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ORIGINAL RESEARCH ARTICLE

Elevated lipoprotein(a) and its association with early-onset myocardial infarction and coronary burden

Lipoproteína(a) elevada y su asociación con el infarto de miocardio de aparición temprana y la carga coronaria

Alim Namitokov

Kuban State Medical University; Scientific Research Institute – Regional Clinical Hospital #1 NA prof. S.V. Ochapovsky. Krasnodar, Russia

Abstract

Objectives: *Cardiovascular diseases (CVDs) remain a leading cause of morbidity and mortality worldwide, with myocardial infarction (MI) representing one of the most severe manifestations. Lipoprotein(a) [Lp(a)], a genetically influenced lipoprotein subclass, has gained attention for its role in atherogenesis and thrombogenesis. This study investigates clinical and demographic differences in early MI patients with varying Lp(a) levels, dividing them into two groups: Lp(a) < 50 mg/dL and Lp(a) ≥ 50 mg/dL. A retrospective analysis assessed demographic and clinical features, lipid profiles, and comorbidities.* **Methods:** *A retrospective cohort analysis was conducted on 189 patients aged 18–55 years with early-onset MI. Patients were grouped by Lp(a) levels (< 50 mg/dL, n = 109; ≥ 50 mg/dL, n = 80). Clinical parameters analyzed included age at MI onset, number of affected coronary vessels, comorbidities (diabetes mellitus, arterial hypertension, smoking status), statin therapy, and lipid profiles (total cholesterol, triglycerides, HDL, non-HDL, and LDL). Statistical comparisons and correlation analyses were performed to evaluate associations between Lp(a) levels and clinical features.* **Results:** *Elevated Lp(a) levels (≥ 50 mg/dL) were associated with younger MI onset, greater vascular burden, and less frequent statin use. Patients with higher Lp(a) had higher BMI and lower HDL levels. Significant differences were observed in age at MI onset (p = 0.0026), number of affected vessels (p = 0.0001), smoking prevalence (p = 0.002), statin use (p < 0.0001), BMI (p = 0.0061), triglycerides (p = 0.0121), and HDL levels (p < 0.0001). A positive correlation between Lp(a) levels and the number of affected vessels (r = 0.303) was identified.* **Conclusion:** *Elevated Lp(a) levels are strongly associated with younger age at MI onset, increased coronary involvement, and a pro-atherogenic lipid profile. These findings underscore the importance of Lp(a) as a biomarker for risk stratification in MI patients and highlight the need for targeted therapeutic approaches for individuals with high Lp(a) levels.*

Keywords: *Lipoprotein(a). Myocardial infarction. Cardiovascular disease. Statin therapy. Biomarker. Risk stratification.*

Resumen

Objectivos: *Las enfermedades cardiovasculares (ECV) siguen siendo una causa principal de morbilidad y mortalidad a nivel mundial, con el infarto de miocardio (IM) como una de sus manifestaciones más graves. La lipoproteína(a) [Lp(a)], una subclase de lipoproteínas influenciada genéticamente, ha recibido atención por su papel en la aterogénesis y trombogénesis. Este estudio analiza las diferencias clínicas y demográficas en pacientes con IM temprano, según los niveles de Lp(a),*

Correspondence:
Alim Namitokov
E-mail: namitokov.alim@gmail.com

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divididos en dos grupos: Lp(a) < 50 mg/dL y Lp(a) ≥ 50 mg/dL. Se realizó un análisis retrospectivo evaluando características demográficas y clínicas, perfiles lipídicos y comorbilidades. **Métodos:** *Se realizó un análisis retrospectivo de cohortes en pacientes con IM temprano, agrupados según niveles de Lp(a) (< 50 mg/dL o ≥ 50 mg/dL). Se analizaron parámetros clínicos como edad de inicio del IM, número de vasos coronarios afectados, diabetes mellitus, hipertensión arterial, tabaquismo, uso de estatinas, índice de masa corporal (IMC) y sexo, junto con los perfiles lipídicos, incluidos colesterol total, triglicéridos, HDL, no-HDL y LDL. Se realizaron comparaciones y correlaciones estadísticas para evaluar las relaciones entre Lp(a) y otras características clínicas.* **Resultados:** *Se encontraron diferencias significativas entre los grupos. Lp(a) elevado (≥ 50 mg/dL) se asoció con un IM más temprano, mayor número de vasos afectados y menor uso de estatinas. Los niveles más altos de Lp(a) se correlacionaron con mayor IMC y niveles de HDL más bajos.* **Conclusiones:** *Los niveles elevados de Lp(a) se asocian con un inicio más temprano del IM, mayor carga vascular y alteraciones del perfil lipídico.*

Palabras clave: *Lipoproteína(a). Infarto de miocardio. Enfermedad cardiovascular. Terapia con estatinas. Biomarcador. Estratificación del riesgo.*

