Lp(a) research in Colombia: Gaps and opportunities

Investigación en Lp(a) en Colombia: Brechas y oportunidades

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Abstract

Lipoprotein(a) [Lp(a)] is a genetically determined cardiovascular risk factor of growing importance in Colombia. This review synthesises the Colombian research on Lp(a) to identify key scientific gaps and propose a strategic agenda for future investigation. The evidence is primarily based on two pillars: foundational research on the biochemical and genetic basis of Lp(a) and clinical retrospective studies that have established a threshold of 50 mg/dL as a significant marker for risk reclassification in patients over 40. However, our analysis reveals that the progress is constrained by significant limitations, including a reliance on small-sample retrospective designs, a lack of standardised measurement assays, and the persistent exclusion of Lp(a) from national cardiovascular risk assessment protocols. Therefore, we conclude that there is an urgent need to advance the Colombian research landscape by prioritising large-scale prospective studies, harmonising Lp(a) measurement techniques, and conducting clinical trials on emerging therapies to define their role in the national context.

Key words: Lipoprotein(a), Apoprotein(a), Coronary artery disease, Atherosclerosis, LDLc

Resumen

La lipoproteína(a) [Lp(a)] es un factor de riesgo cardiovascular determinado genéticamente y de creciente importancia en Colombia. Esta revisión sintetiza la investigación colombiana existente sobre la Lp(a) para identificar vacíos científicos clave y proponer una agenda estratégica para futuras investigaciones. La evidencia revisada se basa principalmente en dos pilares: la investigación fundamental sobre las bases bioquímicas y genéticas de la Lp(a) y los estudios clínicos retrospectivos que han establecido un umbral de 50 mg/dL como un marcador significativo para la reclasificación del riesgo en pacientes mayores de 40 años. Nuestro análisis revela que el progreso está limitado por diseños retrospectivos con muestras pequeñas, la falta de ensayos de medición estandarizados y la exclusión persistente de la Lp(a) de los protocolos nacionales de evaluación del riesgo cardiovascular. Por lo tanto, concluimos que existe una necesidad urgente de avanzar en el panorama de la investigación colombiana, priorizando estudios prospectivos a gran escala, armonizando las técnicas de medición de la Lp(a) y realizando ensayos clínicos sobre terapias emergentes para definir su papel en el contexto nacional.

Palabras clave: Lipoproteína(a), Apoproteína(a), Enfermedad arterial coronaria, Aterosclerosis, C-LDL

Introduction

Lipoprotein(a) [Lp(a)] is a unique, genetically determined lipoprotein particle whose plasma concentration is a causal and independent risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve stenosis[1,2]. Structurally, it is characterised by a low-density lipoprotein (LDL)-like moiety, containing a single molecule of apolipoprotein B-100 (apoB), to which a large, hydrophilic glycoprotein, apolipoprotein(a) [apo(a)], is covalently appended via a single disulfide bond[1]. The apo(a) protein, encoded by the *LPA* gene on chromosome 6q26-27, exhibits a remarkable structural homology to plasminogen, comprising multiple repeats of kringle IV-like domains, a single kringle V domain, and a catalytically inactive protease domain[2]. The primary driver of the >1000-fold variation in Lp(a) plasma levels among individuals is a highly polymorphic copy number variant (CNV) within the *LPA* gene's kringle IV type 2 (KIV-2) region. This genetic architecture establishes a well-defined inverse relationship between the size of the apo(a) isoform and the resulting plasma Lp(a) concentration: smaller isoforms are secreted more efficiently from hepatocytes, leading to higher plasma levels[1,2].

The epidemiological profile of Lp(a) differs from that of other atherogenic lipoproteins. Its plasma distribution is not normal but is markedly right-skewed, meaning most individuals have low levels, while a significant proportion of the global population exhibits very high concentrations[2]. Pronounced inter-ethnic disparities are also a key feature; populations of African and South Asian ancestry, for example, have considerably higher median Lp(a) levels than those of European or East Asian ancestry[1]. Given its strong genetic determination (>90%), Lp(a) levels are largely refractory to lifestyle modifications and conventional lipid-lowering therapies, such as statins[3]. This positions Lp(a) as a critical component of residual cardiovascular risk, and its pathogenic mechanisms are multifaceted, including pro-atherogenic, pro-inflammatory, and pro-thrombotic properties derived from its dual LDL-like and plasminogen-like structure[1,4].

