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# Why are cardiovascular diseases more common among patients with severe mental illness? The potential involvement of electronegative low-density lipoprotein (LDL) L5

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ABSTRACT

Despite tremendous efforts of experimental and clinical studies and knowledge, the pathophysiology of severe mental illness (SMI), including bipolar disorder (BD), unipolar depression (mood disorders, MD), and schizophrenia (SCZ), remains poorly understood. Besides their chronic course and high prevalence in society, mental and somatic comorbidities are really serious problems; patients with these disorders have increased risk of cardiovascular (CV) diseases (CVD) including coronary artery diseases (CAD, i.e. myocardial infarction and angina), stroke, sudden cardiac death, hypertension, cardiomyopathy, arrhythmia, and thromboembolic disease. Although it is determined that triglycerides, cholesterol, glucose, and low-density lipoprotein (LDL) levels are increased in MD and SCZ, the underlying reason remains unknown. Considering this, we propose that electronegative LDL (L5) is probably the main crucial element to understanding CVD induced by SMI and to discovering novel remedial approaches for these diseases. When it is hypothesized that L5 is greatly presupposed in CV system abnormalities, it follows that the anti-L5 therapies and even antioxidant treatment options may open new therapeutic opportunities to prevent CVD diseases secondary to SMI. In this review article, we tried to bring a very original subject to the attention of readers who are interested in lipoprotein metabolism in terms of experimental, clinical, and cell culture studies that corroborate the involvement of L5 in physiopathology of CVD secondary to SMI and also the new therapeutic approaches for these disorders.

## Background

Despite preventive strategies, cardiovascular (CV) diseases (CVD) are the leading cause of death in the U.S. and all over the world [1]. Patients with severe mental illness (SMI), such as bipolar disorder (BD), schizoaffective disorder, and schizophrenia (SCZ), die at least 20 years earlier than the general population. This premature mortality has largely been attributed to CVD. The mechanism of CVD related to SMI has been investigated largely in clinical and experimental settings. These CV symptoms are closely related to metabolic abnormalities, including

*Abbreviations:* AMI, acute myocardial infarction; BAECs, bovine aorta endothelial cells; BD, bipolar disorder; CAD, coronary artery diseases; CV, cardiovascular; CVD, cardiovascular diseases; DM, diabetes mellitus; ECs, epithelial cells; ERK1/2, extracellular signal-regulated kinases 1/2; FPLC, fast protein liquid chromatography; GC, good glycemic control; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; IL-1β, interleukin 1 beta; L5, electronegative low-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LOX-1, lectin like oxidized low-density lipoprotein receptor 1; MAPK, mitogen-activated protein kinase; MCP1, monocyte chemoattractant protein-1; MD, mood disorders; mmLDL, minimally-modified low-density lipoprotein; NEFA, non-esterified fatty acid; NF-κB, nuclear factor kappa B; N-SBG, non-statin benefit groups; oxLDL, oxidized low-density lipoprotein; PAFR, platelet-activating factor receptor; PC, poor glycemic control; PGs, proteoglycans; ROS, reactive oxygen species; SBG, statin benefit groups; SCZ, schizophrenia; SMI, severe mental illness; sPLA2, secretory phospholipase A2 inhibitor; STEMI, ST-elevation myocardial infarction; TC, total cholesterol; TG, triglycerides; TLR4, toll-like receptor 4; VLDL, very low-density lipoproteins

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lipid/glucose levels, obesity, and diabetes mellitus (DM) [2]. On the other hand, patients with SMI have the top-level mortality rate when compared to all mental diseases [3]. An elevated risk of drastic CV problems for SCZ and BD patients was reported in some of the recent metanalyses [4–6]. One of the explanations for the higher incidence of CV events in SMI patients may be the increased prevalence of CV risk elements, such as hypertension, in this patient population. An investigation [7] tests the hypothesis that BD and/or SCZ patients detected in existing studies have a higher risk of developing hypertension than patients without these diseases and receive poorer care. Understanding the risk of hypertension in BD or SCZ populations is particularly important because it has been observed that the incidence of other CV risk factors in these patients may interact with hypertension, leading to poor CV health [8–10].

## Hypothesis

Major risk factors for CVD include metabolic syndrome, hypertension, DM, elevated cholesterol, cigarette smoking, physical inactivity, obesity, and overweight. Electronegative low-density lipoprotein (LDL) (L5) is a slightly oxidized LDL (oxLDL), which naturally exists in the circulation of type II DM and hypercholesterolemia patients as well as active smokers [11–13], and even healthy people to some extent (Fig. 1). Low-density lipoprotein aggregation is a crucial stage in initiating atherosclerotic alteration, as aggregation is essential for the formation of large lipoprotein-like particles and LDL fusion, which may subsequently merge into lipid droplets with atherosclerotic features. Due to the increased proportion of L5 in CV risk and inflammation-related diseases such as DM [14], L5 has been shown to be a dynamic atherosclerotic participant and a putative inflammatory biomarker. Our main motivation on why L5 could be one of the main factors in CVD linked to SMI is that LDL (it can be characterized as electropositive LDL, L1) is internalized within the epithelial cells (ECs) via a receptor-mediated endocytosis through LDL receptor (LDLR), while L5 is embodied through the platelet-activating factor receptor (PAFR) and the lectin like oxidized LDL receptor 1 (LOX-1) [11,15]. The second receptor-mediated path ends with apoptosis of ECs. The LOX-1 receptor behaves like a triggering site where L5 activates alternate pathways up to apoptosis [16]. Because LOX-1 is known to be expressed in intimal smooth muscle cells, neovasculature of human atherosclerotic plaques, and lipid-laden macrophages [17], L5 might have a major impact in developing CVD linked to SMI in some extent.

