 4 weeks followed by 6 weeks of 2 g/40 mg day conducted at 3 centers in Spain, 82 subjects were enrolled. Patients were studied at baseline and at the end of both treatment periods and were enrolled in three groups: normal Lp(a) (<50 mg/dL), high Lp(a) (50–120 mg/dL) and very high Lp(a) (>120 mg/dL). The *LPA* genetic polymorphism was analyzed by a real-time PCR.

Results. There was a significant difference in *LPA* genotypes among Lp(a) concentration groups and an inverse and significant correlation between baseline Lp(a) concentration and *LPA* genotype was found ($R = -0.372$, $p < 0.001$). There were a significant decrease in total cholesterol, triglycerides, LDL cholesterol, apo B and Lp(a), and a significant increase in HDL cholesterol after NA/Laropiprant treatment, without changes in BMI. However, there were no statistical differences in percentage variation of analyzed variables depending on *LPA* genotype.

Conclusion. *LPA* genotype is a major determinant of Lp(a) baseline concentration. However, the lipid lowering effect of NA is not related to *LPA* genotype.

Abbreviations: Lp(a), Lipoprotein(a); Apo(a), Apolipoprotein(a); LDL, Low density lipoprotein; *LPA*, apolipoprotein(a) gene; NA, Nicotinic acid; HDL, High density lipoprotein; PCR, Polymerase Chain Reaction; BMI, Body Mass Index; HOMA-IR, Homeostasis Model of Assessment-Insulin Resistance; PCSK9, Proprotein Convertase Subtilisin/Kexin type 9; CETP, Cholesterol Ester Transfer Protein.

☆ Clinical Trial registration number: NCT01321034.

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1. Introduction

Lipoprotein(a) [Lp(a)] is a type of lipoprotein particle found in human plasma, included in apoB-100 containing particles in which apolipoprotein B-100 is linked by a single disulfide bridge to a unique glycoprotein, apolipoprotein(a) [apo(a)] [1]. Except for apo(a), Lp(a) is essentially indistinguishable from low density lipoproteins (LDLs), both in structure and in its physical and chemical properties. Because of the presence of apo(a), Lp(a) and LDL are metabolically distinct and it is evident that the special characteristics of Lp(a), including its size and density heterogeneity, are almost entirely attributable to apo(a) [2]. Epidemiological studies have documented that high plasma Lp(a) concentrations are associated with a high risk of cardiovascular disease [3,4]. However, the mechanism of atherogenicity of Lp(a) is currently not known [5], but may include the vessels wall loading of cholesterol transported by Lp(a), a high risk for thrombosis by the inhibition of conversion of plasminogen to plasmin [6], and the transport of proinflammatory oxidized phospholipids [7].

Lp(a) is unique among lipoproteins in that its plasma concentrations varies from 0.1 to 300 mg/dL among individuals. Significant variation in plasma Lp(a) concentration is specific to the *LPA* gene locus (OMIM 152200), which codes for the apo(a) moiety of Lp(a) [8]. Several studies have confirmed that variation at the *LPA* gene on chromosome 6q26-27 accounts for most of the variability in plasma Lp(a) concentration [9,10]. This variation is partially due to the highly size heterogeneity of apo(a) that contains repeated domains that bear a high degree of homology to the plasminogen kringle IV sequence [11]. The kringle IV-like domains in apo(a) are divided in 10 types according to amino acid sequence. The kringle IV-2 sequence is present in a variable number of identically repeated copies (from 3 to > 60) and the number of kringle IV-2 repeats is inversely correlated with the Lp(a) concentration [4,12], but positively associated with the development of myocardial infarction, even after adjustment of Lp(a) concentration [4].

Nicotinic acid (NA) is a commonly used drug in the treatment of dyslipidemias because of its capacity to decrease LDL cholesterol and triglycerides and to increase HDL cholesterol [13]. In addition, the lowering effect of NA on Lp(a) concentration has been reported in different studies [14,15]. The Lp(a) reduction by niacin has been described to be highly heterogeneous, ranging between 10% and 40% arguing differences in patients selection, drug dose, length of drug administration, and methods for Lp(a) quantification [16]. However, the effect of baseline Lp(a) concentration and the Lp(a) size in the effect of niacin therapy has not been reported. This topic could be clinically important because the lowering effect of NA on Lp(a) seems to be related to apo(a) hepatic synthesis [15], which is very sensitive to apo(a) size [17].

