Lipoproteins and Their Receptors Association in Cerebrovascular Disease Pathogenesis: A Comprehensive Analysis

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Abstract

Atherosclerosis, a leading cause of cardiovascular and cerebrovascular diseases, is driven by dyslipidemia and inflammatory processes. This study aimed to assess the relationship between lipoproteins and their receptors in patients with acute cerebrovascular accidents, using Receiver Operating Characteristic (ROC) analysis to evaluate their predictive value for stroke risk. A total of 165 patients with acute cerebrovascular events were included, and comprehensive assessments, including enzyme immunoassays for lipoprotein A (Lp(a)) and lipoprotein-associated phospholipase A2 (Lp-PLA2), were conducted. Results revealed significant associations between lipoprotein levels and neurological deficits, with a 2.3-fold increase in Lp(a) and a 2.2-fold decrease in low-density lipoprotein receptors (LDLR) in severe cases. Elevated lectin-like oxidized LDL receptor (LOX-1) and Lp-PLA2 levels were also noted, highlighting their roles in plaque destabilization and inflammation. The findings underscore the complex interplay of lipid metabolism, thrombus formation, and endothelial dysfunction in cerebrovascular events. This study emphasizes the reduce inflammation, offering potential strategies to mitigate stroke risk in atherosclerosis patients.

Keywords: Atherosclerosis, Lipoprotein(a), Low-Density Lipoprotein Receptors, Stroke Pathogenesis, Inflammatory Markers

Significance | This study showed critical biomarkers' roles in cerebrovascular accidents, offering insights into therapeutic strategies for stroke prevention and management.

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Introduction

Atherosclerosis remains a critical challenge in modern medicine, contributing to cardiovascular and cerebrovascular diseases, which are the leading causes of mortality worldwide (Benjamin et al., 2019; Libby et al., 2019). Dyslipidemia, characterized by elevated blood lipid levels, has been recognized as a significant risk factor for the development of atherosclerosis. Despite the availability of numerous lipid-lowering drugs, effective treatment for atherosclerosis remains elusive, highlighting its role as a primary cause of population mortality (Berberich & Hegele, 2019).

The pathogenesis of atherosclerosis is influenced by a complex interplay of genetic, environmental, and inflammatory factors. Inflammation plays a crucial role in all stages of atherogenesis, adversely affecting lipid transport and metabolism within the vasculature, which leads to the transformation of macrophages into foam cells and the formation of atheromatous plaques (Weber & Ley, 2014). Emerging evidence has identified several serum markers of inflammation, such as lipoprotein-associated phospholipase A2 (Lp-PLA2), as important components of the atherosclerotic risk

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profile. Elevated Lp-PLA2 levels have been importance of early detection and targeted interventions to modulate lipoprotein levels and associated with an increased risk of cardiovascular events, including ischemic strokes (Ballantyne et al., 2004).The revised lipid theory of atherosclerosis proposes that dyslipidemia, combined with other factors such as endothelial damage, oxidative stress, and immune responses, contributes to the development of atherosclerosis (Klimchuk et al., 2021). Furthermore, recent research has emphasized the role of lipoprotein(a) [Lp(a)], low-density lipoprotein (LDL) receptors, and oxidized LDL (LOX-1) in atherosclerosis. Lp(a) has been implicated in accelerating atherosclerosis by promoting the formation of atherosclerotic plaques on arterial walls (Khera & Kathiresan, 2016) (Figure 1). Additionally, dysregulated LDL receptor activity and increased LOX-1 expression have been associated with elevated cardiovascular disease risk (Brown & Goldstein, 2009; Hayashida et al., 2013).

This study aimed to assess the relationship between lipoproteins and their receptors in patients with acute cerebrovascular accidents and to conduct Receiver Operating Characteristic (ROC) analysis to determine their predictive value for stroke risk.