## Supporting evidence

*Cardiovascular diseases (CVD) in severe mental illness (SMI)*

The occurrence of SMI is associated with increased incidence, morbidity, and mortality of majority of CVD. Recent evidence suggests that the mortality gap remains to extend, in part because of the increased risk for CV and metabolic disorders [10] and the lack of primary prevention among populations with SMI [18].

*CVD in schizophrenia*

The mortality rate [19]) and prevalence of CVD [20] in SCZ patients are greater than in the normal people. Adults with psychosis often develop CAD at a relatively early age [21] and they are twice as likely to die of CVD compared to general population [22]. In addition, the corresponding risk of death in patients with SCZ has been increasing in recent years [22] because the improvements in health outcomes available to the general population are not partaken in those with SCZ [24]. Traditional risk factors of CVD include diabetes, dyslipidemia, hypertension, obesity, cigarette smoking, and a familial history of CAD [23]. Exposure to CV risk factors, such as smoking [24], typically precede the diagnosis of psychosis; in addition, its pharmacological treatment can aggravate DM, dyslipidemia, and obesity [25]. It is unknown if there are combined effects of CV risk factors or whether antipsychotics affect humans, but in the general population, these risk factors are significantly correlated and have a stronger impact on the overall CV outcome than individuals [26]. According to previous studies, patients receiving antipsychotic therapy are more likely to develop dyslipidemia when receiving antipsychotic agent regiments. Several studies conducted in the UK and North America suggest that SCZ patients that receive antipsychotics have either increased LDL [27] or reduced high-density lipoprotein (HDL) [27,28] cholesterols. However, for SCZ patients under antipsychotic treatment, it is controversial which lipid level is most markedly changed. A study was conducted to analyze separate risk factors for each lipid parameters in terms of the effects of antipsychotic treatment on triglyceride and LDL/HDL cholesterol levels between SCZ patients and healthy control group in the Japanese population [29]. No significant differences were found in either triglyceride levels or LDL-cholesterol between the patients and the control group. However, it was noticed that HDL-cholesterol levels were quite reduced in patients compared to control group. According to a multiple linear aggression analysis, antipsychotics were found to be a predictor of decreased HDL-cholesterol.

*CVD in mood disorders (MD)*

Bipolar disorder is a disabling chronic disease companioned with a proinflammatory systemic state [30,31]. Compared with the general population, BD is remarkably susceptible to numerous metabolic situations [32]. The standardized mortality rate for CVD is 1.5 to 2.5 [33,34], which is also the major source of mortality and morbidity in patients with BD [35]. According to several studies, patients with BD have a significantly higher risk of CVD than non-psychiatric controls and those with major depressive disorder [36,37]. People with MD have five times more CVD risk and exhibit the symptoms 14 years earlier that those without this disease in the U.S. [37,38]. Multiple variables and

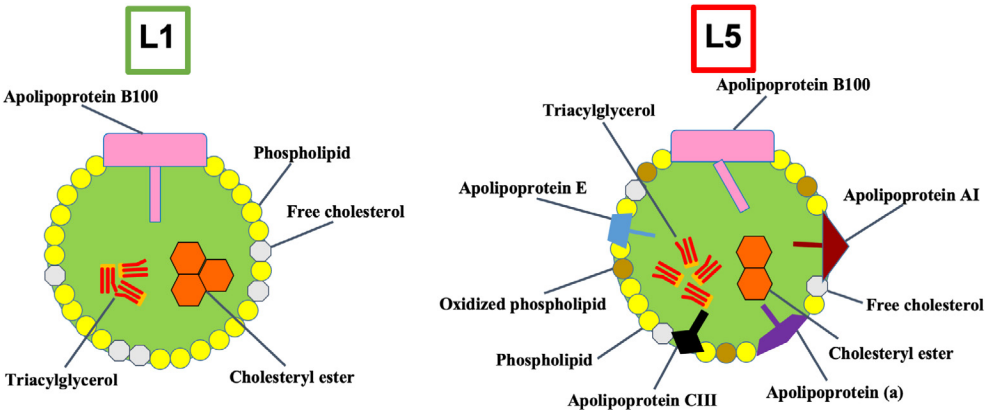


**Fig. 1.** Schematic representation of the structural components of native (less electronegative) LDL (L1) and the most electronegative LDL (L5). Origin of L5 is complex and multiple, and includes some oxidative processes, induced by especially free oxygen radicals. Compared to L1, L5 has higher amounts of apolipoproteins, higher triacylglycerols, and lower cholesteryl esters, but almost the same amount of phospholipids and free cholesterols. Apolipoprotein B100 is misfolded in L5 (Figure modified from Trends Cardiovasc Med 27:239, 2017).

complex mechanisms are components of processes leading to increased risk of CV, among other things such as genetics and behavioral patterns [39]. Patients with BD are susceptible to a range of health issues and are also considered to be risk factors for CVD. Cardiovascular risk factors, including dyslipidemia [40], hypertension [41], obesity [42], metabolic syndrome [43], and diabetes [41] are more prevalent in individuals with BD. Other risk factors include a sedentary lifestyle, higher rates of cigarette smoking [44], and poor dietary habits [45]. A growing risk of CVD in patients with BD [46] is suggested by substantial evidence. In a psychosocial intervention assessment study, it was found that a total of 70% patients had three or more risk factors for CVD, and 60% had a 10-year moderate or high risk of CVD [47]. Compared to the general population, these risk factors are approximately twice that of patients with BD [35]. The rationale for the relationship between BD and CVD include unhealthy lifestyles, which are exacerbated by symptoms of psychosis (e.g., obesity and smoking) and adverse drug reactions [48]. Despite the fact that the risk factors for CVD are related to psychiatric drugs, some studies have shown that BD patients have an excessively high proportion of CVD before tricyclic antidepressants and lithium and before atypical antipsychotics [37]. A study was set up to understand patient perceptions of the causes of psychiatric drug non-compliance and the risk factors for CVD in outpatients with BD [49]. The results suggested that disorders that persist with psychiatric symptoms are related to patient-related causes (stigma, low support for family members, drug-related causes, and provider-related factors).