For that reason, we hypothesized that the Lp(a) lowering effect of nicotinic acid could be dependent on the baseline pretreatment Lp(a) concentration, and that the Lp(a) size could be a major factor related to the variability of lowering effect of nicotinic acid. The aim of this study was to evaluate the Lp(a) lowering effect of 1 g/20 mg and 2 g/40 mg day of Nicotinic acid/Laropiprant in subjects with different baseline Lp(a) concentrations and depending on the number of kringle IV-2 repeated copies of the *LPA* gene. We used NA/Laropiprant coadministration because Laropiprant is a selective antagonist of PGD2-receptor subtype-1 and reduces NA-induced flushing improving patient's compliance to NA treatment [18], although this coadministration has been recently withdrawn from the market due to lack of cardiovascular benefit [19].

2. Material and methods

2.1. Study design

In an open-label, 10-week study, 1 g/20 mg day of NA/Laropiprant for 4 weeks followed by 6 additional weeks of 2 g/40 mg day conducted at 3 centers in Spain, we enrolled 82 subjects (ClinicalTrials.gov Identifier: NCT01321034). The consort diagram for the clinical trial is shown in Fig. 1. The trial was designed by two of the authors (AC and FC) who had full access to the data. NA/laropiprant was obtained from Merck, USA which had no role in the design or interpretation of the results of the study.

2.2. Subjects

Volunteers were selected from three Lipid Units in the Northeast of Spain. All volunteers before any study procedure gave written inform consent to a protocol previously approved for the Ethical Committees of our institutions.

The inclusion criteria were the following: age >18 and <80 years; LDL cholesterol between 70 and 190 mg/dL; triglycerides <500 mg/dL; at least 2 Lp(a) determinations previous to the beginning of the study without differences >20%; and no lipid lowering therapy or on stable doses in the last 3 months. Patients were homogeneously enrolled in three groups: normal Lp(a) (<50 mg/dL), high Lp(a) (50–120 mg/dL) and very high Lp(a) (>120 mg/dL). Exclusion criteria were: liver disease or liver enzymes >2 times higher than reference values; creatinine >2 mg/dL; active peptic ulcer; clinical gout in the last year; uncontrolled diabetes (HbA1c >8%); Lp(a) concentration <10 mg/dL, or enrolment in other drug clinical trial in the previous 3 months.

2.3. Study visits and biochemical determinations

Patients were studied at baseline and at the end of the two treatment periods (weeks 4 and 10). An adverse effects questionnaire and a physical examination were completed in each visit. Volunteers attended all study visits after, at least, 10 h of fasting, and the following parameters were determined in serum: total cholesterol, triglycerides, HDL-cholesterol, Lp(a), apolipoprotein AI and apolipoprotein B, and safety biochemical parameters: glucose, uric acid, creatinine, liver and muscle enzymes. All biochemical determinations were performed in a central laboratory as previously described [20]. The quantitative determination of Lp(a) in plasma was carried out by rate nephelometry, in an IMMAGE 800® Immunochemistry System (Beckman Coulter).

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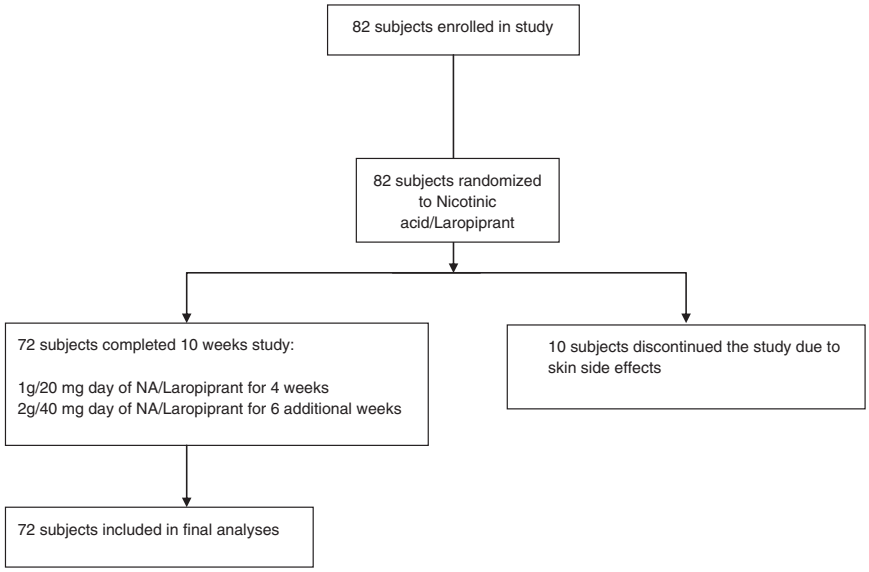

Fig. 1 – Flow diagram of the progress through phases of this clinical trial.