2. Materials and Methods

2.1 Study Design and Participants

This cross-sectional study was conducted at [Hospital Name] from [Start Date] to [End Date]. A total of 165 patients diagnosed with acute cerebrovascular accidents (ACVA) were included in the study. Among these, 25 patients were specifically identified as having dyscirculatory encephalopathy (DE), based on established diagnostic criteria, including clinical evaluation, imaging studies, and neurological assessments. All patients provided written informed consent prior to participation in the study.

2.2 Inclusion Criteria

Participants were included if they were diagnosed with an acute cerebrovascular accident, which could be a stroke or a transient ischemic attack. For those in the DE subgroup, confirmation of dyscirculatory encephalopathy was required based on diagnostic criteria.

2.3 Exclusion Criteria

Patients were excluded from the study if they had pre-existing neurological disorders other than ACVA, conditions affecting lipid metabolism unrelated to ACVA, or if their data was incomplete or if they did not consent to participate.

2.4 Assessments and Data Collection

Upon admission, each patient underwent a comprehensive set of assessments. These included general blood tests to evaluate complete blood count (CBC), blood glucose levels, and lipid profiles. Electrocardiography (ECG) was performed to assess cardiac rhythm and identify any arrhythmias or ischemic changes. Additionally, standard biochemical analyses were conducted to assess liver and kidney function.

2.5 Biomarker Measurement

To measure biomarkers, levels of lipoprotein A (Lp(a)) and lipoprotein-associated phospholipase A2 (Lp-PLA2) were assessed using enzyme immunoassays. Lp(a) levels were quantified with the Human Lipoprotein Lp-a ELISA Kit (Elabscience, USA), while Lp-PLA2 levels were measured using the Lipoprotein A2 Phospholipase ELISA Kit (Elabscience, USA). These assays were performed according to the manufacturer's standardized protocols using the Mindray Enzyme Immunoassay Analyzer BA-88 A.

2.6 Statistical Analysis

Data analysis was performed using IBM SPSS Statistics 19 software. Descriptive statistics, including means and standard deviations, were used to summarize continuous variables. Categorical variables were expressed as frequencies and percentages. To compare biomarker levels between patients with ACVA and those with DE, independent t-tests or Mann-Whitney U tests were employed, depending on data distribution. Pearson's or Spearman's correlation coefficients were used to assess the relationships between biomarker levels and clinical parameters such as severity of ACVA and comorbid conditions. A p-value of less than 0.05 was considered statistically significant.

2.7 Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of [Institution Name], ensuring that all research was conducted in accordance with ethical standards. Informed consent was obtained from all participants or their legal guardians. Patient confidentiality was upheld by anonymizing data and securely storing it in a password-protected database. The study adhered to the Declaration of Helsinki and local regulations concerning human research subjects.

2.8 Limitations

The study's cross-sectional design limits the ability to establish causal relationships. Furthermore, the findings may not be generalizable beyond the study population and setting. Future research using longitudinal designs is recommended to explore the predictive value of Lp(a) and Lp-PLA2 levels in the progression of ACVA and DE.

3. Results

The study revealed a significant association between lipoprotein levels and the severity of neurological deficits in stroke patients. Table 1 demonstrated a 1.8-fold decrease in thrombomodulin (TM) levels as neurological deficits progressed, indicating a significant association with mild deficits ($P < 0.01$). Conversely, Lp(a) levels increased by 2.3 times ($P < 0.01$) during the development of neurological deficits, suggesting its role in promoting thrombus formation by inhibiting plasminogen and increasing fibrin levels.

Moreover, a 2.2-fold decrease in low-density lipoprotein receptors (LDLR) was observed in patients with severe neurological deficits compared to those with mild deficits ($P < 0.01$), with LDLR levels averaging 0.240±0.01. Additionally, lectin-like oxidized low-density lipoprotein receptor (LOX-1) levels significantly increased in correlation with the development of neurological deficits ($P < 0.01$). Endothelin levels in ischemic stroke patients also increased, reaching 14.6±1.8 pg/ml in severe cases, nearly double the reference values. Furthermore, Lp-PLA2 levels were significantly elevated in ischemic stroke patients, with a 1.2-fold increase in severe neurological deficits ($P < 0.05$).