### *The properties of L5 and the difference between L1 and L5*

Lipoproteins are vital in the transport of all forms of lipids from the central organ, liver, to surrounding organs and tissues in both absorption and transport phases of dietary lipids by the small intestine and in the reverse transportation of lipid into the liver. An ordinary lipoprotein is composed of three different parts; apolipoproteins, a lipid soluble (hydrophobic) center of triglycerides and cholesteryl esters, and a monolayer on the surface consisting of free cholesterol and phospholipids. Lipoproteins are technically categorized according to their densities upon ultracentrifuge separation, depending on their lipid and protein compositions: chylomicrons (lowest density), very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), LDL, and HDL (highest density) (Table 1). Lipids within lipoproteins, apolipoprotein, and the organ in which lipoproteins synthesized, intestine and/or liver, determine their specific functions.

LDLs in the blood plasma are a cluster of particles that have different densities, electrical charges and compositions. One of the minor forms of modified plasma LDL is L5 [16] (Fig. 1), which is a diverse subpopulation of particles that vary in density and size but share the same electronegative charge [50]. However, mechanism of L5 production is not understood clearly. Although electronegative LDL was originally considered to be oxidized particles in the blood, it is now widely used as a group of modified LDLs. These LDLs have different characteristics but have common electronegativity characteristics [14] based on the fact that LDL oxidized *in vitro* are more electronegative than are unoxidized LDL. Chen and coworkers described that L5 is a mild oxLDL subfraction contained in the whole pool of LDL and suggested that L5 from familial hypercholesterolemia patients is malondialdehyde modified [51]. Suggested mechanisms for the oxidation of LDL *in vivo* has been summarized as lipoxygenase reaction, cytochrome complex reactions, xanthine oxidase, NADPH oxidase, and other superoxide generators as well as copper and ceruloplasmin-mediated, iron-mediated, peroxidase-mediated (including myeloperoxidase and heme), peroxynitrite-mediated, and thiol-mediated oxidations [52]. Lipid molecules especially polyunsaturated fatty acids are quite vulnerable to reactive oxygen species (ROS) attack and readily oxidized [53,54] to give multifaceted products such as malondialdehyde that in turn react with apolipoproteins leading their functional loss. On the other hand, L5 itself may trigger reactive

**Table 1**
Lipoprotein classification according to their physical and structural properties.

| Lipoprotein class | Diameter (nm)[a] | Density (g/ml)[b] (high to low) | Major lipid found in the structure | Major apolipoprotein(s) | Other constituent(s) | Electrophoretic mobility[c] |
|---|---|---|---|---|---|---|
| HDL | 5–12 | 1.063–1.210 | Cholesterol, phospholipids | ApoA-I, ApoA-II, ApoC, ApoE | CETP, LCAT, PON1 | α |
| LDL | 18–25 | 1.019–1.063 | Cholesterol | ApoB-100 | Vit E | β |
| IDL | 25–35 | 1.006–1.019 | Cholesterol, triglycerides | ApoB-100, ApoC, ApoE | Vit E | Slow pre-β |
| VLDL | 30–80 | 0.930–1.006 | Triglycerides | ApoB-100, ApoC, ApoE | Vit E | Pre-β |
| Chylomicron remnants | 30–80 | 0.930–1.006 | Cholesterol, triglycerides | ApoB-48, ApoE | Retinyl-acetate and/or -palmitate | Slow pre-β |
| Chylomicron | 75–1200 | < 0.930 | Triglycerides | ApoA-I, A-II, AIV, ApoB-48, ApoC, ApoE | Retinyl-acetate and/or -palmitate | Origin |
| Lp (a) | ~30 | 1.055–1.085 | Cholesterol | Apo(a), ApoB-100 | – | Pre-β |
| L5[d] | 24–26.5 | ? | Cholesterol, triglycerides | ApoA-I, Apo(a), ApoB-100, ApoC-III, ApoE | – | β |

Note that all the lipoproteins contain triglycerides, esterified and unesterified cholesterol, and phospholipids to varying degrees and amounts.
**Abbreviations**: CETP, cholesteryl-ester transfer protein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; L5, electronegative low-density lipoprotein, LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp (a), small a lipoprotein; PON1, paraoxonase 1; Vit E, vitamin E; VLDL, very low-density lipoprotein.
(Table modified from Feingold KR and Grunfeld C. Introduction to Lipids and Lipoproteins. https://www.ncbi.nlm.nih.gov/books/NBK305896/).
[a] The size of lipoprotein particles is measured by using gel electrophoresis.
[b] Lipoprotein density is calculated by the method based on ultracentrifugation.
[c] The electrophoretic mobility of any kinds of lipoprotein on agarose gel indicates the size and charge of lipoprotein fragment with α and β indicating the positions HDL and LDL, respectively.
[d] No data was found regarding the L5 particle's exact density but it can be estimated being between 1.019 and 1.063.