Introduction

Cardiovascular diseases (CVDs) are among the leading contributors to global morbidity and mortality, accounting for millions of deaths annually[1]. Myocardial infarction (MI), a severe manifestation of CVD, results from the sudden occlusion of coronary arteries, typically due to atherosclerosis or thrombosis, leading to myocardial ischemia and irreversible tissue damage. Among the various biomarkers of cardiovascular risk, lipoprotein(a) [Lp(a)] has recently received considerable attention due to its unique structure, heritable nature, and apparent role in cardiovascular pathology[2]. Lp(a) is composed of an LDL-like particle with an additional protein, apolipoprotein(a), that is highly polymorphic, conferring it with unique properties that influence thrombosis and inflammation[3].

The association between elevated Lp(a) levels and adverse cardiovascular outcomes has been recognized for decades. However, unlike other lipid components such as LDL and HDL cholesterol, Lp(a) levels are largely genetically determined and cannot be easily modified by lifestyle changes[4]. In contrast to other lipid-lowering therapies, statins have little effect on Lp(a) levels, which may explain why Lp(a) is underutilized in routine clinical assessments. Yet, accumulating evidence suggests that elevated Lp(a) is independently associated with early-onset MI and greater severity of coronary atherosclerosis[5].

This study aims to investigate the differences in clinical and demographic characteristics of MI patients with varying levels of Lp(a). Specifically, we aim to compare clinical features such as age of MI onset, number of affected vessels, and comorbid conditions in patients with high and low Lp(a) levels. Understanding these differences could inform clinical guidelines and improve risk assessment and therapeutic management in patients predisposed to cardiovascular complications due to elevated Lp(a).

Materials and methods

Study design and population

The study employed a retrospective cohort design. The 189 patients database used included individuals aged 18 to 55 years who experienced early-onset MI. Patients were stratified based on their Lp(a) levels into two groups: those with Lp(a) levels below 50 mg/dL (total 109 patients, 9 women) and those with Lp(a) levels at or above 50 mg/dL (total 80 patients, 14 women). Inclusion criteria were limited to patients with documented Lp(a) levels and available clinical and demographic data. Exclusion criteria included patients with oncological, rheumatological, or systemic diseases, heart valve pathology, or reduced ejection fraction, to ensure a uniform patient population. Patients who had ever received alirocumab, evolocumab, and inclisiran were also excluded from the analysis.

When assessing the number of affected coronary arteries, stenosis of 50 or more in one of the main coronary arteries was considered clinically significant.

Data collection

Data were obtained from electronic medical records of the Scientific Research Institute - Regional Clinical Hospital No. 1 named after prof. S.V. Ochapovsky (Krasnodar, Russian Federation) and included demographic characteristics, comorbid conditions, lipid profiles, and information on prescribed therapies. Parameters assessed included age at MI onset, number of affected coronary vessels, smoking status, AH, DM, BMI, family history of cardiovascular disease (FH), and statin use. Lp(a) determination was performed on an outpatient basis within 1 to 3 months after discharge from the hospital. Since Lp(a) levels are not affected by antiplatelet agents, fibrinolytics, and statins, we did not

take into account the type of coronary intervention and concomitant therapy. The only exclusion criterion for therapy was the use of PCSK-9 targeted agents. Additionally, lipid profiles comprising TC, TG, HDL, non-HDL, and LDL levels were collected and analyzed for both groups. The comparative characteristics of the groups are presented in table 1.

All individuals included in the study are of the European (Caucasian) race. Ethical approval was obtained from the institutional review board, and all participants provided informed consent before enrollment in the study.

Table 1. Comparative characteristics of the groups.

Parameter	Lp (a) < 50 mg/dL (n = 109)	Lp (a) ≥ 50 mg/dL (n = 80)	p
Age (years)	48.9 ± 8.2	45.4 ± 7.7	0.0026
Number of vessels	1.54 ± 0.79	2.01 ± 0.81	0.0001
BMI (kg/m²)	27.81 ± 3.6	30.3 ± 7.3	0.0061
Smoking (%)	40	63	0.0020
Statin use (%)	71	34	< 0.0001
TG (mg/dL)	1.64 ± 1.12	2.68 ± 3.54	0.0121
HDL (mg/dL)	1.21 ± 0.35	0.99 ± 0.30	< 0.0001

Statistical analysis

Data were analyzed using Python (version 3.x). Descriptive statistics, including means, standard deviations (SD), frequencies, and percentages, were calculated for each parameter within both Lp(a) groups. Continuous variables were compared using Student's t-tests, while categorical variables were analyzed using chi-square tests. Pearson correlation coefficients were computed to explore the relationships between Lp(a) levels and other clinical parameters. A p value of less than 0.05 was considered statistically significant.

