Small, dense LDL: an update

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Abstract: PURPOSE OF REVIEW: In this review, we summarize the latest findings on small, dense LDL (sdLDL) atherogenic particles, including their associations with other biomarkers. RECENT FINDINGS: Increased sdLDL levels have been reported not only in different metabolic disorders such as diabetes, obesity and metabolic syndrome, but also in patients with rheumatoid and psoriatic arthritis as well as hypothyroidism. A wide range of lipid-lowering, as well as other drug classes, including novel antidiabetic agents and nutraceuticals, exert favourable effects on these atherogenic particles. The 'gold standard' methodology for the assessment of sdLDL has not been established yet. However, the association between sdLDL and several biomarkers could facilitate their assessment. SUMMARY: Estimation of sdLDL in daily clinical practice may help with the identification of patients at high cardiovascular risk and further contribute in directing specific interventions to prevent and/or decrease such risk.

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Small, dense LDL: an update

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In this review, we summarize the latest findings on small, dense LDL (sdLDL) atherogenic particles, including their associations with other biomarkers.

Recent findings
Increased sdLDL levels have been reported not only in different metabolic disorders such as diabetes, obesity and metabolic syndrome, but also in patients with rheumatoid and psoriatic arthritis as well as hypothyroidism. A wide range of lipid-lowering, as well as other drug classes, including novel antidiabetic agents and nutraceuticals, exert favourable effects on these atherogenic particles. The 'gold standard' methodology for the assessment of sdLDL has not been established yet. However, the association between sdLDL and several biomarkers could facilitate their assessment.

Summary
Estimation of sdLDL in daily clinical practice may help with the identification of patients at high cardiovascular risk and further contribute in directing specific interventions to prevent and/or decrease such risk.

Keywords
cardiovascular risk, lipid-lowering therapies, small, dense LDLs

INTRODUCTION

Small, dense LDL (sdLDL) particles are associated with an increased cardiovascular risk [1] that further extends the individual risk assessment beyond the traditional risk markers in patients with dysglycaemia [2], obesity [3] or different ethnicities [4]. LDL particles transport lipids as well as carry proteins involved in inflammation and thrombosis, and the sdLDL proteome in diabetic individuals differs significantly from that of larger LDL [5]. Further, a lipid profile with a prevalence of sdLDL is associated with cardiac autonomic neuropathy in diabetic women [6]. Some studies also report elevated sdLDL-cholesterol (sdLDL-C) concentrations in chronic kidney disease patient [7]. Thus, sdLDL, together with other clinical parameters, may have a predictive role in screening as well as provide a novel approach in lipid management and further cardiovascular benefit [8], potentially becoming a new therapeutic target.

In this review, we summarize the latest findings on these atherogenic particles, including their associations with other biomarkers.

PREDICTIVE ROLE OF SMALL, DENSE LDL

The association between sdLDL and different cardiovascular risk markers has not been thoroughly investigated. One prospective longitudinal cohort study in 39 patients with (pre)diabetes with a follow-up of 2 years showed that the proportion of sdLDL particles and changes in this proportion are predictive of changes in carotid intima–media thickness (cIMT) and insulin resistance. There was also an association with other determinants of an adverse metabolic status (e.g. serum resistin levels increased with the increasing in sdLDL, whereas serum adiponectin increased only in patients with unaltered sdLDL) [2]. On the other hand, the change in flow-mediated dilation was predicted by LDL-C levels [2]. Thus, sdLDL-C may be a useful risk marker when assessing changes in cIMT, including Japanese and Chinese populations [9,10], as well as in the risk assessment for atherosclerotic disease in patients with psoriatic arthritis [11]. Consecutive studies

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KEY POINTS

- sdLDL is a determinant of atherosclerosis associated with different traditional risk markers in a wide range of metabolic disorders.
- The evidence supports favourable effects of different lipid-lowering, as well as other drug classes on these atherogenic particles.
- Estimation of sdLDL, together with other clinical parameters, may have a predictive role in the identification of patients with cardiovascular risk. sdLDL might also provide a novel approach in lipid management with specific interventions for cardiovascular prevention and by decreasing residual cardiovascular risk after use of standard and/or novel lipid-lowering drugs.

regarding peripheral arterial disease extended the predictive value of sdLDL, which was shown to be able to predict the early outcome of angioplasty [12].

