ORIGINAL ARTICLE

CONTENTS

Beyond traditional lipid markers: why lipoprotein(a) screening matters

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ABSTRACT

Aim: To assess the correlation between lipoprotein(a) levels and traditional lipid profile markers in statin-naive men and women without established atherosclerotic cardiovascular disease.

Materials and Methods: Sixty-seven statin-naive adult patients without a prior history of established atherosclerotic cardiovascular disease were included in the study. Lipoprotein(a) levels were determined using nephelometry in all patients.

Results: According to the results of the correlation analysis, it was found that there is no statistically significant correlation between lipoprotein(a) level and traditional parametres of lipid profile in both groups ($p>0.05$). Reliable direct correlation of moderate strength was observed between lipoprotein(a) and age in the group A ($R=0.46$, $p=0.04$).

Conclusions: Elevated lipoprotein(a) levels, independent of other lipid profile parameters, can significantly contribute to cardiovascular risk, emphasizing the importance of routine lipoprotein(a) screening in clinical practice. It is particularly noteworthy that lipoprotein(a) concentrations tend to increase after menopause, potentially placing postmenopausal women at an elevated risk for cardiovascular events. Consequently, it is imperative to monitor lipoprotein(a) levels in females, especially during the peri-menopausal and postmenopausal stages, to more accurately assess and manage cardiovascular risk in this population.

KEY WORDS: Lipoprotein(a), atherosclerotic cardiovascular disease, lipid profile

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INTRODUCTION

Lipoprotein(a) (Lp(a)) has garnered increasing attention in the medical community due to its potential role as a significant biomarker and therapeutic target in cardiovascular and renal diseases. Recent studies have provided substantial evidence linking elevated Lp(a) levels with various health conditions, including calcific aortic valve stenosis (CAVS), chronic kidney disease (CKD), and atrial fibrillation (AF). The findings from several recent studies suggest that Lp(a) may be a modifiable risk factor in these diseases, opening new avenues for prevention and treatment strategies.

A recent systematic review and data analysis examined the relationship between elevated Lp(a) levels and the progression of CAVS. The study revealed a significant association between higher Lp(a) concentrations and accelerated CAVS progression, suggesting the potential for targeting Lp(a) as part of therapeutic strategies for managing this condition. As CAVS continues to rise in prevalence, understanding the underlying mechanisms may provide new insights into its treatment and management [1-3].

Lp(a) is a large macromolecular complex composed of an low-density lipoproteins (LDL) particle containing apolipoprotein B-100 (apoB-100) and a large, highly variable glycoprotein known as apolipoprotein(a) (apo(a)), which is produced by the liver. Apo(a) contains kringle domains, triple-loop structures, which play a crucial role in the particle's structure. A disulfide bond links one of the kringle domains in apo(a) to apoB-100, forming the Lp(a) complex. Lp(a)'s plasma concentration is highly variable, with significant differences between individuals, populations, and even ethnic groups. Lp(a) concentrations range from less than 0.1 mg/dl to over 200 mg/dl, with levels in individuals of African descent being 2–3 times higher than those in Asian and European populations [4,5]. Lipoprotein(a)'s concentration is largely genetically determined, and it

is believed to have atherogenic, proinflammatory, and prothrombotic properties [6].

In renal health research, several studies have explored the link between Lp(a) levels and kidney disease. A Mendelian randomization study investigated the causal relationship between elevated Lp(a) levels and CKD, utilizing genetic variants associated with Lp(a). Analysis of data from large population cohorts showed that higher genetically determined Lp(a) levels were linked to an increased risk of CKD, supporting the notion that Lp(a) may be a causal factor in kidney disease and highlighting its potential as a modifiable risk factor for CKD prevention and treatment.

Another study analyzed the relationship between Lp(a) levels, renal function indicators, and CKD risk in a large cohort of 329,415 participants. With a median follow-up of 12.5 years, it found that elevated Lp(a) levels were associated with a 32% increased risk of CKD, particularly in individuals with high-normal urine albumin-to-creatinine ratio (UACR). These findings underscore the importance of considering both Lp(a) and UACR when assessing CKD risk, offering valuable insights for early detection and prevention strategies [7, 8].

In the cardiovascular field, research explored the role of Lp(a) as a risk factor for cardiovascular events in both diabetic and non-diabetic populations. Analysis of clinical records indicated that elevated Lp(a) levels were independently linked to an increased risk of cardiovascular events in both groups, with a stronger association seen in individuals without diabetes. This highlights the importance of monitoring Lp(a) levels in non-diabetic individuals for early cardiovascular risk assessment and intervention [9].

The potential link between elevated Lp(a) levels and atrial fibrillation (AF) was also explored through a systematic review and meta-analysis of Mendelian randomization studies. The findings revealed a significant association between higher genetically determined Lp(a) concentrations and an increased risk of AF, suggesting a causal relationship. This emphasizes the need to consider Lp(a) in cardiovascular health, particularly in the prevention and management of arrhythmias like AF [10, 11].

