SCIENTIFIC TRENDS IN MEDICINE - НАУЧНЫЕ ТЕНДЕНЦИИ В МЕДИЦИНЕ – TIBBIYOTDA ILMIY TENDENSIYALAR

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ACUTE CORONARY SYNDROME IN PATIENTS WITH NORMAL LDL-C LEVELS: CLINICAL FEATURES AND POSSIBLE MECHANISMS

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Abstract: *Acute coronary syndrome (ACS) is one of the major manifestations of coronary artery disease and remains an important cause of morbidity and mortality worldwide. Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for atherosclerosis and an important target of cardiovascular prevention. However, ACS can also occur in patients whose LDL-C concentration is not markedly elevated. This observation suggests that the development of ACS cannot always be explained by the current LDL-C level alone. The aim of this review is to summarize possible mechanisms of ACS in patients with apparently normal LDL-C and to describe the clinical factors that may contribute to cardiovascular risk in these patients. Particular attention is given to endothelial dysfunction, inflammation, plaque instability, lipoprotein(a), apolipoprotein B, triglyceride-rich lipoproteins, diabetes mellitus, hypertension, and smoking. Current evidence indicates that a normal LDL-C value does not necessarily mean a low lifetime exposure to atherogenic lipoproteins or the absence of coronary atherosclerosis. Additional lipid and clinical parameters may therefore be useful for a more complete assessment of cardiovascular risk.*

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Understanding these mechanisms is important for the clinical evaluation and secondary prevention of patients with ACS.

***Keywords**: acute coronary syndrome, LDL-C, atherosclerosis, plaque instability, lipoprotein(a), apolipoprotein B, inflammation, cardiovascular risk.*

Introduction

Acute coronary syndrome includes unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. Although the clinical manifestation is sudden, the pathological process usually develops over a long period through the progression of coronary atherosclerosis.LDL-C is one of the most important modifiable risk factors for atherosclerotic cardiovascular disease. Increased exposure to atherogenic LDL-containing particles promotes their retention in the arterial wall and contributes to the formation and progression of atherosclerotic plaques. For this reason, lipid-lowering therapy, particularly statins, remains a fundamental part of cardiovascular prevention. Current guidelines recommend high-intensity statin therapy in patients with ACS and additional lipid-lowering treatment when the LDL-C level remains above the recommended threshold [1].At the same time, clinical practice demonstrates that myocardial infarction may occur in patients without markedly elevated LDL-C. A patient may present with ACS while having an LDL-C concentration that would not initially appear to indicate severe dyslipidemia. This does not mean that LDL-C is unimportant. Rather, it suggests that the current LDL-C concentration cannot fully describe the patient's cardiovascular risk.Atherosclerosis is a multifactorial process involving lipid accumulation,

Issue - 9(2026) / E-ISSN: 3030-3516 Available at www.uznauka.uz

endothelial dysfunction, inflammation, metabolic abnormalities, and changes in plaque structure. In addition, cardiovascular risk depends not only on the concentration of LDL-C at one point in time but also on cumulative exposure to atherogenic particles throughout life [2].

The aim of this review is to describe the main possible mechanisms and clinical factors that may explain the occurrence of ACS in patients with apparently normal LDL-C.

LDL-C and Cardiovascular Risk

The interpretation of a “normal” LDL-C value requires consideration of the patient's clinical situation. A laboratory reference range does not necessarily correspond to an optimal cardiovascular target. In a patient with established coronary artery disease or previous ACS, substantially lower LDL-C concentrations are generally targeted than in individuals without cardiovascular disease.Another important issue is lifetime exposure. Atherosclerosis develops gradually, and a single LDL-C measurement reflects only the patient's lipid status at the time of testing. A patient may have experienced higher LDL-C levels for many years and subsequently achieved a lower concentration through lifestyle changes or pharmacological treatment. Therefore, a relatively low LDL-C at the time of ACS does not necessarily indicate a low cumulative exposure to atherogenic lipoproteins.The 2026 ACC/AHA guideline on dyslipidemia emphasizes that atherosclerotic risk is related to cumulative exposure to atherogenic particles over time rather than to an isolated LDL-C measurement [2].LDL-C also does not directly indicate the number of circulating atherogenic

Issue - 9(2026) / E-ISSN: 3030-3516 Available at www.uznauka.uz

particles. Apolipoprotein B (apoB) can provide additional information because each LDL and other major apoB-containing atherogenic particle contains one apoB molecule. Therefore, patients with similar LDL-C concentrations may have different numbers of atherogenic particles.

Endothelial Dysfunction and Atherosclerosis

One of the earliest important processes in atherosclerosis is endothelial dysfunction. The vascular endothelium regulates vascular tone, permeability, inflammation, and thrombosis. When endothelial function is impaired, the vascular wall becomes more susceptible to the retention of atherogenic particles and inflammatory cells.Hypertension, smoking, diabetes mellitus, obesity, and insulin resistance can contribute to endothelial dysfunction through oxidative stress and reduced nitric oxide availability. These factors can therefore promote atherosclerosis even when LDL-C is not markedly elevated.The development of atherosclerosis can be simplified as a sequence in which atherogenic particles are retained in the arterial wall, inflammatory cells are recruited, and macrophages accumulate modified lipids. Over time, atherosclerotic plaque develops and may become increasingly vulnerable.Therefore, the occurrence of ACS in a patient with normal LDL-C should not be considered surprising if other major cardiovascular risk factors are present.