2.4. *Genetic analysis*

The *LPA* genetic polymorphism responsible of the Lp(a) size variability was analyzed by a real-time PCR-based methodology [21]. Briefly, genomic DNA was extracted from peripheral leukocytes using established protocols. A multiplexed qPCR was carried out using TaqMan probes for *LPA* KIV2 (exon 4) and an endogenous single-copy control gene, RNase P. Thermocycler conditions were: 95 °C hot-start for 10 min, followed by 40 cycles of 95 °C for 15 s, 60 °C for 1 min.

2.5. *Statistic analysis*

Statistical analysis was performed using SPSS software version 15.0 (Chicago, IL, USA) using a significance level of $P < 0.05$. Data are expressed as means ± standard deviation (SD) for continuous variables with normal distribution and medians (percentile 25–percentile 75) for variables with a skewed distribution. ANOVA and Kruskal–Wallis tests were performed for multiple independent variables comparison. Different doses of NA/laropiprant effects on study outcomes were evaluated by repeated measures ANOVA or the Friedman test, as appropriate. The study of the variables independently associated with variation in Lp(a) concentration after 2 g/40 mg of NA/Laropiprant was carried out using multiple linear regression introducing as independent variables: Gender, BMI, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, Apo B, Apo AI, baseline Lp(a) concentration and *LPA* genotype. Linear regression analysis was also performed to study the variation in Lp(a) plasma concentration explained by *LPA* genotype.

3. Results

Of the 82 subjects, 43 subjects were enrolled at Hospital Universitario Miguel Servet, 16 subjects at Hospital Royo Villanova, and 23 subjects at Hospital San Jorge. Ten subjects discontinued the study: 7 from Hospital Universitario Miguel Servet, 2 from Hospital Royo Villanova, and 1 from Hospital San Jorge. All discontinuations were due to skin side effects attributed to NA. Therefore, a total of 72 subjects completed all phases of the study and were included in the final analysis. In Table 1, anthropometric, clinic and lipid characteristics of studied subjects according to tertiles of Lp(a) concentration, are shown. There were no differences in any of analyzed lipid variables between the 3 groups of subjects according to Lp(a) concentration. The 3 groups were also homogeneous in relation to age, sex distribution, tobacco consumption and body mass index (BMI).

Table 1 – Anthropometric, clinic and lipid characteristics of studied subjects by groups of baseline Lp(a) plasma concentration.

	Normal Lp(a)	High Lp(a)	Very high Lp(a)	p [a]
N	24	24	24	
Age, years	51.6 ± 13.2	45.9 ± 11.4	54.8 ± 13.2	0.054
Male, %	58.3	54.2	54.2	0.945
Smoking, %	13.0	27.3	25.0	0.111
BMI, kg/m^2	27.6 ± 4.7	25.8 ± 3.4	26.2 ± 3.3	0.255
TC, mg/dL	230 ± 49.7	207 ± 28.9	211 ± 33.5	0.093
TG, mg/dL	111 (90–206)	108 (70–159)	91 (75–152)	0.521
HDL-c, mg/dL	58 ± 18.1	59 ± 17.1	63 ± 17.4	0.652
LDL-c, mg/dL	140 ± 46.3	124 ± 23.9	123 ± 27.8	0.186
Lp(a), mg/dL	31.8 ± 17.6	90.6 ± 19.2	203 ± 57.0	<0.0001
Apo AI, mg/dL	154 ± 30.6	160 ± 30.3	169 ± 25.5	0.299
Apo B, mg/dL	102 ± 24.2	97.8 ± 18.2	95.5 ± 22.0	0.674

Lp(a), lipoprotein(a); BMI, body mass index; TC, total colesterol; TG, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Apo AI, apolipoprotein AI; Apo B, apolipoprotein B.

[a] ANOVA and Kruskal–Wallis tests were performed for multiple independent variables comparison.

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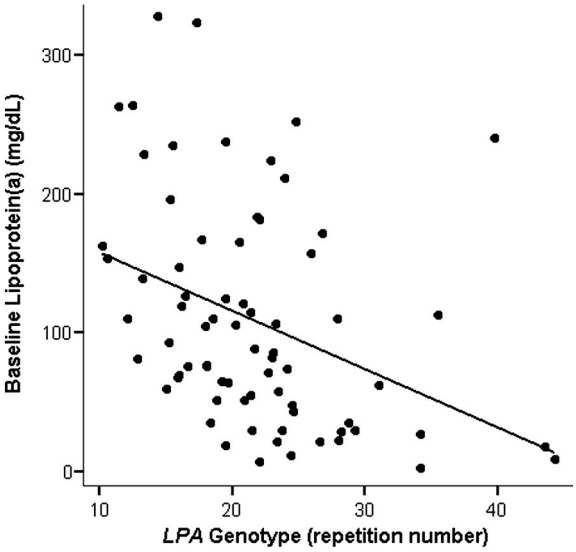

Fig. 2 – Linear regression of LPA genotype and Lp(a) concentration.