Within the Colombian context, where the burden of dyslipidaemia is substantial and affects a large proportion of the adult population[5], understanding the local landscape of Lp(a) is a clinical and public health imperative. The scientific record on Lp(a) in Colombia, though sparse, spans over two decades. Initial investigations in 2002 provided the first characterisation of Lp(a) distribution in a healthy urban cohort in Bogotá, establishing an early risk threshold[6]. More recently, clinical data have emerged from a small retrospective cohort (n=62) in Barranquilla, which proposed a 50 mg/dL cut-off for cardiovascular risk reclassification in patients over 40[7]. This clinical work has been complemented by review articles aiming to contextualise global therapeutic advances, such as antisense oligonucleotides, for the national scientific community [3]. However, a central challenge confounding this nascent field is a profound lack of methodological standardisation, as evidenced by a recent national survey of clinical laboratories. This study highlighted significant heterogeneity in assay methodology (e.g., immunoturbidimetry versus nephelometry) and reporting units (mg/dL versus nmol/L), which critically undermines the ability to compare findings across studies or establish a unified, population-specific risk threshold[8].

Therefore, the primary objectives of this review are threefold: first, to systematically identify and synthesise the principal findings of studies on Lp(a) conducted in Colombia; second, to critically evaluate the methodological gaps and limitations of the existing national evidence base; and third, to outline the key opportunities and propose a strategic framework for future research that can facilitate the effective clinical integration of Lp(a) assessment in Colombia.

Clinical Implications and Cardiovascular Risk Stratification

A consistent theme emerging from the Colombian clinical literature is the significant association between elevated Lp(a) concentrations and an increased burden of cardiovascular risk. The research led by Campos Del Valle, in particular, provides a key clinical insight from a national cohort. This work demonstrated that an Lp(a) level exceeding 50 mg/dL was associated with a reclassification of cardiovascular risk in patients aged 40 or older. This finding is of considerable clinical importance, as it reveals that conventional risk stratification instruments, such as the Framingham or ASCVD risk scores, may substantially underestimate the true 10-year risk in individuals with high Lp(a) levels, who would otherwise not be identified as candidates for more intensive preventive strategies[1].

The data derived from the Colombian setting reinforces the global consensus that Lp(a) contributes to cardiovascular risk independently of, and additively to, traditional atherogenic lipoproteins, most notably LDL-cholesterol[1,2]. This observation is pertinent in the current therapeutic era, which is dominated by statin therapy. While statins are highly effective at lowering LDL-cholesterol, they have a minimal, or even slightly elevating, effect on Lp(a) concentrations[3]. Consequently, a high Lp(a) level constitutes a major source of residual atherosclerotic risk that persists despite achieving guideline-recommended LDL-cholesterol targets. This fact is especially relevant for Colombian populations, where a strong genetic predisposition to elevated Lp(a) may mean that substantial risk remains, even with optimal management of other lipid variables[7].

Collectively, these findings provide compelling evidence for the integration of Lp(a) measurement into the clini-

cal assessment of cardiovascular risk in Colombia. The primary value of such testing lies in its ability to refine risk prediction, particularly by identifying individuals at a higher-than-anticipated risk who may have been misclassified as low or intermediate risk by conventional models. The retrospective analysis from Barranquilla, although limited by its sample size, underscores the potential for Lp(a) to fundamentally alter clinical decision-making and guide more tailored, intensive preventive interventions in a subset of the population[7] and calls for a paradigm shift in the approach to risk stratification, moving beyond traditional lipid metrics to incorporate this key genetic determinant.

Methodological Considerations and Limitations of the Colombian Evidence

While the nascent body of research on Lp(a) in Colombia provides a valuable foundation, it is imperative to critically appraise its significant methodological limitations. These constraints not only temper the interpretation of the available data but also define the strategic priorities for future investigation. The current evidence base is primarily constructed upon small-scale, single-centre studies employing designs that inherently limit their statistical power and external validity.

The most recent source of clinical data originates from a retrospective, cross-sectional analysis by Campos Del Valle in Barranquilla, which included a cohort of 62 patients[7]. Although this study was instrumental in proposing a clinically relevant 50 mg/dL threshold for risk reclassification, its small sample size and retrospective design preclude definitive conclusions regarding causality and limit the generalisability of its findings to the broader, heterogeneous Colombian population. This work builds upon an earlier investigation by Guerra de Muñoz et al., which characterised Lp(a) levels in 200 apparently healthy individuals in Bogotá[6]. Notably, this earlier study suggested a different risk threshold of 26 mg/dL. The discrepancy between these two proposed cut-offs highlights a central challenge for the field in Colombia: establishing a consistent and clinically actionable risk threshold from the existing data is problematic.