Results

Clinical and demographic differences

Patients with elevated Lp(a) levels (≥ 50 mg/dL) were significantly younger at the time of myocardial infarction (MI) compared to those with lower levels (< 50 mg/dL), with a mean age of 45.4 ± 7.7 years versus 48.9 ± 8.2 years, respectively (p = 0.0026). A greater number of coronary vessels were affected in the elevated Lp(a) group, indicating more extensive coronary involvement (2.01 ± 0.81 vs. 1.54 ± 0.79, p = 0.0001). Elevated Lp(a) was also associated with higher body mass index (BMI) (30.3 ± 7.3 vs. 27.81 ± 3.6, p = 0.0061) and a higher prevalence of smoking (63% vs. 40%, p = 0.002).

A notable finding was the lower frequency of statin therapy in patients with elevated Lp(a) levels (34% vs. 71%, p < 0.0001). This discrepancy highlights potential gaps in risk management and lipid-lowering interventions for these patients.

Lipid profile and biomarker analysis

The lipid profile comparison revealed significant differences between the groups. Patients with elevated Lp(a) levels exhibited markedly lower HDL cholesterol (0.99 ± 0.30 mmol/L vs. 1.21 ± 0.35 mmol/L, p < 0.0001) and higher triglycerides (2.68 ± 3.54 mmol/L vs. 1.64 ± 1.12 mmol/L, p = 0.0121). Interestingly, no significant differences were observed in total cholesterol (TC) or LDL cholesterol levels, suggesting that elevated Lp(a) contributes to cardiovascular risk independently of traditional lipid parameters.

Correlation analysis

Correlation analysis revealed a moderate positive association between Lp(a) levels and the number of affected coronary vessels (r = 0.303, p < 0.05), indicating a greater atherosclerotic burden in patients with higher Lp(a) levels. Additionally, a moderate correlation between Lp(a) levels and smoking prevalence (r = 0.234, p < 0.05) underscores the compounded cardiovascular risk in smokers with elevated Lp(a).

Discussion

The findings of this study provide important insights into the relationship between Lp(a) levels and clinical outcomes in MI patients. Elevated Lp(a) levels were associated with an earlier age of MI onset and greater severity of coronary atherosclerosis. These findings are consistent with previous studies that have reported a link between elevated Lp(a) and early-onset cardiovascular events[6]. Given that Lp(a) levels are predominantly genetically determined and unaffected by lifestyle modifications, these results emphasize the need for targeted screening and personalized risk management for patients with high Lp(a).

The lower prevalence of statin use in patients with elevated Lp(a) highlights an important gap in clinical practice. Although statins are less effective in lowering Lp(a) compared to LDL cholesterol, they remain an important component of overall lipid management and cardiovascular risk reduction. The introduction of newer lipid-lowering therapies, such as PCSK9 inhibitors and inclisiran, which have been shown to reduce Lp(a) levels, may provide additional benefits for patients with elevated Lp(a) who are at high cardiovascular risk[7,8]. Moreover, recent studies have demonstrated that PCSK9 inhibitors like evolocumab and alirocumab not only reduce LDL levels but also provide modest reductions in Lp(a), which may contribute to improved cardiovascular outcomes[7,8,9]. Studies like those by Tsimikas et al. (2018) suggest that novel antisense oligonucleotides, such as pelacarsen, specifically target Lp(a) synthesis and may significantly reduce cardiovascular risk in patients with elevated Lp(a) levels[10,11].

The interplay between Lp(a) and other lipid components, such as HDL and TG, underscores the complex and multifactorial nature of cardiovascular risk in these patients. Elevated Lp(a) levels have been associated with impaired reverse cholesterol transport, which is facilitated by HDL, thereby enhancing the atherogenic potential of elevated Lp(a)[12]. Low HDL levels, in conjunction with high Lp(a), create a pro-atherogenic environment that predisposes individuals to accelerated atherosclerosis and MI[13,14]. Further research by Kamstrup et al. (2014) indicates that high Lp(a) levels correlate with increased oxidized phospholipid content, which is known to trigger inflammatory responses and exacerbate vascular damage[15].

Another critical aspect to consider is the pro-inflammatory and pro-thrombotic nature of Lp(a). Elevated Lp(a) has been shown to contribute to increased expression of inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which further accelerates atherogenesis[16,17]. Studies by Boffa and Koschinsky (2017) have demonstrated that Lp(a) carries oxidized phospholipids that directly bind to scavenger receptors on endothelial cells, leading to endothelial dysfunction and an increased risk of thrombus formation[18]. This pro-inflammatory effect is compounded in patients who smoke, as evidenced by our findings of a moderate correlation between Lp(a) levels and smoking prevalence. Smoking further induces oxidative stress and inflammation, compounding the adverse effects of elevated Lp(a)[19,20].