In all studied subjects, *LPA* genotype was determined by real-time PCR, calculating the repetition number of kringle IV-2 of Lp(a). There was a significant difference in *LPA* genotypes among Lp(a) concentration groups (normal Lp(a) concentration: 26 ± 7.2 repetitions, high Lp(a) concentration: 20 ± 5.0 repetitions; very high Lp(a) concentration: 18 ± 6.6 repetitions; $p < 0.0001$). An inverse and significant correlation between baseline Lp(a) concentration and *LPA* genotype was found ($R = -0.372$, $p < 0.001$). In Fig. 2, the baseline Lp(a) concentration versus *LPA* genotype is shown. The linear regression analysis demonstrated that the 14% of variation in Lp(a) serum concentration was explained by *LPA* genotype.

In Table 2, variations of lipid and glucose parameters and BMI after 4 and 10 weeks of NA/Laropiprant treatment are shown. There were a significant decrease in total cholesterol, triglycerides, LDL cholesterol, apo B and Lp(a), and a significant increase in HDL cholesterol after NA/Laropiprant treatment, without changes in BMI. Also, an increase in glucose and insulin levels, and the HOMA-IR index after treatment was also observed.

The variation of lipid and anthropometric variables after 10 weeks of NA/Laropiprant treatment according baseline Lp(a) concentration groups is shown in Table 3. There were no statistical differences in percentage variation of any analyzed variable depending on baseline Lp(a) concentration. Although a trend towards higher Lp(a) and apo B concentration decreases with higher baseline Lp(a) concentration was observed (−9.2% ± 3.7%, −20.7% ± 5.4%, −29.5% ± 2.2% for Lp(a) and −0.01% ± 5.4%, −5.0% ± 5.0%, −8.5% ± 4.6% for apo B), it was not statistically significant. Fig. 3 shows the percentage of Lp(a) variation after 10 weeks of NA/Laropiprant treatment according to Lp(a) baseline concentration.

Also, variation of lipid and anthropometric variables after 10 weeks of NA/Laropiprant treatment was analyzed according to *LPA* genotype. As shown in Table 4, there were no statistical differences in percentage variation of analyzed variables depending on *LPA* genotype quintiles. When analyzing by linear regression the factors influencing the variation in Lp(a) concentration after 2 g/40 mg of NA/Laropiprant, neither baseline Lp(a) concentration nor *LPA* genotype was found to be an important factor in determining the Lp(a) percentage decrease.

4. Discussion

The strong association between high Lp(a) and cardiovascular disease has led the European Atherosclerosis Society to establish a concentration < 50 mg/dl as a desirable Lp(a) in the population, and to recommend a reduction of plasma Lp(a) as a secondary priority after reduction in LDL and total cholesterol levels in patients with established cardiovascular disease or diabetes [22]. Although there are no therapeutic drugs that selectively target elevated Lp(a) [23], there are in the horizon potent new drugs, such as PCSK9 antibodies [24], apo B synthesis inhibitors [25] or cholesterol ester transfer protein (CETP) inhibitors [26], which markedly reduce Lp(a), but NA is at present time the drug of choice for the treatment of elevated Lp(a) [22,27]. Therefore, the identification of subjects that could benefit most of NA use is highly relevant.

We have evaluated, for the first time, the influence of Lp(a) concentration and apo(a) size, measured through *LPA*

Table 2 – Lipid concentrations at baseline and after 1 g and 2 g/day of Nicotinic Acid.