This disparity is likely explained, in large part, by a fundamental methodological gap: the lack of assay standardisation. A pivotal national survey by Paez et al. of eleven clinical laboratories confirmed this issue, revealing a near-even split between immunoturbidimetry and nephelometry as the primary measurement techniques. Furthermore, the study documented inconsistent use of reporting units, with some laboratories reporting in mass units (mg/dL) and others in molar concentration (nmol/L)[8]. This heterogeneity is a critical barrier, as it is well-established that different assay methods can yield disparate results, particularly across the range of apo(a) isoform sizes, and there is no reliable conversion factor between mass and molar units[1]. The lack of a national reference material and standardised protocol makes it exceedingly difficult to compare results between studies, aggregate data, or establish a unified clinical practice guideline.

The Colombian evidence landscape for Lp(a) is constrained by a reliance on small, single-centre, retrospective designs and a profound absence of methodological harmonisation. This landscape not only curtails the generalisability of current findings but also underscores the urgent need for large-scale, prospective, multicentre studies that employ standardised, isoform-insensitive assays reporting in nmol/L. Only through such methodologically rigorous efforts can the field advance from preliminary observation to the development of robust, evidence-based guidelines for the clinical use of Lp(a) in Colombia.

Emerging Therapeutic Approaches and Future Research Directions

The strong genetic determination of Lp(a) and its resistance to conventional lipid-lowering agents present a significant therapeutic challenge[3], catalysing the development of novel pharmacological strategies that directly target the synthesis of the apo(a) protein. The most promising of these are RNA-targeted therapies, including antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs), which have demonstrated the ability to reduce plasma Lp(a) concentrations by 80% or more in clinical trials[1,3]. While these agents represent a potential paradigm shift in the management of Lp(a)-mediated risk, their long-term safety and efficacy in reducing cardiovascular events are still under investigation in large-scale phase III outcome trials. Their eventual application in the Colombian clinical setting will require careful evaluation, ideally through local participation in international trials, to ensure their benefits are realised within the national population.

The limitations of the current Colombian evidence base illuminate a clear and compelling agenda for future investigation. The overarching priority must be the design and execution of large-scale, prospective, multicentre longitudinal studies. Such initiatives are essential to definitively validate the predictive value of Lp(a) for incident cardiovascular events over time, and to characterise its distribution across the diverse ethnic and socioeconomic backgrounds that comprise the Colombian population.

A second, parallel priority is to address the critical issue of methodological standardisation. The Colombian scientific and clinical laboratory communities must establish a consensus on Lp(a) measurement involving the nationwide adoption of isoform-insensitive assays, the harmonisation of reporting units to the internationally recommended molar concentration (nmol/L), and the development of validated, population-specific risk thresholds[1,8]. Achieving such standardisation is a prerequisite for generating comparable data across the country and for translating research findings into coherent clinical practice guidelines.

Finally, future research should explore advanced screening strategies to identify high-risk individuals and families. The autosomal codominant inheritance pattern of Lp(a) makes it an ideal candidate for cascade screening protocols, which involve systematically testing the first-degree relatives of individuals identified with very high Lp(a) levels[9,10]. Implementing such programmes could be instrumental in early risk detection, enabling timely, targeted preventive interventions long before the clinical manifestation of atherosclerotic disease. By integrating these local research priorities with global collaborative efforts, Colombia can accelerate the development of effective, evidence-based strategies to mitigate the significant public health burden posed by elevated Lp(a).

Discussion

The cumulative evidence from Lp(a) research in Colombia, while nascent, consistently points towards its role as a clinically significant but underappreciated factor in the national cardiovascular risk landscape. The foundational studies have successfully established its presence and potential impact, from the early characterisation of its distribution in a healthy cohort in Bogotá to the more recent demonstration of its value in risk reclassification in a clinical setting in Barranquilla[6,7]. These investigations have laid the critical groundwork for integrating Lp(a) into the broader discourse on cardiovascular disease prevention in the country.

However, a central challenge that emerges from a critical synthesis of the reviewed literature is the heterogeneity in the reported clinical thresholds. The discrepancy between the 26 mg/dL risk alert level proposed by Guerra de Muñoz et al. and the 50 mg/dL reclassification cut-off identified by Campos Del Valle is significant[6,7]. This disparity should not be interpreted as a simple contradiction. However, rather as a predictable and telling consequence of the profound lack of methodological standardisation that characterises the field in Colombia, as explicitly demonstrated by Paez et al.[8]. The use of different assay platforms and a failure to harmonise reporting units renders any direct comparison of these mass concentration thresholds scientifically untenable and highlights the difficulty in deriving a single, reliable cut-off from the current data[1].

