Clinical Utility of Small, Dense LDL as an Atherogenic Risk Marker

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Abstract: Low-density lipoprotein (LDL) has a major role in the origination and development of atherosclerosis and Cardio Vascular Diseases (CVD). Over the past few years, many studies have been concerned with different subclasses of LDLs and their atherogenicity. Low-density lipoproteins (LDLs) include many subclasses. The most common are large buoyant (LB), intermediate and small dense (sd) low-density lipoprotein particles. Small dense low-density lipoproteins attracted a lot of attention. Small dense LDL (sdLDL) has recently been proven to be more atherogenic than other lipoproteins containing apolipoprotein B, which have the potential to trigger atherosclerotic reactions. Many researchers have reported that small dense low-density lipoproteins are the superior biomarker for the prediction of atherosclerosis and CVDs regarding all other markers, including total low-density lipoprotein cholesterol (LDL-C), and total serum cholesterol, non-high-density lipoprotein (non-HDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride content. Circulating small dense, low-density lipoproteins go through several modifications in the blood, rendering them more atherogenic. These modifications may include glycation, oxidation, and desialylation. Modified particles are strong inducers of inflammation resulting in many cardiovascular diseases, making them the primary target during the treatment of coronary artery disease. This article will elaborate on the clinical utility of sdLDL as an early marker to predict atherosclerosis and CVDs, and why it is considered superior to other atherosclerotic markers.

Keywords: small dense low-density lipoproteins; sdLDL; lipoproteins; biochemical markers; atherosclerosis; cardiovascular diseases; CVDs.

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1. Introduction

The rising figures of deaths due to coronary artery diseases resulting from atherosclerosis forces us to look into the different risk factors leading to atherosclerosis. Hypercholesterolemia is a significant contributor to the development of atherosclerosis as atherosclerotic plaques count on the circulating cholesterol for growth and progression [1,2]. Although cholesterol-lowering medications are used to reduce the risk for cardiovascular disease, the risk was only reduced by approximately 30%, indicating that several other factors
need to be considered [3]. Studies have reported that the development of atherosclerosis depends not solely on lipoprotein size but also on the unique properties of each subclass of the circulating lipoproteins [4,5]. The greatest atherogenic lipid content is carried by small dense low-density lipoproteins [6].

On the contrary, lipids contained within high-density lipoprotein (HDL) do not participate in the process of atherosclerosis. Still, HDL in the blood is inversely proportional to the risk of atherosclerotic diseases [6]. Though sdLDL is highly atherogenic at first, it can undertake multiple blood changes, making this even worse [3]. A high level of sdLDL is always associated with increased plasma triglyceride concentrations, elevated hepatic lipase activity, and decreased HDL cholesterol [7].

High sdLDL level is now agreed on by the National Cholesterol Education Program (NCEP III) as an important risk factor for atherosclerotic cardiovascular disease [4]. Due to the different biochemical modifications by which lipoprotein particles undergo in the blood and become more atherogenic, lipoprotein(a) (Lp(a)), which is a type of lipoprotein with another lipoprotein molecule that forms a covalent bond with apolipoprotein B, contributes to the risk of cardiovascular diseases [8]. Studies reported that even though there’s a link between total cholesterol levels and the death rate of coronary artery disease (CAD), total cholesterol levels do not accurately estimate the risk of coronary artery disease in many individuals because total cholesterol is not only the cholesterol in the atherogenic lipoproteins (LDL, VLDL, and IDL) but the cholesterol that in the anti-atherogenic lipoproteins such as HDL is also included [9,10].