oxidative stress in the body. Fluorescence microscopy showed that L5 treatment increased the production of mitochondrial superoxide compared to L1 or saline treatment. Therefore, L5-induced mitochondrial ROS seems to be important for its pathogenic effect [55]. According to the opposite point of view, it is suggested that non-oxidative LDL modifications can cause the generation of L5 *in vivo*. The experiments managed *in vitro* allows estimations of the process of *in vivo* production of L5. Incubation of isolated LDL with plasma at 37 °C gave rise to the formation of L5 while being blocked by a secretory phospholipase A2 inhibitor (sPLA2), 4-bromophenacyl bromide. This indicates that PLA2 may have a central role and may at least be a modifier in the formation of L5 [56]. These are all the pathways that adds more negative charges on LDL. Free cholesterol is increased in the chromatographic LDL scale from positive to the negative [57] and the amount of phospholipids are decreased. The phospholipid amount being decreased in L5 is associated with the oxidation of phospholipids, causing these molecules to become more susceptible for PLA2 hydrolysis than that of traditional phospholipids.

Cholesterol (total cholesterol, TC) and triglycerides (TG) are measured enzymatically using the cholesterol and TG reagents by auto analyzers in clinical chemistry practice. For HDL cholesterol (HDL-C) measurement, the lipoproteins containing apoB first reacts with the blocking agent, which makes it non-reactive with the enzymatic cholesterol reagent. Lipoproteins containing apoB are thus effectively excluded from the detection and only HDL-C is detected. After all these analyses, LDL cholesterol (LDL-C) is calculated from the measured values of TG, HDL-C, and TC according to the relationship [LDL-C] = TC – [HDL-C] – [TG]/5 (Friedewald formula) where [TG]/5 is an approximate value of VLDL-C and all values are expressed in mg/dL. On the other hand, because of the variability among methods used to isolate highly electronegative LDL, a normal range for L5 has not been previously established. Currently, the use of fast protein liquid chromatography (FPLC) equipped with an anion exchange column is the most common method for the detection and quantification of L5 in human plasma. When using a multi-level linear gradient with a NaCl concentration between 0.15 and 0.20 M to represent normal physiological conditions, the LDL subfractions L1 and L5 can be clearly distinguished [16]. However, the limitation of the current method for quantifying L5 is that it is time-consuming, since the method requires extra treatment with penicillin/streptomycin, protease inhibitor, and EDTA at the preparation step and then ultracentrifugation (using sequential potassium bromide density gradient), dialysis with a special buffer for 3 times for 24 h each time, FPLC separation with anion-exchange column, and monitoring at 280 nm are needed in the second detection step. In addition, it requires a large volume of blood samples. Therefore, a faster alternative method is needed to conduct large-scale clinical trials and to determine L5 in a clinical setting.

### *The roles of LDL and L5 in CVD*

CVD incorporates stroke, CAD (i.e. myocardial infarction and angina pectoris), arrhythmia, thromboembolic disease, congenital heart disease, arterial hypertension, cardiomyopathy, and sudden cardiac death. Atherosclerosis and impaired endothelial function are some of the earliest signs of risk for CVD.

Patients with a higher CV risk, such as DM or familial hypercholesterolemia [58,59] and ST-elevation myocardial infarction (STEMI) [60], have a higher L5 ratio. Lately, it was described that there is a notable elevation in L5 ratio in patients with STEMI [61] and it was found that L5 induces nuclear factor kappa B (NF-κB) and inflammatory activation, followed by interleukin 1 beta (IL-1β) production in macrophages [62]. Previous studies have shown that NF-κB is needed to control granulocyte macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) [63]. GM-CSF and G-CSF are hematopoietic growth factors and are connected with inflammation in majority of inflammatory diseases [64,65]. Hence, L5 may serve as a plausible GM-CSF expression in macrophages and upstream modulator of G-CSF. Research conducted by Yang et al. [66] analyzed the impacts of L5 on GM-CSF and G-CSF synthesis in macrophages and outlined the basic procedure. In patients with acute myocardial infarction (AMI) [64,67], elevated plasma concentrations of endogenous GM-CSF and G-CSF were detected. L5, not Cu-oxLDL or L1, remarkably influenced the synthesis of G-CSF and GM-CSF in macrophages. The fact that the degree of oxidation is critical to the effect of L1 and L5 has been demonstrated by *in vitro* oxidation of them, where the oxidation of L5 and L1 changed their capacity to produce GM-CSF and G-CSF. Antibody neutralization and knockdown experiments showed that the effect was caused by LOX-1. Additionally, NF-κB and extracellular signal-regulated kinases 1/2 (ERK1/2) inhibition resulted in notable decrease in L5-induced GM-CSF and G-CSF synthesis. Furthermore, knockdown of ERK2 instead of ERK1, prevented GM-CSF and G-CSF synthesis induced by L5. The outcomes suggested that L5 induces GM-CSF and G-CSF synthesis via ERK2, NF-κB, LOX-1 dependent biochemical paths in human macrophages.