	Baseline	Nicotinic Acid, 1 g/day	Nicotinic Acid, 2 g/day	p [a]
TC (mg/dL)	214 ± 39.2	207 ± 40.6 (−2.84%)	202 ± 39.4 (−5.41%)	0.013
TG (mg/dL)	109 (74–175)	94 (74–143) (−3.84%)	80 (67–117) (−13.29%)	<0.0001
HDL-c (mg/dL)	59 ± 17.0	65 ± 18.8 (+11.84%)	70 ± 19.3 (+19.65%)	<0.0001
LDL-c (mg/dL)	128 ± 34.5	116 ± 33.8 (−8.59%)	107 ± 29.2 (−13.69%)	<0.0001
Lp(a) (mg/dL)	105 ± 79.0	89 ± 70.1 (−15.37%)	78 ± 57.2 (−23.05%)	<0.0001
Apo B (mg/dL)	98.6 ± 21.7	91.5 ± 22.6 (−6.64%)	93.8 ± 27.6 (−4.36%)	0.028
BMI (kg/m^2)	26.5 ± 3.72	26.5 ± 3.76 (+0.05%)	26.4 ± 3.91 (−0.31%)	0.514
Glucose (mg/dL)	95.6 ± 12.4	100.4 ± 12.7 (+5.55%)	97.5 ± 13.7 (+2.36%)	0.002
Insulin (mUI/L)	7.2 (4.8–10.5)	8.8 (6.9–12.4) (+22%)	10.0 (6.9–15.2) (+39%)	<0.0001
HOMA-IR	1.6 (1.1–2.6)	2.2 (1.6–3.4) (+37.5%)	2.3 (1.6–3.7) (+43.75%)	<0.0001

TC, total colesterol; TG, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Lp(a), lipoprotein(a); Apo B, apolipoprotein B; BMI, body mass index; HOMA-IR, Homeostasis Model of Assessment — Insulin Resistance.
[a] Repeated measures ANOVA or the Friedman test were performed.

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Table 3 – Variation of lipid and anthropometric variables after 10 weeks of NA/laropiprant according to baseline Lp(a) groups.

	Normal Lp(a)	High Lp(a)	Very high Lp(a)	p [a]
N	24	24	24	
% Δ TC	−5.54 ± 3.62	−4.76 ± 3.39	−6.00 ± 2.30	0.961
% Δ TG	−16.34 ± 7.80	−10.79 ± 8.63	−12.97 ± 8.70	0.895
% Δ HDL-c	+18.0 ± 3.8	+22.0 ± 4.5	+18.8 ± 3.0	0.732
% Δ LDL-c	−14.5 ± 5.5	−12.9 ± 6.2	−13.9 ± 4.0	0.976
% Δ Apo B	−0.01 ± 5.4	−5.0 ± 5.0	−8.5 ± 4.6	0.507
% Δ BMI	−0.5 ± 0.7	−0.6 ± 0.5	+0.3 ± 0.5	0.552
% Δ Lp(a)	−19.2 ± 3.7	−20.7 ± 5.4	−29.5 ± 2.2	0.161

TC, total colesterol; TG, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Apo B, apolipoprotein B; BMI, body mass index; Lp(a), lipoprotein(a).
[a] ANOVA test was performed for multiple independent variables comparison.

genotype, in the Lp(a) lowering effect of NA. As expected, our data show an inverse and significant correlation between baseline Lp(a) concentration and *LPA* genotype. This is in agreement with other studies that also found that the lower the number of *LPA* KVI-2 repetitions the higher the plasma Lp(a) concentration [4]. The mechanism of this inverse association is due to some *LPA* alleles producing intracellular very large protein products that are not secreted because they are retained in the endoplasmic reticulum [28]. Furthermore, the endoplasmic reticulum residence time of secreted apo(a) isoforms is determined by their size [28].

NA at a dose of more than 1.5 g/day decreases Lp(a) by approximately 20% [13], but with an important inter-individual variability [16]. In our work we demonstrate that this variability is not due to baseline Lp(a) concentration, or *LPA* KIV-2 variability. However, preliminary data presented recently by Artemeva et al. showed that in a small group of subjects, those with high molecular weight apo(a) isoforms determined by immunoblotting are more resistant to niacin treatment [29]. Our data would suggest that the effect of NA on Lp(a) is probably not related to the post-translational processing and secretion of apo(a) that are highly sensitive to apo(a) size [5,28]. Although the NA mechanism underlying Lp(a) reduction is not fully known, Chennamsetty et al. have recently demonstrated a reduction of hepatic APOA gene expression in transgenic mice and primary human hepatocyte cultures when treated with nicotinic acid [30]. This transcriptional *LPA* effect of NA would explain the lack of effect of apo(a) size found in our study.