Another therapeutic consideration is the role of aspirin and antiplatelet therapy in patients with elevated Lp(a). Aspirin's antiplatelet effect may be particularly important in mitigating the thrombotic risk associated with elevated Lp(a)[21]. However, the evidence supporting the efficacy of aspirin specifically in Lp(a)-mediated thrombosis is still emerging. A recent study by Nicholls et al. (2019) found that while aspirin reduced thrombotic events in patients with high cardiovascular risk, its effect on patients with elevated Lp(a) remains unclear[22]. As such, more focused studies are required to ascertain the benefit of antiplatelet therapy in this specific population.

Furthermore, recent advancements in genetic studies have shed light on the heritability and genetic determinants of Lp(a) levels. Variants in the LPA gene, particularly those that affect the kringle IV type 2 repeat region, are known to strongly influence plasma Lp(a) concentrations[23,24]. The European Atherosclerosis Society Consensus Panel has recommended that individuals with a family history of premature cardiovascular events, especially those with high Lp(a) levels, should undergo genetic testing for LPA variants to help guide clinical management[25]. Incorporating genetic testing into routine clinical practice could allow for earlier identification of individuals at high risk of cardiovascular events due to elevated Lp(a).

The need for early and effective intervention is underscored by the observation that elevated Lp(a) levels are associated with greater vascular burden. Findings by Böhm et al. (2020) indicate that the atherosclerotic lesions in patients with high Lp(a) tend to be more diffuse and calcified, posing challenges for percutaneous coronary interventions (PCI)[26]. Patients with elevated Lp(a) may benefit from alternative or adjunctive therapeutic strategies, including the use of intravascular imaging to better characterize lesion morphology and guide appropriate interventions[27]. Additionally, recent clinical trials have highlighted the potential role of niacin, which, although not a first-line therapy, has been shown to modestly reduce Lp(a) levels and improve endothelial function in some patient subsets[28].

It is also important to recognize that Lp(a) plays a role beyond coronary atherosclerosis. Elevated Lp(a) has been implicated in the pathogenesis of aortic valve stenosis (AVS)[29]. Patients with high Lp(a) are at increased risk for AVS, likely due to the deposition of Lp(a) particles and associated oxidized phospholipids within the valve leaflets, leading to calcific degeneration[25,30,31]. This association further broadens the spectrum of cardiovascular complications linked to elevated Lp(a) and

underscores the need for comprehensive cardiovascular risk management in affected patients.

Clinical implications

The association of elevated Lp(a) levels with earlier MI onset and greater vascular burden highlights the importance of incorporating Lp(a) screening into routine cardiovascular risk assessments, particularly in patients with a family history of premature MI or those who present with unexplained atherosclerosis despite optimal LDL control. Elevated Lp(a) levels should prompt more aggressive risk factor management, including smoking cessation, lifestyle modifications, and the consideration of additional lipid-lowering therapies beyond statins. PCSK9 inhibitors and antisense oligonucleotides are promising agents for reducing Lp(a) levels and may play a critical role in managing these high-risk patients[7,10,32].

Limitations and future research

This study has several limitations. The retrospective design limits the ability to establish causality, and the relatively young age of the study population may not be representative of all MI patients. Additionally, the sample size may limit the generalizability of the findings to broader populations. Future prospective studies are needed to validate these results and investigate the genetic determinants of Lp(a) levels and their interaction with environmental factors. A recent analysis of the long-term results of PCI for single-vessel coronary artery disease in patients with high Lp(a) levels demonstrated almost 60% mortality within 3 years after invasive treatment[33].

Future research should also explore the impact of novel Lp(a)-lowering therapies on clinical outcomes in patients with elevated Lp(a). Recent advances in antisense oligonucleotide therapies, such as pelacarsen, have shown promise in reducing Lp(a) levels and may provide new therapeutic options for high-risk patients[6]. Further clinical trials are warranted to determine the efficacy of these therapies in reducing MI risk and improving cardiovascular outcomes. And most importantly - the active inclusion of Lp(a) determination in routine clinical practice[22,34].

Conclusion

This study demonstrates that elevated Lp(a) levels are associated with significant clinical and demographic differences in MI patients, including younger age at MI onset, increased vascular burden, lower HDL levels, and reduced statin use. These findings underscore the importance of Lp(a) as a biomarker for cardiovascular risk assessment and highlight the need for targeted screening and management strategies in patients with elevated Lp(a). Integrating Lp(a) screening into routine clinical practice could facilitate early identification of high-risk individuals and inform personalized therapeutic interventions aimed at reducing the burden of MI.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The author declare that artificial intelligence was used in the writing of this manuscript [AI (chatGPT 4.0o) was used to achieve 2 goals: help in finding sources of information, including referenced in the article and generate a 250-word summary in Spanish, since the author does not speaks Spanish].

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