This analytical uncertainty translates directly into clinical ambiguity, creating a significant barrier to the effective translation of Lp(a) research into practice. For the practising clinician in Colombia, the evidence base offers no clear, unified guidance on how to interpret an Lp(a) result, neutralising the potential for Lp(a) to act as a valuable tool for risk refinement, leaving a critical gap in the ability to identify high-risk individuals who may be misclassified by conventional risk scores alone. The promise of personalised risk assessment, as suggested by the local data, remains unrealised due to these foundational methodological shortcomings.

Ultimately, the challenges highlighted in this discussion reinforce the strategic imperatives outlined for future research. The path forward requires a decisive shift away from small-scale, retrospective analyses towards large, coordinated, prospective studies. More importantly, it necessitates a concerted, national effort to adopt the harmonised, isoform-insensitive, and molar-reported assays recommended by international consensus bodies[1,8]. Only by building a methodologically robust and standardised evidence base can Colombia move beyond preliminary findings to establish the definitive, population-specific guidelines required to harness the full clinical utility of Lp(a) in mitigating its national burden of cardiovascular disease.

Concluding Remarks

In conclusion, the body of research on Lipoprotein(a) in Colombia reveals a clear yet incomplete understanding of its role: that of a potent, genetically determined, and clinically relevant cardiovascular risk factor that remains largely unaddressed within the national healthcare system. While the existing evidence is foundational, it is insufficient to guide clinical practice due to significant methodological limitations. Therefore, the primary conclusion of this critical review is that these deficiencies represent a profound opportunity. By interpreting the existing gaps as a strategic framework, Colombia is positioned to develop a national programme for the research and clinical implementation of Lp(a) that could serve as a model for the wider Latin American region.

The foremost priority must be to address the foundational gap of methodological standardisation, an essential prerequisite for meaningful progress. The evidence indicates a substantial lack of harmonisation in assay platforms and reporting units across the country[8]. An immediate opportunity lies in convening a national consensus panel, comprising representatives from the Colombian Societies of Cardiology and Clinical Chemistry, laboratory providers, and researchers. The objective of this panel should be to establish a mandatory national standard for Lp(a) measurement, advocating for the adoption of isoform-insensitive assays that report in the internationally recommended molar units of nmol/L[1]. This coordinated action would ensure all future data are comparable, thus enabling the development of robust, population-specific risk thresholds.

In parallel, the research paradigm in Colombia must shift from small-scale, retrospective observation to large-scale, prospective investigation. The opportunity exists to design and launch a multicentre, longitudinal cohort

study specifically focused on Lp(a). Such a study must be designed to capture the ethnic and geographic diversity of the Colombian population, allowing for the characterisation of Lp(a) distributions and associated risks in mestizo, Afro-Colombian, and indigenous communities. This approach would not only validate the predictive value of Lp(a) for incident ASCVD in the national context but would also generate crucial data on the interplay between Lp(a) genetics and local environmental or lifestyle factors, moving the field beyond simple association to a deeper understanding of causality.

Beyond generating new evidence, there is a clear opportunity for immediate clinical translation through targeted screening. Given its strong autosomal codominant inheritance, Lp(a) is an ideal candidate for implementing cascade screening programmes[9,10]. A pragmatic first step would be to pilot such a programme in major cardiovascular reference centres, systematically offering testing to all first-degree relatives of patients with premature ASCVD and confirmed high Lp(a) levels, representing a high-yield, cost-effective public health strategy for the early identification of at-risk individuals and families, enabling the implementation of intensive preventive measures long before the clinical manifestation of atherosclerotic disease.

Ultimately, integrating Lp(a) into Colombian clinical practice requires a cohesive, multifaceted strategy encompassing standardisation, rigorous prospective research, and targeted screening protocols. The insights derived from the limited existing studies have clarified the necessary future directions. By embracing this strategic agenda, the Colombian medical and scientific communities can not only address a critical unmet need in national cardiovascular risk management but also generate a blueprint for other developing nations facing similar challenges. The effective management of elevated Lp(a) represents a critical area for advancement in preventive cardiology, and Colombia has a distinct opportunity to be at the forefront of this progress, facilitating the transition to a more personalised era of medicine and substantially reducing the public health burden of atherosclerotic cardiovascular disease.

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