The ratio (LDL3-to-LDL6)/LDL1 is proposed as a marker for evaluating lipid metabolic status in patients with the metabolic syndrome (MetS) [13]. Among different MetS components, only increased triglyceride level was a differentiating factor for sdLDL-C concentration and sdLDL-C/LDL-C ratio in both sexes, with or without MetS [14]. However, this trend was not seen, unexpectedly, in youths with recent-onset type 2 diabetes (T2DM) (TODAY study) [15].

Compared with simple steatosis, nonalcoholic steatohepatitis (NASH) patients have increased levels of sdLDL that may, at least partly, explain the increased risk for atherosclerosis and cardiovascular diseases in these patients [16▪]. In this context, LDL migration index, an indicator of sdLDL, was higher in patients with NASH compared with those with nonalcoholic fatty liver diseases [17].

sdLDL is an important correlate of atherosclerosis in postmenopausal women, and it has been shown that a decrease in antioxidant capacity of paraoxonase1 (PON1), a HDL-associated enzyme that prevents oxidative modifications in LDL and HDL is associated with an increase in sdLDL-C in these women [18]. On the other hand, although it is clear that lower LDL peak diameter and a predominance of sdLDL are associated with T2DM, it is unclear whether they are a risk factor for gestational diabetes mellitus (GDM) [19]. Apolipoprotein E4 genotype has been shown to be associated with increased total cholesterol (TC) and LDL-C during pregnancy, with a reversible remodelling of LDL to smaller particles, which may further indicate a predisposition to atherosclerosis [20]. The atherogenic lipid profile in both prepregnancy and pregnancy period may help identify women at risk and prevent GDM [21,22].

EFFECTS OF DIFFERENT DRUG CLASSES ON SMALL, DENSE LDL

High-dose statin therapy significantly reduced sdLDL and malondialdehyde-modified LDL-C components of atherosclerotic lipoproteins, as oxidized-LDL (oxLDL) and remnant-like particle-C, without adverse events compared with low-dose statin therapy (The Standard versus high-dose therApy with Rosuvastatin for lipiD lowering trial) [23▪]. Patient-tailored atorvastatin therapy ameliorated atherogenic LDL particle size and inflammation, in addition to achieving the target LDL-C level without an undesirable effect on glycaemic control in patients with T2DM [24]. In addition, switching from atorvastatin (10 mg) to rosuvastatin (5 mg) may be a useful therapeutic option to reduce sdLDL-C levels in Japanese people with diabetes with hypercholesterolaemia [25]. Recently, it has been suggested that targeting distinct LDL subfractions may reduce the residual risk seen in patients taking statins [26].

It has been reported that the effects of the cholesterol ester transfer protein (CETP) variation on LDL subfraction could change in conditions such as coronary heart disease (CHD) and statin therapy. This was based on the findings [27] that the CETP rs708272 single nucleotide polymorphisms together with statin therapy may show a favourable effect on antiatherogenic LDL-1 and large-LDL subfractions in CHD patients with an atherogenic effect on large LDL subfraction in healthy patients.

The effectiveness of ezetimibe on LDL subfractions is controversial [28], although some studies reported that ezetimibe alone and in combination with statin reduced atherogenic sdLDL in patients with T2DM and glucose intolerance as well as in patients with insulin resistance [29]. As an add-on therapy to statins, ezetimibe reduced sdLDL-C-related residual risk of cardiovascular disease without affecting absorption of supplemental eicosapentaenoic acid (EPA) in patients with coronary artery disease [30]. Ezetimibe/simvastatin combination represents a well tolerated and efficacious choice for dyslipidaemia treatment in high-risk patients based on positive results of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial [31].

Cilostazol, a selective inhibitor of phosphodiesterase type 3, improves the proatherogenic lipid profile in patients with peripheral arterial disease or T2DM [32]. However, whether such treatment exerts

clinically relevant effects in high-risk patients remains to be established by future studies.

