Atherosclerosis: Open Access

Kim, Atheroscler Open Access 2023, 8:4

Mini Review Open Access

Elevated Lipoprotein (a) Levels: A Multi-Faceted Predictor of Cardiovascular Risk

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Abstract

Lipoprotein(a) is a unique plasma protein that has garnered increasing attention in recent years due to its significant association with cardiovascular risk. This comprehensive review aims to explore the genetic determinants of Lp(a) levels, its diverse roles in cardiovascular pathogenesis, and its impact on various cardiovascular conditions, with a particular focus on coronary artery disease (CAD) and degenerative aortic valve stenosis (DAS). Through an in-depth analysis of the literature, this review highlights the multifaceted nature of Lp(a) and its implications for risk assessment and preventive strategies in clinical practice.

Keywords: Lipoprotein; Cardiovascular risk; Genetic determinants; Degenerative aortic valve stenosis; Atherosclerosis; Pro-atherogenic; Endothelial dysfunction; Thrombogenic; Biomarker; Antisense oligonucleotides

Introduction

Lipoprotein(a) (Lp(a)) levels have emerged as a significant and independent predictor of several cardiovascular conditions, such as coronary artery disease (CAD), degenerative aortic stenosis (DAS), and heart failure, regardless of the presence of CAD and DAS [1,2]. These levels are genetically determined, exhibiting autosomal dominant inheritance with significant intra- and inter-ethnic diversity. The primary genetic influence on Lp(a) levels arises from variations in the gene encoding the apolipoprotein(a) component of Lp(a), known as the LPA gene. Situated on chromosome 6's long arm, specifically within region 6q2.6-2.7, LPA plays a crucial role in influencing Lp(a) levels. Lp(a) exerts its cardiovascular risk through diverse and unrelated mechanisms. Despite quantitatively carrying the atherogenic risk comparable to low-density lipoprotein cholesterol, Lp(a) is more susceptible to oxidation and endothelial penetration, promoting the formation of foam cells. Additionally, its thrombogenic properties stem from the homology shared between apolipoprotein(a) and plasminogen, leading to competition for binding sites on endothelial cells [3]. This competition inhibits fibrinolysis and fosters intravascular thrombosis. Notably, LPA exhibits up to 70% homology with the human plasminogen gene. Moreover, oxidized phospholipids play a pivotal role in differentiating pro-inflammatory macrophages, releasing pro-inflammatory cytokines like interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α. These inflammatory responses further contribute to the complexity of Lp(a)-mediated cardiovascular risk [4-6]. The objective of this review is to identify the predominant mechanisms through which Lp(a) influences cardiovascular risk in distinct patient groups. By comprehending the intricate pathways associated with Lp(a) and its impact on diverse cardiovascular conditions, we can enhance our understanding of preventive strategies and tailored interventions for at-risk populations.

Lipoprotein(a) (Lp(a)) is a complex plasma protein composed of low-density lipoprotein (LDL) cholesterol and apolipoprotein B-100 (apoB), linked to the plasminogen-like apolipoprotein(a) (apo(a)) through a disulfide bond. The levels of Lp(a) are determined by the LPA gene and exhibit significant variability among individuals. Remarkably, within an individual, Lp(a) levels remain stable throughout life. Apo(a) possesses a protease-like domain and two tri-loop structures known as 'kringles' (KIV, KV), with the KIV domain having 10 types. The number of KIV type 2 (KIV2) repeats in apo(a) contributes to Lp(a) isoform size heterogeneity, with more KIV2 repeats leading to larger apo(a) isoforms. Larger apo(a) isoforms are less efficiently secreted from hepatocytes, creating an inverse correlation between apo(a) isoform size and Lp(a) levels in plasma. Patients with smaller apo(a) isoform size not only exhibit higher Lp(a) levels but also have a significantly greater risk of coronary artery disease (CAD). The number of KIV2 repeats accounts for 69% of the variation in Lp(a) levels [7,8].

In addition to the number of KIV2 repeats, the Lp(a) isoform size and levels are influenced by over 200 single nucleotide polymorphisms (SNPs) in the broader LPA region. Notably, two of these SNPs, rs10455872 and rs3798220, exert the most significant influence on Lp(a) levels, explaining 36% of the variation in Lp(a) levels [8]. Approximately one in six individuals carry LPA variants, making them 1.5 times more likely to develop coronary diseases. Understanding the genetic determinants of Lp(a) levels and their impact on cardiovascular risk can offer valuable insights into personalized risk assessment and preventive strategies. By recognizing the role of genetic variations in Lp(a) metabolism, we can potentially identify at-risk individuals earlier and tailor interventions to mitigate the risk of CAD and other cardiovascular events. Cardiovascular diseases (CVDs) remain a major global health challenge, accounting for a significant number of deaths and disabilities worldwide. As researchers continue to uncover novel risk factors contributing to CVDs, lipoprotein(a) (Lp(a)) has emerged as an independent predictor of various cardiovascular conditions. This comprehensive review aims to delve into the genetic determinants of Lp(a) levels and its diverse roles in cardiovascular pathogenesis, with a specific focus on its association with coronary artery disease (CAD) [9]. Additionally, we explore the potential of Lp(a) as a therapeutic target in CAD management.

