Volume 11 • Number 4 • December 2020 • em00756

JOURNAL OF CLINICAL AND EXPERIMENTAL INVESTIGATIONS

LETTER TO EDITOR

Electronegative Low-density Lipoprotein (L5) may be Associated with the Severity of COVID-19

Suheyla Akyol [1*], *Ferah Armutcu* [2]

[1] Suleyman Demirel University Medical School, Isparta, Turkey

[2] Department of Biochemistry, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey

Correspondence:
Suheyla Akyol

Address: Suleyman Demirel University Medical School, Isparta, Turkey

Email: sakyolmd@gmail.com

Keywords: electronegative LDL, COVID-19, LOX-1, PAFR, endothelial cells

Dear Editor,

Low-density lipoprotein (LDL) plays an important role in the occurrence and development of cardiovascular diseases (CVD), but research is still ongoing to determine how LDL plays its role. The three main subcategories of LDL have different densities: n-LDL subclass A, which includes more of the larger and less dense LDL particles (1.025–1.034 g/mL); n-LDL subclass I, which is regarded to be the intermediate group (1.034–1.044 g/mL); and n-LDL subclass B, which has more smaller and denser LDL particles (1.044–1.060 g/mL) [1]. It is known that the concentration of subclass B is higher in patients with ischemic heart disease and is associated with low levels of high-density lipoprotein (HDL) cholesterol, which suggests that it can be used as a risk marker for coronary heart disease [2]. Recently, it has been discovered that LDL subfractions have different effects on endothelial cell (EC) function. The most electronegative charged part of LDL, L5, has shown its uniqueness in triggering atherosclerotic reactions [3]. The plasma L5 ratio of patients at high risk of CVD increases [4]. As a result, the likelihood of L5 aggregation is increased, and at the same time, the number of smaller subgroups of L5 in plasma is increased [5]. In addition, L5 can activate the *in vitro* aggregation of natural less electronegative monomeric LDL fragments (L1) [5]. Obviously, although L5 circulation accounts for 3-5% of total LDL, it may promote atherosclerosis by promoting LDL aggregation and stimulating the subendothelial maintenance of LDL. In terms of entering EC, there is a big difference between LDL and L5. Electronegative LDL is introduced into EC through lectin-like oxidized LDL receptor 1 (LOX-1) and platelet activating factor receptor (PAFR), while LDL is introduced into EC through receptor-mediated endocytosis through LDL receptor (LDLR) [3]. The LOX-1 receptor acts as a signal center for L5 stimulation of the secondary pathway in EC. Therefore, L5 triggers the second pathway in EC through LOX-1 and PAFR, thereby inhibiting PI3K/AKT signaling and increasing the release of TNF-α. Electronegative LDL then induces the expression of TNF-α, Bax and Bad, and releases cytochrome c from the mitochondria, leading to apoptosis [6].

Dyslipidemia is believed to play an important role in the pathological development of COVID-19, which requires urgent attention to study its mechanism. Fan et al. [7] suggest that the consumption of LDL is related to the pathological process of COVID-19, which may be a factor in disease progression and mortality. It is known that L5 is one of the important factors in the blood that have inflammation and apoptosis effects. Although the mechanism of L5 formation is unclear, the involvement of these inflammatory events in the subendothelial space of blood vessels is very obvious [8,9]. Interestingly, it is claimed that the reduced levels of LDL-cholesterol is correlated with the severity of the disease in COVID-19 patients, indicating that there is a pathological interaction between

Received: 24.07.2020,
Accepted: 03.08.2020
https://doi.org/10.29333/jcei/8565

dyslipidemia and vasculopathy observed in COVID-19 patients [10]. However, although the LDL levels of COVID-19 patients are reduced, the L5 levels of these patients may still be higher, because there is no data in the literature to indicate that changes in L5 levels are always proportional to changes in LDL levels [6]. Since metabolic-associated morbidities are generally accompanied with EC dysfunctions, these pre-existing conditions may make EC more vulnerable to SARS-CoV-2 attack. In addition, changes in the composition and quantity of HDL that is expected to occur in patients with COVID-19 can significantly decrease the anti-oxidative and anti-inflammatory functions of HDL and could contribute to pulmonary inflammation [11].