Together, these studies contribute to a growing body of evidence supporting the role of Lp(a) as a crucial biomarker and potential therapeutic target in both cardiovascular and renal diseases. Elevated Lp(a) levels are associated with increased risks of CAVS, CKD, cardiovascular events, and AF, underscoring the importance of including Lp(a) in routine clinical assessments. Future research focused on the mechanisms behind these associations could lead to more effective prevention and treatment strategies, ultimately improving patient outcomes.

AIM

To assess the correlation between lipoprotein(a) levels and traditional lipid profile markers in statin-naive men and women without established atherosclerotic cardiovascular disease (ASCVD).

MATERIALS AND METHODS

Sixty-seven statin-naive adult patients without a prior established atherosclerotic cardiovascular disease were included in the study: group A – females (n=34), group B – males (n=33). The study groups did not differ statistically in age. Among the examined patients, 50.7% (34/67) were women, while 49.3% (33/67) were men. The average age of the patients of group A was 48.06±13.67 and the patients of group B – 42.12±6.25 years. Exclusion criteria were established atherosclerotic cardiovascular disease, organic heart pathology, arrhythmias, familial hypercholesterolemia and pregnancy. Peripheral blood was collected from each participant via venipuncture. Lipoprotein(a) levels were determined using nephelometry, a technique that measures the concentration of particles in a sample by detecting the scattering of light. In this method, a sample containing lipoprotein(a) is mixed with specific antibodies that bind to the lipoprotein particles. When light passes through the sample, the scattered light is detected by a photodetector. The intensity of the scattered light correlates with the concentration of lipoprotein(a) in the sample, allowing for quantitative measurement. This technique is highly sensitive and specific, providing accurate results for lipoprotein(a) determination [12].

The results were statistically analyzed using Office Excel 2010 and the Statsoft Statistica 12.0 software on a personal computer. A discrepancy was deemed significant if the probability value was 95% or greater ($p<0.05$). Variational statistics were employed to analyze the data, with average values and standard error (M±m) taken into account. The analysis of the relationship between two features in the presence of a normal distribution of data was carried out according to the data of the Pearson correlation coefficient (r), in the case of a distribution different from the normal - the nonparametric Spearman rank correlation coefficient (R) was calculated. The correlation coefficient was evaluated according to the criteria generally accepted in statistics: $r<0.3$ - weak connection; 0.3-0.49 - moderate; 0.5-0.69 - significant; 0.7-0.89 - strong; >0.9 is very strong, close to a functional relationship [13].

RESULTS

Despite the study group consisting of patients aged 25 to 72 years with no prior history of atherosclerotic cardiovascular disease, the average total cholesterol levels in groups

Table 1. Parameters of lipid profile and age of examined patients (M ± m)

Parameters	Group A (n=34)	Group B (n=33)	p
Age, years	48.06±13.67	42.12±6.25	p=0.06
Total cholesterol, mmol/l	6.74±1.70	6.20±1.53	p=0.28
HDL, mmol/l	1.69±0.31	1.34±0.77	p=0.06
LDL, mmol/l	4.23±1.44	3.85±1.35	p=0.34
VLDL, mmol/l	0.62±0.56	0.78±0.63	p=0.47
Triglycerides, mmol/l	1.22±0.61	1.90±1.56	p=0.39
Lipoprotein(a), mg/dl	46.85±47.20	29.78±42.99	p=0.04*

p – reliability of correlation; * - statistically reliable correlation.

Table 2. Correlation between lipoprotein(a), indicators of lipid profile and age of examined patients

Parameters	Group A (n=34)		Group B (n=33)	
	Spearman R	p	Spearman R	p
Age, years	0,46	0,04*	0,35	0,08
Total cholesterol, mmol/l	0,01	0,97	0,08	0,71
HDL, mmol/l	0,27	0,15	0,17	0,46
LDL, mmol/l	-0,11	0,64	0,29	0,19
VLDL, mmol/l	0,09	0,68	-0,12	0,61
Triglycerides, mmol/l	-0,01	0,96	0,04	0,86

p – reliability of correlation; R-correlation coefficient; * - statistically reliable correlation.

A and B were (6.74±1.70) mmol/l and (6.20±1.53) mmol/l, respectively, suggesting the presence of hyperlipidemia. Regarding HDL levels, the average value in females was (1.69±0.31) mmol/l, whereas in males it was lower at (1.34±0.77) mmol/l, though no statistically significant difference was observed. LDL levels were elevated in both groups, with average values of (4.23±1.44) mmol/l in group A and (3.85±1.35) mmol/l in group B. The triglyceride level was somewhat higher in men, averaging (1.90±1.56) mmol/l, compared to (1.22±0.61) mmol/l in women. No statistically significant differences were found in the traditional lipid profile parameters between groups A and B (p>0.05). This suggests that despite variations in lipid levels, the two groups had comparable lipid profiles overall. Regarding the average lipoprotein(a) levels, a statistically significant difference was observed between groups A and B. In females, the average lipoprotein(a) level was higher, reaching (46.85±47.20) mg/dl, while in males, it was lower, with an average of (29.78±42.99) mg/dl (Table 1). This difference suggests a potential gender-related variation in lipoprotein(a) concentrations, which could have implications for cardiovascular risk assessment and treatment strategies.