A study [68] was conducted to investigate the levels of blood L5 in hyperlipidemia patients in order to analyze the deviations in L5 levels among patients with major statin benefit groups (SBG) and non-statin benefit groups (N-SBG) defined by AHA/ACC new cholesterol guidelines released in 2013. In addition, the effect of 10 mg/day rosuvastatin (a statin) of 3 months on L5 in SBG versus N-SBG was investigated. The study revealed that statin can effectively reduce the proportion of L5, and that atherogenic L5 was much higher in hyperlipidemia patients of SBG. After 3 months of statin treatment, triglycerides, LDL-C, and total cholesterol were significantly reduced. After statin therapy, the percent decrease of L5 was around 40.9% and it was significant. After statin treatment, the absolute concentration of L5, which is derived from LDL-C multiplied by L5 %, was reduced by about 63.8%. Linear regression analysis showed a significant positive correlation between 10-year CV risk and L5 plasma concentration using the compound cohort equation.

A study provides new perceptions into the qualitative changes in lipoproteins that lead to increased inflammatory activity in type II DM [69]). L5 from patients with poor glycemic control (PC)-type II DM exhibit the extremely inflammatory cytokine release compared with healthy subjects and patients with good glycemic control (GC). Furthermore, patients with PC-type II DM have reduced HDL resistance to L5 inflammatory responses. A recent type II DM study showed that the proportion of L5 is higher than that of healthy people, and that the proportion of PC-type II DM is greater than that of patients with GC-type II DM, conceding with previous observations [70]. In accordance with the previous studies [71,72]; other plasma inflammatory markers, including IL1β, L-selectin, and IL6, elevations were observed in PC-type II DM. L5 from type II DM, particularly from PC-type II DM, induce greater cytokine liberation in monocytes when correlated to L5 from control people. In contrast, the changes in L5 inflammatory activity and HDL anti-inflammatory activity of GC-type II DM were not as significant as those of PC-type II DM, which may be due to better glycemic control. These results [69] show a link between low-grade inflammation found in type II DM and the qualitative nature of LDL and HDL (especially L5), mainly in poorly controlled patient group. The moderate regulation of the L5′s inflammatory action and anti-inflammatory action of HDL in GC-type II DM indicates that hypoglycemic treatment can not only improve the qualitative characteristics of dyslipidemia, but also contribute qualitative characteristics of lipoproteins by reducing inflammation of type II DM.

### *Secondary events mediated by LOX-1 vs LDLR*

L5 and L1 subfractions have been known to be as exclusively incompatible with respect to their post-receptor actions in ECs [15]. L5 is embodied through the LOX-1 and the PAFR [11,15], while L1 is embodied via a receptor-mediated endocytosis through LDLR (Fig. 2). These occurrences prove the hypothesis that LOX-1 might have a crucial

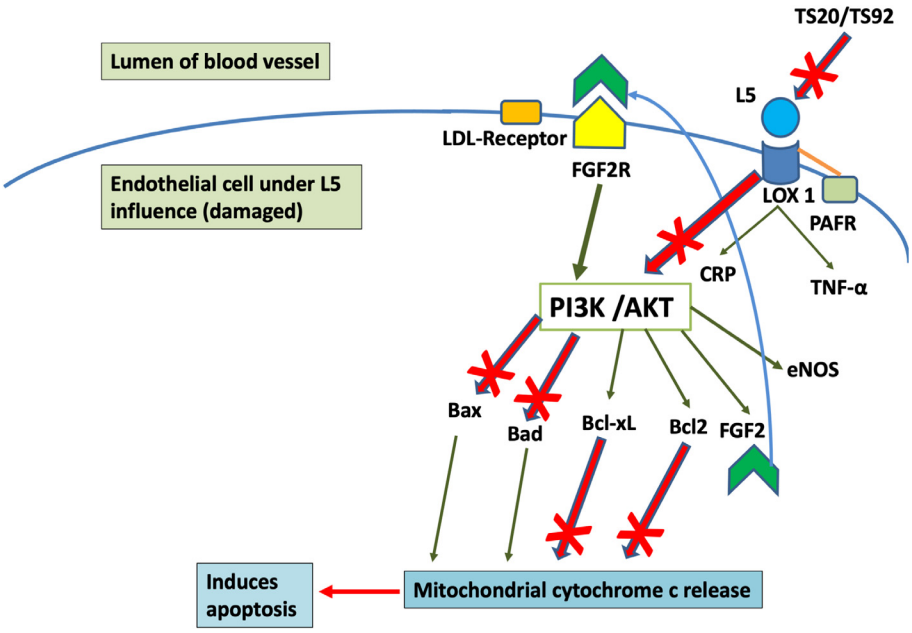


**Fig. 2.** Schematic representation of signaling pathway of electronegative LDL (L5)-induced atherosclerosis in endothelial cells (EC). LOX-1 receptor acts as a signaling center through which L5 triggers secondary pathways within the EC. Therefore, L5 activates EC through LOX-1 and PAFR, suppressing PI3K/AKT signaling and increasing the release of TNF-α. L5 then induces the expression of Bad, Bax, and TNF-α and the release of cytochrome *c* from mitochondria and ends up with apoptosis induction (Figure modified from Trends Cardiovasc Med 27:239, 2017). *Abbreviations*: AKT, protein kinase B; Bcl2, B cell lymphoma 2; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; FGF2, fibroblast growth factor 2; FGF2R, fibroblast growth factor receptor 2; L5, the most electronegative LDL; LOX-1, lectin-like oxidized LDL receptor-1; PAFR, platelet-activating factor receptor; PI3K, phosphoinositide 3 kinase; TNF-α, tumor necrosis factor α; TS20 and TS92, two different types of antibodies which able to neutralize receptor LOX-1.

function in the activation of ECs in proatherogenic milieu and macrophage/smooth muscle cells causing the final stage, atherosclerosis. Furthermore, it is indicated that large human arteries, specifically sites where atherosclerosis often develops, express peak levels of LOX-1 *in vivo* [73]. An EC culture experiment suggested that LOX-1 levels were 3-fold increased upon L5 induction [15]. Expression of LOX-1 was found to be repressed when LOX-1 specific siRNA had been transfected to bovine aorta endothelial cells (BAECs). Using the same experimental setting, in cases of receptor knockdown, the L5 upregulation of LOX-1 was found to be notably repressed [15].