Inflammation and Plaque Instability

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Inflammation plays an important role in the development and progression of atherosclerotic plaques. Retained and modified lipoproteins can activate macrophages and other inflammatory cells within the arterial wall.Persistent inflammation can promote the development of a lipid-rich necrotic core and weaken the fibrous cap covering the plaque. Enzymes such as matrix metalloproteinases can contribute to degradation of the extracellular matrix and reduce the stability of the fibrous cap.A vulnerable plaque is therefore characterized not simply by its size but by its biological and structural properties. A plaque containing a large lipid core, a thin fibrous cap, and significant inflammatory activity may be more likely to undergo disruption.This is important because the occurrence of ACS depends not only on the presence of atherosclerosis but also on the stability of the existing plaque.

Plaque Rupture and Plaque Erosion

Plaque rupture is one of the most recognized mechanisms of ACS. In this process, the fibrous cap of an atherosclerotic plaque ruptures and exposes thrombogenic material to circulating blood. Platelets become activated, the coagulation system is stimulated, and a coronary thrombus develops.However, plaque rupture is not the only mechanism. Plaque erosion is another important cause of coronary thrombosis. In plaque erosion, the endothelial surface is damaged or lost while the underlying fibrous structure may remain relatively preserved. The exposed surface can subsequently promote thrombus formation.Current evidence indicates that plaque erosion accounts for a substantial proportion of ACS cases, with estimates of approximately one-third in pathological

Issue - 9(2026) / E-ISSN: 3030-3516 Available at www.uznauka.uz

and imaging studies [3,4].These mechanisms demonstrate why ACS cannot be explained solely by the concentration of LDL-C in the blood. The characteristics of the coronary plaque and the local vascular environment also influence whether a patient develops an acute event.

Lipoprotein(a) and Apolipoprotein B

Lipoprotein(a), or Lp(a), is an LDL-like lipoprotein whose concentration is largely genetically determined. Elevated Lp(a) is associated with increased risk of atherosclerotic cardiovascular disease and may contribute through atherogenic, inflammatory, and potentially prothrombotic mechanisms.Lp(a) is particularly relevant in patients who develop cardiovascular disease despite apparently favorable conventional lipid values. A patient may have a relatively low LDL-C but a substantially elevated Lp(a) concentration.The 2026 ACC/AHA dyslipidemia guideline recommends measuring Lp(a) at least once to identify individuals with increased inherited cardiovascular risk [2].ApoB may also provide additional information when LDL-C does not adequately reflect the number of atherogenic particles. This may occur particularly in patients with elevated triglycerides, diabetes, obesity, or metabolic syndrome. Recent evidence suggests that apoB can provide useful information about cardiovascular risk when LDL-C and atherogenic particle number are discordant [5]Therefore, LDL-C, apoB, and Lp(a) should not be considered interchangeable measurements. Each provides different information about cardiovascular risk.

Triglycerides and Metabolic Factors

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Patients with insulin resistance and metabolic syndrome may have increased concentrations of triglyceride-rich lipoproteins even when LDL-C is not markedly elevated. These particles and their remnants can contribute to atherosclerotic plaque formation.Diabetes mellitus is another important contributor to cardiovascular risk. Hyperglycemia, oxidative stress, endothelial dysfunction, chronic inflammation, and platelet activation can all promote atherosclerotic disease. Importantly, cardiovascular risk in diabetes cannot be assessed adequately from LDL-C alone.Obesity, particularly visceral obesity, is associated with insulin resistance, inflammation, hypertension, and abnormal lipid metabolism. These factors frequently occur together and may have an additive or synergistic effect on cardiovascular risk.

Consequently, a patient with ACS and normal LDL-C should still be evaluated for diabetes, hypertension, obesity, smoking, and other conventional cardiovascular risk factors.

Clinical Implications

The presence of normal LDL-C in a patient with ACS should not lead to the conclusion that lipid-related mechanisms are irrelevant. Instead, it should encourage a broader assessment of cardiovascular risk.The first step remains appropriate secondary prevention. Current ACS guidelines recommend high-intensity statin therapy, with additional non-statin lipid-lowering therapy when further LDL-C reduction is indicated [1].In selected patients, additional

measurements such as apoB, Lp(a), non-HDL-C, and triglycerides may provide useful information. Lp(a) is particularly relevant when there is premature cardiovascular disease or a family history of cardiovascular disease.Clinical assessment should also include blood pressure, glucose or HbA1c, smoking status, body weight, and other relevant cardiovascular risk factors.The important clinical principle is therefore:normal LDL-C does not equal absence of cardiovascular risk.Instead, LDL-C should be interpreted together with the patient's overall clinical profile.

Future Perspectives

The understanding of cardiovascular risk is gradually moving from a single-marker approach toward a more comprehensive assessment. LDL-C remains an essential treatment target, but additional markers may help identify residual risk in selected patients.Future research will clarify the clinical role of Lp(a), apoB, remnant lipoproteins, inflammatory biomarkers, and advanced coronary imaging. Better identification of patients with apparently normal LDL-C but significant residual risk may allow earlier and more individualized preventive strategies.

Conclusion

Acute coronary syndrome can occur in patients whose LDL-C concentration is apparently normal. This does not contradict the established role of LDL in atherosclerosis but demonstrates that cardiovascular risk is determined by multiple interacting factors.Lifetime exposure to atherogenic lipoproteins, the number and type of circulating particles, lipoprotein(a), metabolic abnormalities, endothelial

dysfunction, inflammation, and plaque characteristics may all contribute to the development of ACS.

Therefore, assessment of patients with ACS should not rely on LDL-C alone. A broader clinical evaluation that includes other lipid parameters and major cardiovascular risk factors may provide a more complete understanding of individual cardiovascular risk and help guide secondary prevention.

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Issue - 9(2026) / E-ISSN: 3030-3516 Available at www.uznauka.uz

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