4. Discussion

The findings from this study underscore the critical role of dyslipidemia and lipoprotein dysregulation in the pathogenesis of stroke. Elevated levels of lipoprotein(a) [Lp(a)] were strongly associated with the severity of neurological deficits observed in stroke patients. This association aligns with previous research that highlights Lp(a)'s role in promoting atherosclerotic plaque formation and thrombus development (Khera & Kathiresan, 2016). Lp(a) has been well-documented as a risk factor for ischemic stroke due to its ability to bind with LDL, calcium, and other components, accelerating atherosclerosis by contributing to plaque formation on arterial walls (Dolgushin et al., 2022). Despite its established risk factor status, the precise physiological function of apolipoprotein(a) [apo(a)] and effective therapeutic strategies to reduce elevated Lp(a) levels remain areas of active investigation (Khalikova & Akhmadalieva, 2020; Virani et al., 2016; Libby et al., 2019).

The study also found a significant decrease in LDL receptor (LDLR) levels in patients with severe neurological deficits. This finding is consistent with the established understanding that reduced LDLR expression leads to elevated plasma LDL levels, which subsequently increases the risk of cardiovascular events (Brown & Goldstein, 2009). The LDL receptor plays a crucial role in mediating the uptake and degradation of LDL, chylomicron remnants, and other lipoproteins. When LDLR levels are decreased, there is reduced clearance of LDL from the bloodstream, resulting in higher plasma LDL concentrations, which are associated with increased cardiovascular disease risk (Herz et al., 1987; Zakrzewska & Czarna, 2021).

Additionally, our study observed a significant increase in levels of lectin-like oxidized LDL receptor 1 (LOX-1) in patients with more severe neurological deficits. LOX-1 is known for its role in the progression of atherosclerosis and plaque destabilization. Elevated LOX-1 levels correlate with plaque instability and are indicative of ongoing inflammatory processes within atherosclerotic lesions (Hayashida et al., 2013). LOX-1 expression is typically low under normal conditions but increases in response to proatherogenic or inflammatory stimuli, contributing to foam cell formation and endothelial activation. The overproduction of oxidized LDL triggers LOX-1 expression in vascular smooth muscle cells (VSMCs) and induces apoptosis, which further destabilizes atherosclerotic plaques (Nave et al., 2015).

The study's findings regarding lipoprotein-associated phospholipase A2 (Lp-PLA2) also reinforce its utility as a biomarker for cardiovascular risk assessment. Elevated Lp-PLA2 levels are associated with increased risk of stroke and other cardiovascular events. Lp-PLA2 is involved in exacerbating intravascular inflammation and promoting atherosclerosis, supporting its role as a critical biomarker for evaluating cardiovascular risk (Ballantyne et al., 2004; Nikolic et al., 2011). The measurement of Lp-PLA2 levels has been shown to provide valuable insights into cardiovascular risk and the progression of atherosclerotic disease (Dekker et al., 2010; Hsu et al., 2003).

The study highlights the complex interplay between lipoproteins, receptors, and inflammatory markers in the development and progression of stroke. This complex interaction underscores the importance of early detection and targeted therapeutic interventions aimed at modulating lipoprotein levels and reducing inflammation. Such interventions could potentially mitigate stroke risk, particularly in patients with atherosclerosis.