As was expected, lipid profile of studied subjects was improved after treatment: total cholesterol, triglycerides, LDL cholesterol, apo B and Lp(a) were diminished, and HDL cholesterol was increased in expected range. However, a negative effect on glucose, insulin and HOMA-IR was also observed and it was also unrelated to the lipid lowering effect including Lp(a). Several studies have demonstrated that NA treatment is associated with hyperglycemia and insulin resistance, although the exact mechanisms responsible for this adverse effect of NA are not known [31]. NA causes a transient suppression of lipolysis followed by an increase in fatty acid release from adipose tissue. It would be possible that NA impairs insulin sensitivity by increasing plasma free fatty acids, which are delivered to muscle and liver and then

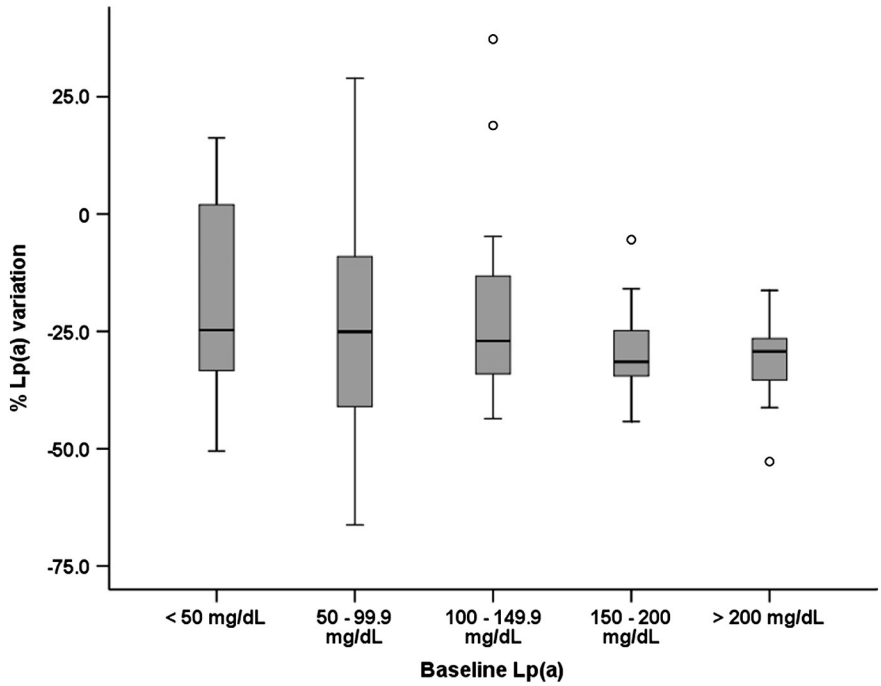

Fig. 3 – Percentage of Lp(a) variation after 10 weeks of NA/Laropiprant treatment according to Lp(a) baseline concentration.N subjects per group: <50 mg/dL: 18 subjects; 50–99.9 mg/dL: 20 subjects; 100–149.9 mg/dL: 14 subjects; 150–199.9 mg/dL: 10 subjects; >200 mg/dL: 10 subjects.

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Table 4 – Variation of lipid and anthropometric variables after 10 weeks of NA/laropiprant according to *LPA* genotype.

N	*LPA* Q1	*LPA* Q2	*LPA* Q3	*LPA* Q4	*LPA* Q5	p [a]
	15	15	14	14	14	
% Δ TC	−9.83 ± 3.09	−3.38 ± 4.77	−8.21 ± 3.18	−2.89 ± 6.55	−2.75 ± 1.69	0.611
% Δ TG	−25.55 ± 9.44	−2.52 ± 11.37	−13.02 ± 8.92	−1.23 ± 13.65	−23.18 ± 9.72	0.354
% Δ HDL-c	+21.22 ± 3.35	+14.63 ± 4.65	+20.51 ± 3.98	+15.34 ± 5.37	+26.34 ± 6.68	0.438
% Δ LDL-c	−17.10 ± 6.16	−8.20 ± 7.63	−20.54 ± 5.24	−20.45 ± 6.80	−4.66 ± 5.52	0.344
% Δ Apo B	−13.02 ± 6.68	−4.08 ± 5.62	−0.65 ± 4.92	−5.22 ± 9.06	+0.05 ± 5.38	0.673
% Δ BMI	+0.13 ± 0.64	−1.14 ± 0.78	+0.42 ± 0.71	−0.30 ± 0.53	−0.61 ± 0.96	0.621
% Δ Lp(a)	−23.48 ± 5.63	−22.25 ± 4.36	−30.47 ± 4.70	−19.97 ± 6.83	−19.15 ± 4.83	0.594

LPA Q1, first quintile of *LPA* genotype; *LPA* Q2, second quintile of *LPA* genotype; *LPA* Q3, third quintile of *LPA* genotype; *LPA* Q4, fourth quintile of *LPA* genotype; *LPA* Q5, fifth quintile of *LPA* genotype; TC, total colesterol; TG, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Apo B, apolipoprotein B; BMI, body mass index; Lp(a), lipoprotein(a).
[a] ANOVA test was performed for multiple independent variables comparison.