We believe that oxidized lipoproteins, especially L5, may be related to virus-related endothelial damage, vascular and pulmonary inflammation, and pneumonia. Because one cause of abnormal lipid levels in COVID-19 patients is due to increased viral-induced inflammation. Understanding the role of L5 in inducing endothelial dysfunction and inflammatory processes may help improve the accuracy of diagnosis to evaluate the COVID-19 progress and treatment methods. In order to prove the correlation between L5 and disease progression, plasma L5 levels should be analyzed in COVID-19 patients.

Declaration of interest: The authors report no conflicts of interest.

Financial Disclosure: No financial support was received.

REFERENCES

1. Yee MS, Pavitt DV, Tan T, Venkatesan S, Godsland IF, Richmond W, et al. Lipoprotein separation in a novel iodixanol density gradient, for composition, density, and phenotype analysis. J Lipid Res. 2008;49:1364-71. doi: 10.1194/jlr.D700044-JLR200.
2. Austin MA. Small, dense low-density-lipoprotein as a risk factor for coronary heart-disease. Int J Clin Lab Res. 1994;24:187-92. doi: 10.1007/BF02592460.
3. Akyol S, Lu J, Akyol O, Akcay F, Armutcu F, Ke LY, et al. The role of electronegative low-density lipoprotein in cardiovascular diseases and its therapeutic implications. Trends Cardiovasc Med. 2017;27(4):239-46. doi: 10.1016/j.tcm.2016.11.002.
4. Sanchez-Quesada JL, Benitez S, Ordonez-Llanos J. Electronegative low-density lipoprotein. Curr Opin Lipidol. 2004;15(3):329-35. doi: 10.1097/00041433-200406000-00014.
5. Bancells C, Villegas S, Blanco FJ, Benitez S, Gallego I, Beloki L, et al. Aggregated electronegative low density lipoprotein in human plasma shows a high tendency toward phospholipolysis and particle fusion. J Biol Chem. 2010;285(42):32425-35. doi: 10.1074/jbc.M110.139691.
6. Akyol O, Chowdhury I, Akyol HR, Tessier K, Vural H, Akyol S. Why are cardiovascular diseases more common among mood disorders and schizophrenia? The potential involvement of electronegative low-density lipoprotein (LDL) L5. Med Hypotheses 2020;142:109821. doi: 10.1016/j.mehy.2020.109821.
7. Fan J, Wang H, Ye G, Cao X, Xu X, Tan W, et al. Low-density lipoprotein is a potential predictor of poor prognosis in patients with coronavirus disease 2019. Metabolism 2020;107:154243. doi: 10.1016/j.metabol.2020.154243.
8. Khosravi M, Hosseini-Fard R, Najafi M. Circulating low density lipoprotein. Horm Mol Biol Clin Investig. 2018;35(2). doi: 10.1515/hmbci-2018-0024.
9. Rivas-Urbina A, Rull A, Ordonez-Llanos J, Sánchez-Quesada JL. Electronegative LDL: An active player in atherogenesis or a by-product of atherosclerosis? Curr Med Chem. 2019;26(9):1665-79. doi: 10.2174/0929867325666180330093953
10. Cao X, Yin R, Albrecht H, Fan D, Tan W. Cholesterol: A new game player accelerating endothelial injuries caused by SARS-CoV-2? Am J Physiol Endocrinol Metab. 2020. doi: 10.1152/ajpendo.00255.2020.
11. Sorokin VA, Karathanasis SK, Yang ZH, Freeman L, Kotani K, Remaley AT. COVID-19-associated dyslipidemia: Implications for mechanism of impaired resolution and novel therapeutic approaches. FASEB J. 2020 Jun 26. doi: 10.1096/fj.202001451.