The prevalence and clinical manifestations of atherosclerosis worldwide are influenced by a myriad of genetic and environmental factors (Musunuru & Kathiresan, 2016; Libby, Ridker, & Maseri, 2005, 2010; Hsue, Grinspoon, & Fichtenbaum, 2015). Inflammation plays a central role throughout all stages of atherogenesis, adversely affecting intravascular lipid transport and metabolism. This leads to the transformation of macrophages into foam cells and the formation of fatty streaks and atheromatous plaques (Weber & Ley, 2014; Ridker, 2009; Ridker, Cook, & Rifai, 2004; Ridker et al., 2006). Serum markers of inflammation, such as Lp-PLA2, have emerged as crucial components of the cardiovascular risk profile. Elevated Lp-PLA2 levels exacerbate intravascular inflammation and contribute to the development of atherosclerosis, as supported by epidemiological studies (Ballantyne et al., 2004; Jayaraman et al., 1999). The association between elevated Lp-PLA2 levels and increased risk of stroke further underscores the importance of this biomarker in assessing cardiovascular risk (Nikolic et al., 2011; Hsu et al., 2003).

Dyslipidemia remains a primary driver of atherosclerosis and its associated cardiovascular diseases and strokes (Latfullin, 2015; Berberich & Hegele, 2019; Benjamin et al., 2019). Dysregulated lipid metabolism, often compounded by conditions such as diabetes, hypertension, and hypertriglyceridemia, significantly contributes to cardiovascular disease risk. Dysbiotic liver function can also lead to bacterial translocation and endotoxemia, exacerbating dyslipidemia and contributing to atherosclerosis (Libby et al., 2019).

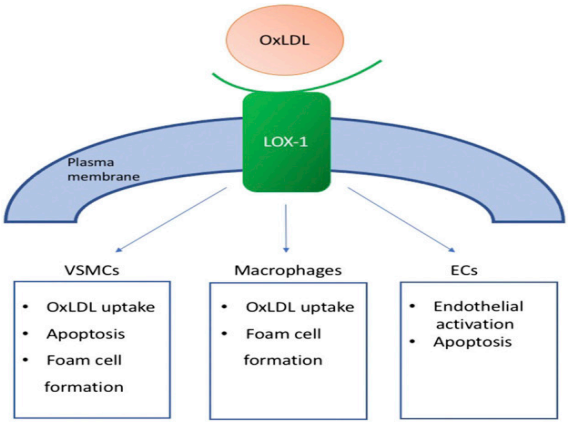

Figure 1. Overproduction of oxidized LDL triggers LOX-1 expression in vascular smooth muscle cells (VSMCs) and apoptosis,

Table 1. The content of lipid metabolism indicators depending on the degree of neurological deficit

Indicators	"Control group (mean ± standard deviation)"	mild neurological deficit	moderate degree of neurological deficit	severe neurological deficit
TM (mg/l)	12.5 ± 3.0	9.8±4.3	6.2±0.4*	5.5±0.18**
Lp -a (mg/ml)	82.0 ± 5.0	88.9±6.7	107.4±8.1*	206.5±23.3**
ET (pg /ml)	11, 6± 1.7	13.9±3.8	14.3±1.9	14.6±1.8*
LpPLA2(ng/ml)	20.0 ± 1.5	21.3±1.2*	22.9±1.8	23.6±1.4
LOX-1(ng /ml)	0.150 ± 0.015	0.169±0.018	0.204±0.03*	0.300±0.11**
LDLR (ng /ml)	0.570 ± 0.15	0.521±0.19	0.352±0.07*	0.240±0.01**

*Note: * - reliability of data for indicators of mild neurological deficit (* - P< 0.05; ** - P<0.01)*

Lipoprotein(a) [Lp(a)] is a complex lipoprotein consisting of apolipoprotein B (apo-B100) and apolipoprotein(a) [apo(a)] (Khera & Kathiresan, 2016; Roden et al., 2016; Williams & Krauss, 2017). It accelerates atherosclerosis by incorporating LDL, calcium, and other components into arterial plaques. Despite Lp(a) being an independent risk factor for ischemic stroke, the precise role of apo(a) and effective methods for reducing elevated Lp(a) levels are not yet fully understood (Khalikova & Akhmadalieva, 2020; Virani et al., 2016; Libby et al., 2019).