generating fatty acid metabolites that reduce insulin signaling [32,33]. Recently, an animal model for niacin's lowering of proatherogenic lipids and mechanisms of action relative to lipid metabolism has been developed, the high-fat high-fructose fed hamster. With the exception of HDL-C, the lipid effects of niacin treatment in the dyslipidemic hamster closely parallel those observed in humans. Moreover, the effects of niacin treatment on gene expression of hepatic proteins related to HDL metabolism were similar to those observed in human cells in culture. This animal model could serve to better understand the mechanisms responsible for the adverse effects of niacin in relation with hyperglycemia and insulin resistance [34].

There are several limitations to our study. First, we only studied white subjects, and therefore, our results may not apply to other ethnicities, since Lp(a) levels and its distribution differ between ethnic groups. Second, our method to determine *LPA* genotype reflects the sum of repeats on both alleles, and assumes an additive effect of both alleles on Lp(a) concentration. It would be possible that a more precise determination of *LPA* genotype with both alleles separately could add new information to our study.

The strength of this study is the novelty, as this is the first time that the Lp(a) lowering effect of Nicotinic acid/Laropiprant in subjects with different baseline Lp(a) concentrations and depending on the *LPA* genotype has been evaluated. However, a weakness is that the number of analyzed subjects is small, although enough for statistical power. Another weakness is the fact that the clinical use of Nicotinic acid/Laropiprant has been limited as it has been recently withdrawn from the market.

In conclusion, our work supports that *LPA* genotype is a major determinant of Lp(a) basal concentration. However, the lipid lowering effect of NA on the concentration of total cholesterol, LDL cholesterol, triglycerides and Lp(a) is not related to *LPA* genotype. There is a trend to higher reductions of Lp(a) concentration with NA in those subjects with very high levels of baseline plasma Lp(a). The translational potential of this paper is that although our results do not support the use of *LPA* genotyping in the clinical use of NA, *LPA* genotyping may still prove to be clinically useful in the use of niacin if patients with high Lp(a) levels or a given *LPA* genotype experience greater outcome benefits for a given niacin induced lipid effect.

Author contributions

Ana Cenarro: Conduct research (conduct of the experiments and data collection), analysis and interpretation of data, drafting the article.

José Puzo: Acquisition, analysis and interpretation of data, revising the manuscript.

Juan Ferrando: Acquisition, analysis and interpretation of data, revising the manuscript.

Rocío Mateo-Gallego: Acquisition, analysis and interpretation of data and perform statistical analysis, revising the manuscript.

Ana M Bea: Conduct of experiments, acquisition of data, revising the manuscript.

Pilar Calmarza: Conduct of experiments, acquisition of data, revising the manuscript.

Estíbaliz Jarauta: Acquisition, analysis and interpretation of data, revising the manuscript.

Fernando Civeira: Conception and design of research, acquisition, analysis and interpretation of data, revising critically the article for important intellectual content.

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Conflicts of interest

All authors confirm independence from the sponsors and no conflicts of interest. The sponsors have not influenced the content of the article.

REFERENCES

[1] Gaubatz JW, Heideman C, Gotto Jr AM, et al. Human plasma lipoprotein [a]. Structural properties. J Biol Chem 1983;258(7):4582–9.

