Small Dense Low-Density Lipoprotein Cholesterol - The Atherogenic Molecule

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ABSTRACT

Multifactorial coronary artery disease (CAD), the commonest cause of mortality and morbidity world over is associated with various risk factors. Lowering of low-density lipoprotein cholesterol (LDL-C), thought to be the important target of therapeutic intervention has been proved to be not enough. Rather subfractions of LDL-C, that vary in their content, density and size, with different physic-chemical properties have been claimed to be associated with subclinical atherogenesis and risk of CAD with conflicting evidences. Small dense LDL-C (sdLDL-C), has been shown to be a predictor for future cardiovascular events in patients with coronary artery disease. There is also novel association of genetic variants with sdLDL-C which provides new insights into role of this gene with lipid metabolism. Therapeutic life style modification, in combination with new lipid lowering drugs after risk assessment for CAD have been suggested to reduce all LDL particle numbers and preferentially the sdLDL-C.

Keywords: Small dense low-density lipoprotein cholesterol (sdLDL-C), triacylglycerol, dyslipidemia, coronary artery disease

INTRODUCTION

LDL-C that represents a final stage in the catabolism of VLDL-C, is the major cholesterol carrying lipoprotein in the circulation. Its main component is cholesterol ester surrounded by amphipathic phospholipids and proteins with a single apolipoprotein, apoB100, that is critical for lipid transport. LDL-C was initially thought to be composed of particles differing slightly in size from one another with a mean particle size of 20-25nm and a peak density of 1.035g/ml. Various studies have identified that LDL-C can be fractionated by various methods like density gradient, PAGE, ultracentrifugation and NMR. (1-3)

As many as seven distinct subspecies of LDL-C has been indicated depending on their metabolic behavior and pathological roles. (4-6) Austin et al, have shown LDL-C particles to have a bimodal distribution and thus two phenotypes have been identified. A large and buoyant type called pattern A with LDL-C >25.5nm and a small and dense type called pattern B with LDL-C ≤ 25.5nm. (7) Also called the sdLDL-C. (7) LDL-C can also be subdivided into large, light LDLI(d 1.025-1.034g/ml) and small dense LDLII(d
Prevalence of sdLDL-C

sdLDL-C is seen in 15-25% of post-menopausal women, 30% adult men, and 5-10% in young population (<20 years). Its estimated heritability is 35-45%. Predominance of sdLDL-C has been linked to various genetic loci. The key quantitative trait loci for sdLDL-C is on chromosomes 3 and 4 with additional probable locus on chromosome 6. Interestingly women who become pregnant exhibit a temporary redistribution of LDL-C towards smaller sized particles. Abdominal obesity, weight gain, use of oral contraceptives, smoking and diet high in carbohydrates and low fat content predisposes to an increase in sdLDL-C formation. It is also elevated in patients with diabetes, renal disease and other disorders like pre-eclampsia. Therefore presently sdLDL-C is a new entrant in the list of other prime features of ‘insulin resistance’ or ‘metabolic’ syndrome. However, the most powerful condition is plasma triglyceride levels, with Kazumi T et al, observing that LDL-C size can be influenced by plasma triglyceride level even in the normal range.

In another study to test whether the predominance of sdLDL-C and increased triglyceride levels were independent risk factor for myocardial infarction, it was observed that, pattern B of LDL-C was found in 47% patients who later developed myocardial infarction, in comparison to 35% men who did not develop myocardial infarction. An appreciable increase in sdLDL-C has been observed in all familial disorders of lipoprotein metabolism like familial combined hyperlipidaemia, hyper-beta-lipoproteinemia, hypo-alpha-lipoproteinemia etc, which are related with augmented risk of premature coronary artery disease.

The pattern of raised triacylglycerols (elevated VLDL-C, very low density lipoprotein), low HDL-C, also termed as the atherogenic lipoprotein phenotype leads to a predominance of sdLDL-C. This partly transmissible trait is linked with greater cardiovascular risk. Nevertheless, LDL-C size assumes to be an imperative predictor of cardiovascular events. The National Cholesterol Education Program Adult Treatment Panel III has acknowledged sdLDL-C, to be a potential cardiovascular risk factor.