Two meta-analyses have confirmed the association between elevated Lp(a) levels and increased risk of ischemic stroke (Latfullin, 2015). This study aimed to further investigate Lp(a) levels in stroke patients at risk of stroke, building on existing evidence linking elevated Lp(a) levels to increased stroke risk.

The LDL receptor, found in the liver and various tissues, is crucial for the uptake and degradation of LDL and other lipoproteins. Reduced LDLR expression leads to decreased LDL clearance from the bloodstream and elevated plasma LDL levels, which are associated with increased cardiovascular disease risk (Herz et al., 1987; Zakrzewska & Czarna, 2021). Cellular cholesterol levels regulate LDLR expression, with decreased cholesterol levels promoting LDLR expression and increased cholesterol levels inhibiting it (Shimano, 2009). Hypercholesterolemia, which may be asymptomatic, can manifest as metabolic syndrome and increase cardiovascular risk (Nelson, 2013; Rohatgi, 2011).

Effective management of LDL levels is crucial for reducing cardiovascular risk. Lifestyle modifications, such as dietary changes and increased physical activity, play a significant role in managing LDL levels. Pharmacological interventions, including statins and PCSK9 inhibitors, are also effective in lowering LDL levels and reducing cardiovascular risk (Conrad & Bartenschlager, 2013; Monami et al., 2019).

Dyslipidemia is increasingly recognized as a major factor in atherosclerosis-related stroke, with variations in lipid metabolism among different stroke types and ischemic stroke subtypes (Berberich & Hegele, 2019; Laloux et al., 2004). Under normal conditions, LOX-1 expression is low, but it increases in response to proatherogenic or inflammatory stimuli. Elevated LOX-1 levels contribute to foam cell formation, endothelial activation, and plaque destabilization (Hayashida et al., 2013). The revised understanding of atherosclerosis emphasizes the interplay of lipid metabolism with immune system responses, highlighting the role of autoimmune complexes containing lipoproteins as antigens in atherosclerosis development (Libby et al., 2019; Klimchuk & Kozlov, 2021).

Acute circulatory disorders (ACIs), including stroke, remain a significant medical and societal concern due to their impact on morbidity, disability, and mortality. Lifestyle factors, such as high-carbohydrate and high-fat diets, smoking, and sedentary behavior, contribute to the prevalence of ACIs. Clinical and experimental studies have validated the role of these factors in lipid metabolism disturbances and atherosclerosis. As such, atherosclerosis and its complications, including stroke, represent outcomes of complex interactions among nutritional, autoimmune, oxidative, and genetic factors. Addressing these factors through preventive and therapeutic measures remains crucial in mitigating the risk of stroke and improving patient outcomes.

5. Conclusions

This study demonstrated the crucial role of specific biomarkers in the development and severity of neurological deficits associated with acute cerebrovascular accidents. Decreased thrombin-modulating (TM) levels and increased lipoprotein A (LpA) levels in mild deficits suggest a link to early thrombus formation. In contrast, the disparity between reduced low-density lipoprotein receptor (LDLR) and elevated lectin-like oxidized LDL receptor-1 (LOX-1) levels in severe deficits underscores their potential contribution to worsened outcomes. Additionally, elevated endothelin and lipoprotein-associated phospholipase A2 (LpPLA2) levels in severe cases point to the significance of endothelial dysfunction and lipid metabolism in exacerbating neurological damage. These findings emphasize the intricate interplay between lipid metabolism, thrombus formation, and endothelial dysfunction in the pathophysiology of cerebrovascular events, offering insights that could guide future therapeutic interventions.

Author contributions

N.M.V. conceptualized the study and drafted the manuscript. M.M.A. and G.S.R. contributed to data analysis and interpretation. N.A.Q.B. and A.S.U.U. assisted in writing sections of the manuscript and provided critical revisions. All authors reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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