The association of sdLDL with a novel regulator of LDL metabolism, proprotein convertase subtilisin kexin type 9 (PCSK9), is still unclear. It has been demonstrated that plasma sdLDL-C are positively related to PCSK9 in patients undergoing coronary angiography, suggesting an interaction between sdLDL-C and PCSK9 in CHD [33▪].

Significantly, baricitinib, a drug for the treatment of rheumatoid arthritis, led to a mean increase in LDL-C increasing large and reducing sdLDL particles [34].

After glimepiride treatment in addition to dipeptidyl peptidase-4 (DPP-4) inhibitors, LDL-C and sdLDL levels decreased, whereas after mitiglinide/voglibose fixed-dose combination LDL-C levels did not change, but sdLDL and sdDL/LDL-C decreased and LDL-C/apoB increased significantly. Such differences after treatment with these two agents in addition to DPP-4 inhibitors have been suggested to be related to fluctuations in blood glucose levels [35].

Very recently, it has been reported that a sodium/glucose cotransporter 2 inhibitor, dapagliflozin, decreases atherogenic sdLDL-C and increases HDL2-C [36▪]. LDL-C levels were elevated by dapagliflozin; however, this was due to increased concentrations of the less atherogenic lb LDL-C. Such findings were not seen after treatment with DPP-4 inhibitor, sitagliptin [36▪].

EFFECTS OF NUTRACEUTICALS ON SMALL, DENSE LDL

Bedard *et al.* [37] highlighted the importance of considering sex in cardiovascular benefits of the consumption of Mediterranean diet (MedDiet) on LDL Particle Size Distribution and Oxidation, because only men experienced a favourable redistribution of LDL subclasses, whereas an opposite trend was observed in women. Similarly, only men experienced a reduction in cholesterol concentrations among sdLDL, whereas oxLDL were reduced with no sex difference [37].

Lower sdLDL-C concentrations have been reported after 12-week supplementation with flaxseed oil, a rich source of alpha-linolenic acid [38]. Four-week supplementation with curcuminoids, polyphenolic compounds with diverse potential cardioprotective functions, was not associated with changes in sdLDL concentrations [39], whereas a beneficial effect of chitosan on LDL subclasses, with a significant increase in LDL-2 particles and a decrease (although not significantly) in atherogenic sdLDL, was found [40].

Avocados are known as a nutrient-dense source of monounsaturated fatty acids (FAs) that can be used to replace saturated FAs in a diet to lower LDL-C. Inclusion of one avocado per day as part of a moderate-fat, cholesterol-lowering diet, has beneficial effects on cardiometabolic risk factors that extend beyond their heart-healthy FA profile, especially for sdLDL [41]. In addition, the combination of a standard diet with Armolipid Plus; MEDA-Rottapharm S.p.A. (Monza, Italy) treatment (nutraceutical combination of red yeast rice extract, berberine, policosanols, folic acid, coenzyme Q10 and astaxanthin) in patients with familial combined hyperlipidaemia was able to reduce the LDL score and increase LDL particle diameter after only 8 weeks of treatment [42▪].

Dietary supplementation with marine n-3 polyunsaturated FAs may have a beneficial effect on sdLDL particles, but had no effect on LDL density or sdLDL levels in patients with end-stage renal disease [43▪]. On the other hand, the lipid effects of two different prescription omega-3 FA therapies [omega-3-acid ethyl esters (EPA and docosahexaenoic acid 4 g/day and then switched to icosapent ethyl (high-purity EPA ethyl ester) 4 g/day] are described as well tolerated in a 55-year-old statin-treated and niacin-treated woman with severe dyslipidaemia and high cardiovascular risk, with improvements maintained over 2 years [44]. Approximately, 28 months after switching to icosapent ethyl, LDL-C, triglycerides, non-HDL-C and TC decreased, whereas HDL-C increased. Importantly, total and sdLDL particle concentrations decreased by 60 and 59%, respectively [44].