[2] Dubé JB, Boffa MB, Hegele RA, Koschinsky ML. Lipoprotein(a): more interesting than ever after 50 years. Curr Opin Lipidol 2012;23(2):133–40.
[3] Emerging Risk Factors CollaborationErqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009;302(4): 412–23.
[4] Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 2009;301(22):2331–9.
[5] Kostner KM, März W, Kostner GM. When should we measure lipoprotein (a)? Eur Heart J 2013;34(42):3268–76.
[6] Grainger DJ, Kemp PR, Liu AC, et al. Activation of transforming growth factor-beta is inhibited in transgenic apolipoprotein(a) mice. Nature 1994;370(6489):460–2.
[7] Tsimikas S, Mallat Z, Talmud PJ, et al. Oxidation-specific biomarkers, lipoprotein(a), and risk of fatal and nonfatal coronary events. J Am Coll Cardiol 2010;56(12):946–55.
[8] McLean JW, Tomlinson JE, Kuang WJ, et al. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. Nature 1987;330(6144):132–7.
[9] Boerwinkle E, Leffert CC, Lin J, et al. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest 1992;90(1):52–60.
[10] Berglund L, Ramakrishnan R. Lipoprotein(a): an elusive cardiovascular risk factor. Arterioscler Thromb Vasc Biol 2004;24(12):2219–26.
[11] Utermann G. The mysteries of lipoprotein(a). Science 1989;246(4932):904–10.
[12] Clarke R, Peden JF, Hopewell JC. et al; PROCARDIS Consortium. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med 2009;361(26):2518–28.
[13] National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106(25):3143–421.
[14] Gurakar A, Hoeg JM, Kostner G, et al. Levels of lipoprotein Lp(a) decline with neomycin and niacin treatment. Atherosclerosis 1985;57(2–3):293–301.
[15] Seed M, O'Connor B, Perombelon N, et al. The effect of nicotinic acid and acipimox on lipoprotein(a) concentration and turnover. Atherosclerosis 1993;101(1):61–8.
[16] Scanu AM, Bamba R. Niacin and lipoprotein(a): facts, uncertainties, and clinical considerations. Am J Cardiol 2008;101(8A):44B–7B.
[17] Frank S, Krasznai K, Durovic S, et al. High-level expression of various apolipoprotein(a) isoforms by "transferrinfection": the role of kringle IV sequences in the extracellular association with low-density lipoprotein. Biochemistry 1994;33(40):12329–39.
[18] Paolini JF, Mitchel YB, Reyes R, et al. Effects of laropiprant on nicotinic acid-induced flushing in patients with dyslipidemia. Am J Cardiol 2008;101(5):625–30.
[19] HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J 2013;34(17):1279–91.
[20] Solanas-Barca M, de Castro-Orós I, Mateo-Gallego R, et al. Apolipoprotein E gene mutations in subjects with mixed hyperlipidemia and a clinical diagnosis of familial combined hyperlipidemia. Atherosclerosis 2012;222(2):449–55.
[21] Lanktree MB, Rajakumar C, Brunt JH, et al. Determination of lipoprotein(a) kringle repeat number from genomic DNA: copy number variation genotyping using qPCR. J Lipid Res 2009;50(4):768–72.
[22] Nordestgaard BG, Chapman MJ, Ray K. et al; European Atherosclerosis Society Consensus Panel. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J 2010;31(23):2844–53.
[23] Hoover-Plow J, Huang M. Lipoprotein(a) metabolism: potential sites for therapeutic targets. Metabolism 2013;62(4): 479–91.
[24] Roth EM, McKenney JM, Hanotin C, et al. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med 2012;367(20):1891–900.
[25] Gouni-Berthold I, Berthold HK. Antisense oligonucleotides for the treatment of dyslipidemia. Curr Pharm Des 2011;17(9):950–60.
[26] Cannon CP, Shah S, Dansky HM, et al. Determining the Efficacy and Tolerability Investigators. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med 2010;363(25):2406–15.
[27] Berthold HK, Gouni-Berthold I. Hyperlipoproteinemia(a): clinical significance and treatment options. Atheroscler Suppl 2013;14(1):1–5.
[28] White AL, Hixson JE, Rainwater DL, Lanford RE. Molecular basis for "null" lipoprotein(a) phenotypes and the influence of apolipoprotein(a) size on plasma lipoprotein(a) level in the baboon. J Biol Chem 1994;269(12):9060–6.
[29] Artemeva N, Safarova M, Ezhov M, et al. Niacin efficacy and safety in apparently healthy men with lipoprotein(a) excess. Program of the 81st European Atherosclerosis Society Congress, Lyon, France; 2013. p. 87 [abstract].
[30] Chennamsetty I, Kostner KM, Claudel T, et al. Nicotinic acid inhibits hepatic APOA gene expression: studies in humans and in transgenic mice. J Lipid Res 2012;53(11):2405–12.
[31] Goldberg RB, Jacobson TA. Effects of niacin on glucose control in patients with dyslipidemia. Mayo Clin Proc 2008;83(4):470–8.
[32] Kelly JJ, Lawson JA, Campbell LV, et al. Effects of nicotinic acid on insulin sensitivity and blood pressure in healthy subjects. J Hum Hypertens 2000;14(9):567–72.
[33] Poynten AM, Gan SK, Kriketos AD, et al. Nicotinic acid-induced insulin resistance is related to increased circulating fatty acids and fat oxidation but not muscle lipid content. Metabolism 2003;52(6):699–704.
[34] Connolly BA, O'Connell DP, Lamon-Fava S, et al. The high-fat high-fructose hamster as an animal model for niacin's biological activities in humans. Metabolism 2013. http://dx.doi.org/10.1016/j.metabol.2013.08.001.

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