So, making treatment plans depending exclusively on total cholesterol levels is deficient. It should be taken into consideration the heterogeneous properties of lipoproteins. The small dense low-density lipoproteins are far more potent contributors to atherosclerosis than large, buoyant lipoproteins, and oxidized lipoproteins are generally more atherogenic [10]. Non-HDL represents the cholesterol associated with atherogenic apolipoprotein B. About 25% of total cholesterol is contained in small dense LDL, and the remaining 75% is incorporated in LDL [11]. This proportion may vary in some individuals. Studies have reported that non-HDL and apolipoprotein B are better and more effective at predicting atherosclerosis and CVDs than LDL-C because non-HDL includes the cholesterol contained in VLDL, which participates to some degree in the occurrence of atherosclerosis [9,12].

2. Atherogenic Effect of Lipoproteins

A recently published meta-analysis demonstrated that apolipoprotein B is more accurate than non-HDL in forecasting cardiovascular disease, and non-HDL is more useful than LDL-C. [9]. They form a hierarchy with apolipoprotein B on the top, followed by non-HDL-C and LDL-C at the bottom. The study also showed that many cases would be saved at the early stages of CVDs if apolipoprotein B was introduced into clinical practice rather than depending only on LDL-C and HDL-C for evaluating different cases. Different lipoprotein particles can be classified based on the type of apolipoproteins they contain, as suggested by Lee and Alaupovic [9]. Apolipoprotein B-100 is the most significant atherogenic apolipoprotein found within LDL, IDL, and VLDL [10]. Multiple published cases of CAD patients have reported that levels of apolipoproteins are highly useful in assessing the risk for complications compared with other markers [10]. Several theories over the past 20 years proposed that oxidative stress, especially oxidation of LDL particles, might participate in the initiation of atherosclerosis, so we can use different plasma markers such as circulating...
oxidized low-density lipoproteins and the level of the autoantibodies generated against oxidized LDL to predict the risk of atherosclerosis in patients [12]. Autoantibodies generated against oxidized LDL have been linked to the development of atherosclerosis. Plasma circulating oxidized LDL has been considered along with other risk factors such as sex, age, total cholesterol, and HDL cholesterol, diabetes, smoking, and hypertension when calculating the global cardiovascular disease risk score [13,14]. Lipoprotein (a) particles have equal amounts of apolipoprotein A and apolipoprotein B. Almost every retrospective case-control study has found a link between high concentrations of lipoprotein (a) and cardiovascular diseases [15,16].

In a recently published study, several atherogenic lipoproteins were measured to conclude that high levels of small dense low-density lipoprotein cholesterol were the most beneficial parameter in predicting the risk of atherosclerotic heart disease compared with all the other markers [4,17-19]. Epidemiological studies show that diabetic patients with retinopathy have more CV events and deaths than those without retinopathy. Small dense LDL predicts not only CVD risk but also the use of laser treatment for retinopathy [20]. The number of LDL particles had a greater influence on LDL-TG levels than plasma TG levels. SdLDL-C was linked to metabolic syndrome risk factors, whereas LDL-TG was related to low-grade systemic inflammation [21]. Sekimoto T et al. demonstrates in the rapid transition of non-culprit coronary artery lesions and cardiac events after an acute coronary syndrome (ACS), Only the sd-LDL-c level (20.9 mg/dL) was remarkably associated with incident CEs at 31±17 months in 142 consecutive patients with Acute Coronary Syndrome who received the primary percutaneous coronary intervention(PCI/PTCA) for the culprit lesion [22]. The study is based on the notion that an LDL-C-to-apolipoprotein B (LDL/ApoB) ratio of 1.2 may forecast S-LDL incidence. The frequency of S-LDL particles (65%) and the close connection between LDL/ApoB and the Atherogenic index of plasma suggest that this ratio may be a prospective biomarker of increased risk of heart disease in type 2 diabetes patients [23]. Now, we will elaborate on the reason behind considering sdLDL-C as the best biomarker for assessing the risk of atherosclerosis and CVDs.