LOX-1's total influence through L5 binding to the receptor binding sites in ECs might be better interpreted by close examination of secondary signal transducing elements in the L5-induced LOX-1 models. Two oppositely charged LDLs, L1 and L5, differ in size and density, apoB-100 conformation (apoB), and in lipid and protein composition [74]. Phospholipolytic activities in L5 appears to provide to its higher levels of aggregation and greater binding capacity to the proteoglycans [74,75]. Multiple studies indicate that L5 contributes to inflammation in cells, primarily by inducing release of the cytokines [14]. Lately, it was found that L5 triggered production of IL-1β, IL-6, and TNF-α through a LOX-1/NF-κB/ERK-dependent pathway in macrophages [76] confirming the previous studies [66] and suggested that L5 was more potent than substantially oxLDL or native LDL in stimulating cytokines and proinflammatory signals. These findings support the thesis that atherosclerosis, which has become increasingly evident in recent years, is an immune and chronic inflammatory disease. Epithelial cells were the first cell types where the release of inflammatory cytokines by L5 induction was first reported [77]. Additionally, L5 activates the inflammatory mediator discharge (such as IL6 and 10) and monocyte chemoattractant protein-1 (MCP1) release in monocytes thereby promoting gene transcription [78,79]. The release of these cytokines is moderated by toll-like receptor 4 (TLR4) and CD14 [80]. Furthermore, the increased ceramide content in L5 apparently activates CD14-TLR4 pathway [81]. L5 has recently been shown to activate the TLR4 pathway in monocytes in the release of the potential anti-inflammatory cytokine IL1β [82]. Signaling pathways induced by oxLDL and minimally-modified LDL (mmLDL) have comprehensively been investigated including the stimulation of NF-κB transcription factors [83], AP-1 [84], ERK [85], and PI3k/Akt-mediated p38 mitogen-activated protein kinase (MAPK) [86,87]. However, a small number of researches using only ECs were conducted regarding L5-induced signaling pathways. L5 promotes the transcription factors AP-1 and NF-κB [88], activation of p38 MAPK [88,89] and inhibition of the PI3k/Akt pathway [13,15] in this cell type. Estruch et al. identified signaling pathways that lead to L5-induced monocyte release of cytokines [90]. This investigation indicated that L5 stimulates the phosphorylation of p38 MAPK through PI3k/Akt1 and TLR4 pathways. P38 MAPK phosphorylation is included in the activation of cAMP response element-binding protein, AP-1, and NF-κB, leading to stimulation of cytokine release by L5. For each cytokine, the involvement of the above-mentioned L5-activated signaling pathways varies.

### *The formation of atherosclerosis – classical pathway*

The event that initiates the initial lesions for atherosclerosis is the confinement of LDL in subendothelial region, which is moderated by the attaching of LDL to the arterial proteoglycans (PGs) [91]. LDL binding is activated by chemical modification of LDL (like proteolysis, lipolysis, and oxidation), thereby promoting LDL aggregation [92] (Fig. 2). LDL particles that are aggregated contain several PG binding sites and a higher affinity for PGs in the arterial wall compared to their natural nonaggregated matches. LDL aggregation can develop into irreversible fusion of LDL, followed by lipoprotein degradation and nuclear lipid rupture (or release) and coalescence into lipid droplets and vesicles, which has been known to be too big to leave the subendothelial matrix area of the arterial wall [92,93]. In an environment like this, macrophages incorporate the captured lipoproteins which leads to cholesterol-forming particular cells (foam-cells), an indication of atherosclerotic lesions [94]. LDL particles exhibit heterogeneity in lipid composition, density, and size [95,96]. Surrounded by the LDL particles, the denser and smaller LDL particles are more likely to cause atherosclerosis [97] and the LDL phenotype with smaller dense is extremely correlated with CAD [98]. It has been reported that alterations in lipid distribution of particular lipoproteins, especially LDL, such as oxidative changes, are associated with onset and development of atherosclerosis and have become key triggers [96]. Studies have shown that reduced inflammatory stress and oxLDL as well as eNOS-mediated improvements in EC function can affect the efficacy of LDL apheresis in the treatment of atherosclerotic patients with severe peripheral arterial disease [99]. Compared to powerful association among DM and pathogenic changes in lipids, plasma lipid profiles (including hyper-apoB, low HDL cholesterol, and hypertriglyceridemia) in these patients are

usually abnormal, and it is a biological marker of high incidence of microvascular and macrovascular complications [100–101]. Additionally, the concurrence of decreased HDL-cholesterol and hypertriglyceridemia usually stimulates the formation of dense and small particles of LDL. Moreover, complications of DM exacerbate other pathological characteristics such as systematic inflammation, lipid peroxidation, and hyperglycemia [100,101]. The function of lipoproteins is altered by these processes to contribute the configuration of modified-LDL, like oxLDL, glycosylated LDL, and L5 [100,101].