Recently, the effects of considerable weight loss and intensive exercise training on lipid atherogenicity and low-grade inflammation were estimated in a high-risk population with CHD. A low-energy diet (LED) and 12 weeks' aerobic interval training decreased total and LDL lipoprotein. LED was superior in decreasing atherogenicity (shift in density profile and increased particle size), whereas the effect on low-grade inflammation was limited [45▪]. Other studies could show that exercise training increases the proportion of large LDL particles even in the context of an unfavourable diet with fructose [46], which is known to reduce LDL particle size in nonexercising patients [47].

COULD OTHER BIOMARKERS HELP ESTIMATE THE LEVELS OF SMALL, DENSE LDL?

A potential new link between lipid metabolism dysregulation, innate immunity and atherosclerosis

has been suggested as atherogenic sdLDL is associated with an increase of nonclassical monocytes and a decrease of monocytes [48]. In addition, plasma resistin and peripheral blood mononuclear cells (PBMCs) resistin mRNA were significantly higher in CHD patients with a proportion of sdLDL particles at least 50%, compared with the group with proportion of sdLDL particles less than 50%. Such findings indicate that increased gene expression of resistin in PBMCs and higher resistin levels in plasma are related to proatherogenic LDL particle phenotype [49]. Yet, multiple linear regression analysis revealed LDL particle diameter as the only independent predictor of resistin mRNA.

Yu *et al.* [50] investigated the serum levels of beta2-glycoprotein I-LDL (β2-GPI-LDL) and oxLDL in patients with T2DM and further evaluated the associations between these two parameters *in vivo* and with the presence of diabetic microvascular complications. The authors concluded that elevated serum β2-GPI-LDL levels may be a serological hallmark of enhanced LDL oxidation *in vivo* and closely associated with the presence of diabetic microvascular complications [50]. Further, lipoprotein-associated phospholipase A(2) may be a novel biomarker for the presence of rupture-prone atherosclerotic lesions in elderly patients, whereas its level in diabetic patients may accompany the higher sdLDL particles levels [51].

Obstructive sleep apnea (OSA) is associated with dyslipidaemia and increased cardiovascular risk, and the effects of apoE genotype on both LDL and HDL particle size and lipid subclasses were assessed recently in 181 patients with OSA [52▪]. Both the apoE genotype and MetS are independently related to smaller LDL size in patients with OSA. Of interest, LDL size was independently predicted not only by apoE genotype, but also by male sex, and the presence of MetS.

The mean platelet volume (MPV) and red cell distribution width (RDW) have attracted interest because of their association with an increased cardiovascular risk. Therefore, Kucera *et al.* [53] aimed to determine if an association exists among MPV, RDW and lipoprotein subfractions, and to show the impact of statin therapy on these new possible biomarkers of atherosclerotic risk. Forty patients with hypercholesterolaemia, without previous hypolipidaemic treatment, were enrolled and treated with atorvastatin (40 mg/day for 12 weeks). Values of MPV and RDW seem to reflect a proatherogenic lipoprotein profile represented by the presence of sdLDL-C [53].

It has been shown that in overweight T2DM patients, triacylglycerol/HDL ratio, a surrogate marker of LDL particle size (small, dense), could be used as a reliable marker for insulin resistance [as measured by HomeOstasis Model Assessment for estimating insulin resistance (HOMA-IR)] with thyroid comorbidity (as measured using free thyroxine [T4]), while small dense LDL particles could represent a link between insulin resistance and thyroid disease [54].

CONCLUSION

The literature indicates that sdLDLs play a role in the atherosclerotic process, may have a predictive role in different cardiometabolic states and interact with several traditional cardiovascular markers. Clinical estimation of these atherogenic particles may represent a fundamental marker in prompt assessment of a high cardiovascular risk, but also might help in designing effective treatment options. Future studies will establish if a decrease in sdLDL can improve cardiovascular and/or residual risk after use of standard and/or novel lipid-modifying therapy, including natural supplements.

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Conflicts of interest

The authors have given talks, attended conferences and participated in advisory boards and trials sponsored by various pharmaceutical companies.

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