Generation and atherogenicty of sdLDL-C

sdLDL-C is not seen until plasma triacylglycerol levels exceed approximately 1.5mmol/L. Small, dense LDL is associated with a two times increase in plasma TG, higher plasma Apo B 100, reduced HDL-C and Apo AI concentration. sdLDL-C is not seen until plasma triacylglycerol levels exceed 1.5mmol/L. It is associated with a two times increase in plasma triacylglycerol, higher plasma Apo B 100, reduced HDL-C and Apo AI concentration. As plasma triacylglycerol levels rise, large VLDL-C (VLDL1) accumulates either due to overproduction by the liver or defective clearance by the circulation. TG rich VLDL-C particles get remodeled intravascularly to form the sdLDL-C particle with help of hepatic lipase(HL) and cholesterol ester transfer protein(CETP). CETP regulates by facilitating transfer of cholesterol esters and triacylglycerols between lipoproteins. Triacylglycerol enriched LDL-C is a good substrate for HL which removes the core lipid as well as surface lipid to promote a shift in particle size into the small dense range.
important role for HL in the lipolytic conversion has been corroborated by showing that hepatic lipase has a greater affinity for LDL-C and is positively correlated with plasma triacylglycerol, apolipoprotein B, as well as with mass of large VLDL-C and sdLDL-C, however it is not related with the mass of large LDL-C, (22,23) thus hepatic lipase plays an important role in this lipolytic conversion of triacylglycerol rich LDL-C. The strong association of LDL-C size and triacylglycerol is based on their significance as substrates for hepatic lipase and their reduction in size as LDL-C particles. Guerin M et al, have demonstrated that in type 2 diabetes patients, a favoured cholesteryl ester (CE) relocation takes place from HDL-C to sdLDL-C with an enhanced CE transfer from HDL-C to VLDL 1, contributing towards a greater extent of elevated sdLDL-C. (24)

Individuals with normal LDL-C levels also suffer from coronary artery disease (CAD) due to the characteristic atherogenic dyslipidemia of elevated triacylglycerol and sdLDL-C and reduced HDL-C. The altered properties of surface lipid layer having high oxidizability, low cholesterol, high PUFA and Apo B content leads to enhanced oxidative susceptibility and is an important factor for its atherogenicity. (25) Also sdLDL-C is cleared slowly by receptors as a result of conformational change due to structural change of Apo B. (26-28) Therefore, they remain for a longer time in plasma, giving more time for them to be oxidized and engulfed by macrophages in extravascular spaces. (28,29) sdLDL-C are taken up more easily by arterial tissue having a greater transendothelial transport and are more glycated, resulting not only in reduced uptake by receptors but also increased aggregation and binding to arterial proteoglycans, therefore building up their atherogenicity. This increased aggregation and binding to arterial proteoglycans is contributed to its sialic acid content of pattern B phenotype. (30,31) Small dense low-density lipoprotein has also been shown to be associated with increased fibrinogen(>2.9g/L), (32) and also with increased concentration of plasminogen activator inhibitor protein-1 (PAI-1). (21) Oxidised LDL-C stimulates PAI-1 release from endothelial cells which in turn inhibits fibrinolysis and thus increases the risk of coronary artery disease. (33,34) Berneis et al, using apoB transgenic mice found that sdLDL-C particles, due to its own intrinsic features has reduced metabolism and decreased intra as well as extravascular equilibration which contribute to greater atherogenicity of sdLDL-C. (35)

Relation of sdLDL-C with atherogenesis

The National Cholesterol Education Program Adult Treatment Panel III has accepted sdLDL-C as an emerging cardiovascular risk factor. (19) In the 13 year follow up Quebec Cardiovascular Study, sdLDL-C strongly predicted the rate of coronary heart disease independent of LDL-C. (36) LDL-C characteristics when investigated by polyacrylamide gel electrophoresis, sLDL showed the strongest association with the risk of IHD. Using multivariate logistic and survival models it was indicated that sdLDL-C was an independent risk factor for coronary heart disease. (37) The Epic Norfolk Study observed that sdLDL-C is related with reduced survival rates. (38) A recent case control analysis from the Framingham Offspring study showed sdLDL-C/LDL-C ratio was significantly higher in subjects with coronary artery disease (CAD) than in those without CAD. (39) A number of studies have reported that sdLDL is strongly associated with cardiovascular diseases (CVD) (40-45) The Suita study, which assessed a prospective cohort study of a
Japanese urban general population, reported that increases in sdLDL-C were significantly associated with the onset of CVD, especially myocardial infarction, independently of LDL-C. (40)

However as sdLDL-C was metabolically linked to lipids like triglycerides, many studies also pointed out that LDL-C size was not completely independent of lipids especially triglycerides. Capell et al in their study observed comparable LDL-C-triacylglycerol in the phenotype A and B population, after adjustment of LDL-C-triacylglycerol for plasma triglyceride concentration. (46) While investigating the association of cellular carotid plaque composition with cholesterol concentrations in lipoprotein sub-fractions, reported that it was the cholesterol content in the sdLDL fraction, and not the plasma LDL-C or HDL-C positively correlated with the macrophage content, while it negatively correlated with smooth muscle cell content. This suggests that increased cholesterol in sdLDL is associated with unstable plaque. (44)