*The formation of atherosclerosis - the involvement of L5*

With a high risk of CVD, the plasma L5 ratio increases [102]. Consequently, L5 increases the tendency to aggregate and at the same time minor L5 subpopulations accumulate in plasma [74,75]. Furthermore, L5 can stimulate *in vitro* aggregation of native, none-lectronegative, monomeric LDL fragments, called L1 [75,103]. These studies indicate that, despite L5 constituting only 3–5% of total LDL in plasma, it can promote atherosclerosis by contributing LDL aggregation and stimulating LDL subendothelial maintenance. A distinct characteristic of L5 is that it has comparatively high non-apoB protein content [104]. In the L5′s aggregation behavior, the function of non-apoB proteins is uncertain, but some, such as apoA-I and apoJ, may restrain rupture, aggregation, and fusion of LDL [105,106]. The function of apoA-I and apoJ in LDL subclass aggregations was investigated [107]. Modifications of lipid and apoB hydrolysis, which are particularly unstable in LDL, drives these processes primarily *in vivo*. Modifications of hydrolysis process can be moderated through multiple elements. For instance, elevated appearance of lipases and proteases in the atherosclerotic region of the total area of arterial wall [108,109] enhances LDL's lipid and protein content degradation in the sub-endothelial area. The degeneration of both phospholipids and apoB apolipoprotein in LDL can be stimulated by redox status alteration, which is considered to be widespread in the injuries of atherosclerosis [110]. It is challenging to examine LDL aggregation *in vivo* in a laboratory setting as it can be a very gradual procedure requiring many participants. A crucial biochemical variation between the fractions of total LDL is the non-esterified fatty acid (NEFA) content, which is elevated at the L5 baseline, but exhibits a higher heat energy-induced elevation in all parts. NEFA are extremely fused, and even a few percentage points elevation in NEFA can greatly accelerate rupture, aggregation, and fusion of other lipoproteins or LDL, yet albumin removal of NEFA slows these transitions [111]. Thus, it has been suggested that the initial fusion and quick aggregation of L5 and its stimulation ability for aggregation of L1 are due in part to its higher baseline NEFA. Additionally, it was proposed that secondary apolipoproteins found in LDL (like apoA-I and apoJ), which are relatively abundant in L5 but nearly absent from L1, help stabilize lipoprotein complexes during degradation and denaturation. ApoA-I and ApoJ [112] are both thermally stable to some extent, and they are both meaningfully elevated in L5. The balancing action of apoA-I and apoJ may be due to independent several mechanisms. There is a unique function of extracellular chaperone ApoJ, which is the protection of proteins from high temperature and all other stress-induced aggregations [113,114]. Thus, apoB can be stabilized by apoJ against conformational alterations that stimulate thermally induced LDL degradation. According to a latest investigation, it was found that apoJ-deficient LDL is some more sensitive to enzymatically-induced aggregation and apoB degradation by α-chymotrypsin when compared to apoJ-containing LDL [105]. Likewise, ApoJ can also slow the conformational degradation and remodeling of apoB, thereby protecting LDL from thermal interference. A prevalent characteristic of glycosylated LDL and oxLDL is an increase in negative charge they have. Therefore, L5 contains glycosylated and oxLDLs, but most portion of L5 particles are created by other mechanisms such as NEFA loading and lipolysis [100,101]. This diversity put in some value to L5 measurement and can be viewed as a set of modified LDL that might be assessed as a reserve of modified LDL fragments in blood [100]. It has been reported that the fraction of glycosylated LDL, L5, and oxLDL is elevated in patients with DM [101,115]. Yet, DM patients were not tested whether or not there are some extent of effect of HDL on L5's inflammatory action. As mentioned previously, this particular subject has been investigated by Estruch et al. in a different perspective [69]. The authors intended to investigate whether or not qualitative characteristics of HDL and L5 were changed in type II DM patients [69]. Investigators separated blood monocytes from type II DM patients, and evaluated the proinflammatory action of L5 and the anti-inflammatory activity of HDL on the monocytes [69]. They presented that plasma inflammatory markers and L5 proportion were increased in PC-type II DM patients. Additionally, L5 from healthy people were compared to those of type II DM patients with good GC and found that L5 from PC-type II DM patients generated the maximal IL10, IL6, and IL1β discharge from isolated monocytes [69]. The same study also showed that the maximum NEFA level was found in monocytes from PC-type II DM patients [69]. The NEFA content of LDL is related to the production of cytokines since NEFA-rich LDL induces the release of cytokines by monocytes [116]. In addition, the authors suggested that HDL separated from PC-type II DM patients demonstrated the lowest ability to inhibit the release of cytokines by L5-induced monocytes, while also having the ability to reduce NEFA levels in L5. The above-mentioned discoveries can help us understand the association between changes in the characteristics of HDL and L5 and the inflammatory status of type II DM [69]. Further research is needed to additional improve the effectiveness of anti-atherosclerotic therapies to determine the exact molecular mechanism of the abnormal communication between HDL and modified LDL, and its effect on the EC function and balancing of monocytes. This is because activating EC function will be a principal strategy for reducing vascular processes of atherosclerosis [117], and uncertain factors might play a key function in moderating the therapeutic effects of currently accessible treatments on EC function.

*Putative roles of LDL and L5 in SMI and SMI-related CVD*

BD and SCZ patients are under threat of medical conditions such as hyperlipidemia and DM. It has been suggested that these two severe conditions should be monitored, particularly when a patient was given antipsychotic treatment regimen [118].