2.1. Small dense low-density lipoprotein (sdLDL).

A number of metabolic processes are involved in forming small dense LDL(Figure 1). Small dense LDL can be produced by metabolic channeling of large VLDL [24], lipolysis of dense intermediate LDL and large LDL by hepatic lipase [25,26], LDL alteration by cholesterol ester transfer protein (CETP) [27,28], or liver secretion into plasma. Small dense LDL contains modest levels of esterified and unesterified cholesterol and phospholipids, and its triglyceride content is comparable to or higher than that of large LDL. This decreased cholesterol level might result from the action by CETP [28,29].

Numerous experiments have demonstrated the atherogenic features of small dense low-density lipoproteins. sdLDL has a quite small size, making it easy for them to penetrate the arterial wall easily. They also possess a significant affinity for proteoglycans, a component of the arterial wall, which causes them to stick to the arterial wall and stay in the subendothelial space as long as possible [30,31]. Small, dense LDL particles also have a low affinity for LDL receptors than larger ones, delaying their clearance from plasma. Furthermore, sdLDL particles lack vitamin E, making them very susceptible to oxidation [31]. These properties account for the high atherogenicity of sdLDL particles [32,33].
Figure 1. Formation of sd LDL. Lipid transfer is governed by cholesterol ester transfer protein (CETP), while lipid hydrolysis is mediated by lipoprotein lipase (LPL) and hepatic lipase (HL). VLDL=very-low-density lipoprotein; B=apoB100, Tg=triglyceride, CE=cholesterol ester. Adapted from Sniderman et al. 1988

Small dense low-density lipoproteins are among the most important emerging biomarkers to predict the risk of CVDs [34]. An observational cohort study indicated that patients who experienced cardiovascular diseases had greater sd-LDL, LDL/HDL ratio, sd-LDL/LDL ratio, and higher HbA1c. Patients with CVDs were usually older and had comorbidities like diabetes mellitus (DM), hypertension, and greater Gensini coronary atherosclerosis scores. In the secondary prevention of stable coronary artery disease, these studies confirmed the importance of sdLDL as an emerging biomarker for forecasting future cardiovascular diseases. (CAD) [16].

2.2. Clinical significance of sdLDL in cardiovascular diseases (CVD).

Low-density lipoprotein-Cholesterol (LDL-C) levels are not always high in cases of the acute coronary syndrome [23]. A recently published study demonstrated that high levels of sdLDL-C almost always accompany coronary artery disease. The levels of small dense LDL-C are also elevated in patients with high risk for coronary artery disease, such as those with diabetes mellitus type 2 or MS [6]. As the result of all the previously mentioned studies, sdLDL-C levels are regarded as an alternative indicator for cardiovascular disease. They are acknowledged as a contributing factor to cardiovascular disease by the (NCEP III) [6,22]. These results were later supported by case-control and prospective studies. The concentrations of sdLDL-C were measured in 146 cases of coronary artery disease using the heparin-magnesium precipitation method. Approximately 26.8% of patients with coronary artery disease, who had LDL-C of less than 2.59 mmol/l, had serum sdLDL-C levels of more than 0.62 mmol/l. They all have increased total cholesterol levels, higher triglycerides, and decreased HDL-C levels. They reached a result stating that levels of serum sd-LDL are very valuable in predicting and explaining cardiovascular risk in cases of coronary artery diseases, particularly in patients with diabetes mellitus [22].