A sub-analysis of the HDL-Atherosclerosis Treatment study, in patients with CAD showed that on-study sdLDL concentrations were related to coronary atherosclerosis progression and cardiovascular events. (45) Similarly Nishikura et al, demonstrated sdLDL to play an important role in cardiovascular disease progression and a promising biomarker to predict future cardiovascular events, making sdLDL/LDL-C ratio an important residual risk in secondary prevention. (47) Also epidemiological studies like the Atherosclerosis Risk in Communities (ARIC) Study, have shown than sdLDL-C was significantly associated with increased risk for CHD. However, it was not an independent predictor of incident CHD even after adjustment for other lipid factors. (48) Role of therapeutic drugs on LDL-C size

Treatment of atherogenic lipid profile starts with lifestyle modifications followed by use of lipid lowering drugs that decrease total cholesterol, LDL-C and increase HDL-C. The most common drugs used are statins and fibrates, however niacin and resins are also used.

Statins reduce the hepatic cholesterol synthesis, by affecting the rate limiting enzyme HMG CoA reductase. These drugs lower intracellular cholesterol, increase LDL-C receptor and accelerate removal of LDL-C and triacylglycerol rich lipoprotein. (49-51) Treatment with atorvastatin and fluvastatin seems to be more beneficial where they shift the LDL-C profile more towards buoyant particles. (52,53) Fluvastatin has been shown to improve endothelial dysfunction by decreasing the small dense LDL-C fraction in post-menopausal overweight female population. (54) Pravastatin and simvastatin have shown mixed results with some studies showing favourable alteration in LDL-C size, but not in others. (55-59) Mipomersen, a second generation, antisense oligonucleotide that inhibits human apolipoprotein(apo-B)-100 production, preferentially reduces the small LDL particles and has less effect on large LDL particles. (60,61)

In comparison to statins, fibrates like fenofibrate, bezafibrate and gemfibrozil appear to have more consequences on LDL-C size and shift it towards the buoyant size. (62-64) These are also effective in treating patients with raised triglyceride and reduced HDL-C. (37) Both the study groups i.e., Helsinki Heart Study and the Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trials Study, have reported a reduction of CHD risk, due to a modification of LDL-C size, when treated with fibrates. (65-68) Niacin has been shown to be effective to reduce triacylglycerol and increase HDL-C as well as LDL-C concentration and LDL particle size with
some adverse effects. (69,70) Role of ezetimibe on sdLDL-C size and concentration is debatable. (71) In type-2 DM, thiazolidinedione alter both LDL-C number and size of LDL-C showing their effect on metabolic syndrome. (72,73)
Combination therapy with different drugs can be used to reduce cardiovascular risk by modulating sdLDL-C, as a second line of treatment after physical therapy and dietary modification.

CONCLUSION
With evidence of a negative correlation with plasma HDL-C and positive association with plasma triglyceride level, sdLDL-C is linked with metabolic syndrome and elevated risk for cardiovascular disease. Preponderance of sdLDL-C has been acknowledged as a reason behind rising cardiovascular risk factor by the National Cholesterol Education Programme Adult Treatment Panel III. However when the concentration of both large and sdLDL-C are taken into consideration, both of them are linked with subclinical atherosclerosis independent of each other, conventional lipids as well as the known risk factors having no association between LDL-C size and atherosclerosis. Therapeutic alteration of LDL-C particle size or number has been of advantage in reducing risk of cardiovascular events. Decreased LDL-C particle size can be normalized by a change in life style, and the use of available drugs such as fibrates, statins and even those with the ability to improve insulin resistance. However the rational combination of lipid lowering agents along with life style modification with diet and physical activity targeting towards risk profile must be justified for etiological and economical reasons.

REFERENCES


31. Soran H, Durrington PN. Susceptibility of LDL and its subfractions to glycation.


O’Keefe JH Jr, Harris WS, Nelson J, Windsor SL. Effects of pravastatin with niacin or magnesium on lipid levels and postprandial lipemia. Am J Cardiol 1995 Sep 1; 76(7):480-4. DOI:http://dx.doi.org/10.1016/S0002-9149(99)80134-9


70. Knopp RH. Evaluating niacin in its various forms. Am J Cardiol 2002; 86 (12A): 51L- 56L.DOI:http:// dx.doi.org/10.1016/S0002-9149(00)01471-5


72. Khan M A, St Peter JV, Xue JL. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type-2 diabetes who were previously treated with troglitazone. Diabetes Care 2002; 25: 708-711. doi: 10.2337/diabetes.25.4.708

73. Hanefeld M. The role of pioglitazone in modifying the atherogenic lipoprotein profile. Diabetes ObesMetab 2009; II: 742- 756. DOI: 10.1111/j.1463-1326.2009.01048.x