According to the results of the correlation analysis, it was found that there is no statistically significant correlation between lipoprotein(a) level and traditional parametres of lipid profile in both groups (p>0.05) (Table 2). Reliable direct correlation of moderate strength was observed between lipoprotein(a) and age in the group A (R=0.46, p=0.04).

The results of the correlation analysis revealed that there was no statistically significant correlation between lipoprotein(a) levels and traditional lipid profile parameters in both groups (p>0.05) (Table 2). However, Reliable direct correlation of moderate strength was observed between lipoprotein(a) and age in group A (R=0.46, p=0.04). This finding suggests that while lipoprotein(a) is generally considered genetically determined, it appears that in women, lipoprotein(a) levels may increase with age. This highlights the potential role of aging in influencing lipoprotein(a) concentrations, which could have significant implications for cardiovascular risk assessment, particularly in postmenopausal women, who may experience an increase cardiovascular risk due to hormonal changes.

DISCUSSION

Lipoprotein(a) is a genetically determined lipoprotein that has been identified as an independent risk factor for cardiovascular disease. Elevated levels of Lp(a) are closely associated with an increased risk of atherosclerotic cardiovascular diseases, including heart attacks and strokes, making Lp(a) a crucial biomarker for assessing cardiovascular risk. Genetic factors predominantly influence Lp(a) concentrations, with approximately 70% to ≥90% of interindividual variability attributed to genetic determinants. Notably, Lp(a) levels remain relatively constant throughout an individual's life and are not

significantly affected by lifestyle factors or conventional lipid-lowering therapies.

It is important to measure Lp(a) levels in individuals with a personal or family history of premature ASCVD. Lp(a) levels can be elevated independently of other lipid parameters, such as total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. This characteristic makes Lp(a) a unique cardiovascular risk factor that can remain hidden unless specifically tested for, even when other lipid markers are within normal ranges. Recognizing elevated Lp(a) levels can aid in identifying individuals at increased risk for ASCVD, facilitating early interventions and personalized treatment strategies [14-16].

Anagnostis, P. et al. suggest in their study that menopause can influence Lp(a) concentrations in women, potentially contributing to their increased cardiovascular risk. They examined the impact of menopause on Lp(a) levels, finding that the transition to menopause is associated with an increased cardiovascular risk, primarily attributed to atherogenic dyslipidemia. However, the study did not establish a clear conclusion regarding the specific effect of menopause on Lp(a) levels, leaving this aspect of the relationship unclear [17].

In contrast, a study by Aljawini, N. et al. explored the relationship between age, menopause, and Lp(a) levels in Saudi women. The findings revealed that Lp(a) concentrations increased significantly after the age of 50, with postmenopausal women exhibiting markedly higher levels than their premenopausal counterparts. This suggests that menopause could be a contributing factor to the elevation of Lp(a) levels in this population, pointing to a potential link between hormonal changes and lipid metabolism during menopause [18].

Additionally, Simony, S. B. et al. examined sex differences in Lp(a) levels and their association with cardiovascular risk. The study found that plasma Lp(a) levels increased with age, with a notable rise around age 50 in women. Postmenopausal women exhibited Lp(a) levels that were 22% higher compared to premenopausal women, underscoring the significant increase in Lp(a) concentrations after menopause [19].

Taken together, these studies suggest that menopause may be associated with increased Lp(a) levels, contributing to the heightened cardiovascular risk observed in postmenopausal women. However, further research is needed to better understand the mechanisms underlying this association and its clinical implications for cardiovascular risk assessment and management in this population.

Understanding the impact of menopause on Lp(a) levels could ultimately guide more precise cardiovascular risk stratification and personalized interventions for postmenopausal women.

CONCLUSIONS

While traditional lipid profile parameters are valuable in assessing cardiovascular risk, they do not encompass the full spectrum of lipid-related risk factors. Elevated Lp(a) levels, independent of other lipid profile parameters, can significantly contribute to cardiovascular risk, emphasizing the importance of routine Lp(a) screening in clinical practice. It is particularly noteworthy that Lp(a) concentrations tend to increase after menopause, potentially placing postmenopausal women at an elevated risk for cardiovascular events. Consequently, it is imperative to monitor Lp(a) levels in females, especially during the peri-menopausal and postmenopausal stages, to more accurately assess and manage cardiovascular risk in this population.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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