Chronic SCZ has been known to be associated with lipid disorders, specifically raised triglyceride levels and reduced HDL-C compared with the healthy control population [119]. In spite of claims that antipsychotic treatment is the cause of this blood chemistry changes, some studies found considerable evidence that these changes in lipid metabolism exist since the onset of the illness [120–122], suggesting that lipid metabolism changes might be intrinsic to SCZ. As a matter of fact, Misiak et al. reported that first-episode non-affective psychosis patients who are totally antipsychotic-naïve presented subclinical dyslipidemia [123]. One of the recent *meta*-analyses revealed that compared with healthy controls, primary psychosis was related with lower LDL-C and TC levels, but elevated triglycerides and unchanged HDL-C, indicating that hypercholesterolemia seen in chronic disorder is secondary and potentially modifiable [124]. It was also suggested that elevated plasma levels of triglyceride during SCZ attack are predictive metabolic indicators of extended possibility of DM. On the other hand, dyslipidemia, which is defined as low HDL and/or high LDL and/or high TG levels, constitutes an important risk factor for CVD as its prevalence has been found to reach almost 55% in SCZ patients receiving antipsychotic drugs [125]. This side effect of antipsychotic drugs has mainly been attributed to the drug-induced weight gain, but in recent years weight-independent molecular factors have also been charged for that effect because lipogenic adverse effects may occur in early stages of the disease, even preceding weight gain [126]. A post-hoc analysis revealed that a significant variation in HDL-C levels in Japanese patients with SCZ obesity were due to the use of multiple antipsychotics such as

olanzapine, risperidone, or aripiprazole [127]. If the clinicians have doubt about the causative antipsychotic effect, after a careful evaluation of the risk–benefit ratio of drug change, a less lipid-offending antipsychotic agent has been recommended to be replaced if clinically possible, considering the major impact of obesity and dyslipidemia and the major consequences of them on mortality and morbidity [128]. The efficacy and safety of a lipid lowering agent, rosuvastatin, treatment was evaluated in SCZ patients who already been treated with antipsychotics in terms of the effect of this regimen on the components of metabolic syndrome, glucose homeostasis, and lipid profile. Serum triglyceride levels was found to be the only parameter of metabolic syndrome, which was influenced greatly by statin treatment [129]. A recent study reported that the data available on the effectiveness and safety of adjunctive rosuvastatin in treating dyslipidemia for patients with SCZ is insufficient to obtain a definitive interpretation about its efficacy and safety [130]. Despite the fact that there has been inconsistency with the benefit of adjuvant therapy with statins of severity of negative symptoms in SCZ, a recent *meta*-analysis reported that adjunctive therapy could improve both negative and positive symptoms of SCZ [131].

Lipid profile interferences are often observed in unipolar disorder and BD and account for high mortality rates [2]. According to the *meta*-analyses, there is a relationship between low serum LDL and depression modeled with serum LDL as a constant parameter [132]. However, opposite findings are also available from the studies that takes serum LDL as a categorical parameter, emphasizing the importance of prospective analysis in time assessment. While a majority of researches show the association in depressed patients between suicidal behavior and decreased total and LDL cholesterol [133], some others show higher HDL-C and TC levels in BD patients with suicidal thoughts as compared with the corresponding controls [134]. Immune-inflammatory, oxidative and nitrosative stress pathophysiology has been accused to be a causative factor for major depression assuming that increased peroxides and oxLDL antibodies may cause neurodegeneration in this disease [135]. It was found that the incidence of DM, elevated fasting glucose, hypertriglyceridemia, or obesity in BD was higher than presumed from age-appropriate, gender-proportioned, national general population estimates [46] showing high prevalence of obesity and metabolic syndrome in patients with BD. A smaller proportion of patients were found to have a low HDL in the same study. On the top of it, a low HDL may not only be associated with risk for CVD but also with increased risk for SMI [136].

There is no clinical or experimental study investigating the role of L5 in SCZ and other SMIs up until now. From this perspective, the subject is quite original and needs to be investigated despite the fact that some *meta*-analyses found decreased LDL levels in the onset of SCZ and/or BD because there is no evidence in the literature that shows that changes in L5 levels are always proportional to the changes in LDL levels.

## Conclusion

The hypothesis of the present work is that L5 might be involved in the pathophysiology of CVD in SMI. The mixture and integration of medical information will help bring new translational measures. Therefore, the main purpose of this study is to integrate scientific knowledge we have about L5 metabolism, LDL metabolism, and their involvement in the pathophysiology of CVD in SMI. We reviewed this topic basically and summarized experimental, clinical, and cell culture investigations that endorse the key role of L5 in explaining the pathophysiology of CVD in SMI and new therapy approaches in these disorders. There have been many research areas for lipoprotein metabolism in SMI and there have also been many opportunities to explore this topic from the perspectives of technology, genetics, metabolomics, genomics, molecular biology, and biochemistry. Triglycerides, cholesterol, and LDL levels are increased in SMI but the underlying causes remain unknown. In this article, we proposed that L5 may be a key picture in understanding SMI-related CVD and discovering new treatments for these chronic diseases. If the hypothesis is considered to be correct and L5 is involved greatly in CV system abnormalities, it follows that the anti-L5 therapies and even antioxidant therapies may provide clinicians more chances to impede CVD diseases secondary to SMI. Studies should be concentrated to determine the true risk of L5 in patients with CVD in SMI. Much more research efforts in the area of L5 analysis and assays should continue, always focusing on the simultaneous verification of all lipoproteins in order to reach true conclusions on the topic. However, the limitation of the current methods for quantifying L5 is that it is not compatible with automated analyzer measurement methods, time-consuming, and requires large volume of blood. There is also a need to move forward in search of more simple, accurate, fast, and standardized L5 assays that can be more easily transferred to institutions, hospitals, and laboratories.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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