Genetic determinants of Lp(a) levels: The genetic regulation of

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Received: 28-Jun-2023, Manuscript No. asoa-23-107610; **Editor assigned:** 30-Jun-2023, PreQC No. asoa-23- 107610(PQ); **Reviewed:** 14-Jul-2023, QC No. asoa-23-107610; **Revised:** 20-Jul-2023, Manuscript No. asoa-23-107610(R); **Published:** 27-Jul-2023, DOI: 10.4172/asoa.1000216

Citation: Kim A (2023) Elevated Lipoprotein (a) Levels: A Multi-Faceted Predictor of Cardiovascular Risk. Atheroscler Open Access 8: 216.

Lp(a) levels is influenced by the LPA gene, situated on chromosome 6q26–q27. This gene encodes the apolipoprotein(a) (apo(a)) component of Lp(a) and plays a crucial role in determining its circulating levels. Multiple genetic variants, including single nucleotide polymorphisms (SNPs) and the number of kringle IV type 2 (KIV2) repeats, contribute to the isoform size heterogeneity of Lp(a) in different individuals. We discuss the complex interplay of these genetic factors and their implications for cardiovascular risk.

Lp(a) and coronary artery disease (CAD): The relationship between Lp(a) levels and CAD risk has been extensively studied. Evidence suggests that individuals with smaller apo(a) isoform size tend to have higher Lp(a) levels, which in turn is associated with an increased risk of CAD [10]. We explore the mechanisms by which Lp(a) contributes to atherosclerosis, including its ability to transport oxidized lipids and promote the formation of foam cells in the arterial walls. Moreover, Lp(a) has been implicated in endothelial dysfunction, inflammation, and oxidative stress, further contributing to CAD pathogenesis. Understanding these mechanisms is crucial in identifying Lp(a) as a potential therapeutic target in CAD management.

Therapeutic implications of Lp(a) in CAD management: Given the strong association between Lp(a) levels and CAD risk, there is growing interest in developing therapeutic strategies to reduce Lp(a) levels and its associated cardiovascular risk. We discuss current and emerging therapies targeting Lp(a), including antisense oligonucleotides, RNA interference, and Lp(a)-lowering agents. These novel therapeutic approaches show promise in effectively reducing Lp(a) levels and may hold the potential to improve outcomes in CAD patients [11,12]. Lipoprotein(a) has emerged as a novel and independent risk factor for various cardiovascular conditions, with a specific association with coronary artery disease. Genetic determinants, including the LPA gene and KIV2 repeats, play a crucial role in determining Lp(a) levels and its impact on cardiovascular risk. Understanding the mechanisms by which Lp(a) contributes to atherosclerosis and CAD pathogenesis is essential in developing targeted therapeutic interventions. Novel Lp(a)-lowering therapies offer promising potential in reducing cardiovascular risk and may revolutionize CAD management. As we continue to unravel the complexities of Lp(a) in cardiovascular health, further research is needed to identify the most effective therapeutic strategies and improve patient outcomes in the battle against cardiovascular diseases.

Lipoprotein(a) and degenerative aortic valve stenosis (DAS): In this section of our review, we delve into the intriguing link between Lp(a) levels and the development of degenerative aortic valve stenosis (DAS). Through a comprehensive analysis, we explore the genetic influences that contribute to an increased risk of DAS in both homozygote and heterozygote carriers of specific polymorphisms. Additionally, we investigate the role of KIV2 repeats in connection with the risk of DAS, shedding light on the complex interplay between Lp(a) genetics and the pathogenesis of aortic valve stenosis [13].

Mechanisms of Lp(a) in cardiovascular pathogenesis: This section delves into the diverse mechanisms by which Lp(a) exerts its impact on cardiovascular risk. We unravel the pro-atherogenic properties of Lp(a), including its role in the transport of oxidized lipids and the formation of foam cells within the arterial walls. Moreover, we explore its involvement in endothelial dysfunction, a critical event in the initiation and progression of atherosclerosis. Additionally, we delve into the thrombogenic nature of Lp(a) resulting from its homology with plasminogen. By competing for binding sites on endothelial cells, Lp(a) interferes with fibrinolysis, potentially leading to intravascular thrombosis [14]. This section offers a comprehensive understanding of the multifaceted mechanisms through which Lp(a) influences cardiovascular pathogenesis.

Clinical implications and therapeutic strategies: Our review highlights the clinical implications of Lp(a) in risk assessment and preventive strategies for cardiovascular diseases [15]. We explore the potential of Lp(a) as a biomarker for stratifying cardiovascular risk in patients, providing valuable insights into personalized risk assessment. Additionally, we discuss emerging therapeutic interventions that specifically target Lp(a) to reduce cardiovascular risk. This includes innovative approaches such as antisense oligonucleotides and RNA interference, which show promise in effectively lowering Lp(a) levels. The identification of potential therapeutic strategies can pave the way for novel treatments aimed at mitigating the adverse cardiovascular effects associated with elevated Lp(a) levels.

Conclusion

Lipoprotein (a) is a complex plasma protein that holds significant implications for cardiovascular risk assessment and prevention. By unraveling the genetic determinants and multifaceted mechanisms of Lp(a), we gain valuable insights into the development and progression of various cardiovascular conditions, including degenerative aortic valve stenosis and atherosclerosis. Understanding these intricate processes may lead to the development of personalized preventive strategies for individuals at high risk of cardiovascular diseases. Furthermore, continued research in this area is crucial for advancing our knowledge and improving patient outcomes, ultimately reducing the global burden of cardiovascular diseases.

Acknowledgement

Not applicable.

Conflict of Interest

Author declares no conflict of interest.

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