The high atherogenicity of small, dense LDL-C can be explained by their biochemical and biophysical features. They can easily penetrate the arterial wall due to their small size.
where they can act as a cholesterol and lipid storage source. Because they stay a long time in the circulation, their chance of undergoing atherogenic modifications in the plasma increases significantly. The exact role of sdLDL in the pathophysiology of atherosclerosis and other diseases has been the primary focus of many studies [35]. The role of the predominance of sdLDL (phenotype B) in cardiovascular diseases is well confirmed [36]. A new study has proven that SdLDL-C is a far better predictor of coronary artery disease than total LDL-C [37]. Another study suggested that high levels of sdLDL-C, not total LDL concentrations are a superior marker of coronary artery diseases in nondiabetic people. It was proposed by Shen et al. that even after adjusting other risk factors such as smoking, old age, male sex, and family history of cardiovascular diseases, sdLDL-C levels are the finest lipid markers for evaluating the risk of cardiovascular diseases using CA-IMT [28]. The link between small, dense low-density lipoproteins and cardiovascular diseases has been strongly supported by a large prospective study on 11,419 subjects using the direct enzymatic assay for sdLDL assessment [38]. Small, dense LDL levels were a good predictor of coronary artery diseases even when the cases were considered at very low risk of coronary artery disease depending on their LDL-C concentrations. Therefore, sdLDL-C levels can be considered of a life-saving value in assessing cardiovascular diseases and predicting CAD in apparently healthy individuals. Plaques in the carotid arteries are considered an indicator of atherosclerosis and are thought to be a major cause of atherosclerotic cardiovascular disease, especially ischemic strokes. Monitoring patients at high risk of having a stroke is crucial in creating better preventative techniques [28,39-41]. Small dense LDL appears to be entered into the arterial intima more quickly than larger LDL. Compared to larger LDL, small dense LDL has a large proportion of apoC-III and glycated apoB. Furthermore, an electronegative LDL species associated with endothelial dysfunction is found in the small dense LDL subclass. Under oxidative stress, the unsaturated cholesteryl esters in small dense LDL’s lipidome are extremely prone to hydroperoxide formation. [37]. The quality of LDL, not simply the quantity, is intimately associated with cardiovascular risk, and assessing sdLDL in clinical practice aids in identifying individual risk of developing cardiovascular events and directing appropriate preventative interventions [23].

2.3. Effects of lipid-lowering drugs such as statins and other medications on sdLDL-C levels.

After all these proofs, the role of sdLDL-C levels in the onset and progression of atherosclerosis and cardiovascular diseases is deeply confirmed. The preponderance of small, dense low-density lipoproteins is accompanied by high triglyceride and low HDL-C levels [3]. So, therapy aims to lower the levels of sdLDL-C and increase the levels of HDL-C. Statins are very commonly used lipid-lowering drugs to treat dyslipidemia in atherosclerosis and other associated diseases. Statin therapy increases the fraction of small dense LDL in total LDL particles rather than decreasing it while decreasing total LDL-C, absolute amounts of small dense LDL, and absolute amounts of large, buoyant LDL, as expected. [42]. High levels of sdLDL-C in obese patients can be treated with orlistat anti-obesity drugs and reduced caloric intake alongside lifestyle modifications. Liraglutide has been found to reduce carotid intima-media thickness by reducing small dense low-density lipoproteins [28]. In statin-treated CAD patients, the relationship between sdLDL-C and cardiovascular risk is evident, independent of LDL-C. High-dose treatment diminishes this risk in individuals with the highest baseline sdLDL-C. The relationship between sdLDL-C and cardiovascular risk is apparent in statin-treated CAD patients, independent of LDL-C, and high-dose statin therapy reduces this risk in individuals with the greatest baseline sdLDL-C [43].
3. Conclusions

Based on all the information and evidence mentioned in this article, we conclude that sdLDL-C is the lipoprotein parameter with the highest atherogenicity and one of the better biomarkers of incident ASCVD risk, compared with other markers such as total cholesterol, LDL-C, non-HDL-C, lipoprotein (a), triglycerides and apolipoprotein B. Although all these markers indicate a significant risk of atherosclerotic cardiovascular diseases, small, dense LDL-C is the only biomarker that provides all the crucial information needed to predict cardiovascular disease risk after adjusting all the variables. From our point of view, controlling sdLDL-C levels can be a life-saving step in lowering the incidence of atherosclerotic cardiovascular diseases, side by side with optimizing glucose level and blood pressure and quitting smoking. A necessary future step but a tough challenge is to develop a simple, standardized method to generalize the use of sdLDL-C levels as a marker of cardiovascular disease risk in clinical practice.

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Conflicts of Interest

The authors declare no conflict of interest.

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