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Is sdLDL a valuable screening tool for cardiovascular disease in patients with metabolic syndrome?

Radwa Momtaz Abdelsamie Zaki Khalil [a,*], Dalia Ahmed Mohamed Al-Azab [b], Ola Abdelmoneim Akl [c]

[a] Cardiology and Angiology Department, Faculty of Medicine, Alexandria University, Egypt
[b] Anesthesia and Surgical Intensive Care Department, Faculty of Medicine, Alexandria University, Egypt
[c] Primary Health Care Department, High Institute of Public Health, Alexandria University, Egypt

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ABSTRACT

Many patients with cardiovascular disease have their low density lipoprotein cholesterol within normal range. This raises the question about the most important lipoprotein to use as a marker of atherogenecity. In fact, small dense low density lipoprotein has recently been suggested as a strong predictor of cardiovascular disease. Among high risk patients, those with metabolic syndrome represent an important target population.

Different methods of small dense low density lipoprotein measurement were developed. Accordingly, two phenotypes of low density lipoprotein are recognized: Phenotype A (predominance of large buoyant low density lipoprotein) & phenotype B (predominance of small dense low density lipoprotein). However, none of the methods has been yet considered as a gold standard one. A lot of studies confirmed the role of small dense low density lipoprotein in the development of cardiovascular disease through atherogenic properties & clinical trials. However, others failed to do so. These discrepancies may be due to different sample sizes, different populations, different age groups, different methods of measurement & other possible confounding factors.

The aim of this review is to discuss the role of small dense low density lipoprotein as a valuable screening/preventive tool of cardiovascular disease in patients with metabolic syndrome.

Contents

Abbreviations: AAA, abdominal aortic aneurysm; AACE, American Association of Clinical Endocrinologists; ACS, acute coronary syndrome; AIS, acute ischemic stroke; ALP, atherogenic lipid profile; ARIC, atherosclerosis risk in communities; BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular diseases; DGU, Density Gradient Ultracentrifugation; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; GGE, gradient gel electrophoresis; GH, growth hormone; HDL, high density lipoprotein; HIV, human immunodeficiency virus; HT, hypertension; IDF, International Diabetes Federation; IMT, intima media thickness; IR, insulin resistance; KHGS, Korean Health and Genome Study; LDL, low density lipoprotein; LDL-C, Low Density Lipoprotein Cholesterol; LDL I, large buoyant LDL; LDL II, intermediate density LDL; LDL III, smaller dense LDL; MetS/MS, metabolic syndrome; NCEP:ATP III, National Cholesterol Education Program Adult Treatment Panel III; NMR, Nuclear Magnetic Resonance Spectroscopy; PCOS, polycystic ovary syndrome; PVD, peripheral vascular disease; RCTs, randomized controlled trials; SCORE, Systematic Coronary Risk Evaluation; sdLDL, small dense low density lipoprotein; sd-LDL-C, small density LDL-cholesterol; T2DM, type 2 diabetes mellitus; VAP, Vertical Auto Profile; VLDL, very low density lipoprotein; WHO, World Health Organization; WHR, waist–hip ratio.

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* Corresponding author at: 15, Mohammed Amin Shoheb Street, Mostafa Kamel, Alexandria, Egypt.
E-mail addresses: radwa_momtaz@yahoo.com (R.M.A. Zaki Khalil), dr.dalia2014.da@gmail.com (D.A.M. Al-Azab), ola_akl@yahoo.co.uk (O.A. Akl).

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1. Introduction

1.1. Cardiovascular diseases: Definition and epidemiological studies

Cardiovascular diseases (CVD) include any medical conditions concerning the heart and blood vessels**;** such as coronary heart disease (CHD), strokes, peripheral vascular disease (PVD), and abdominal aortic aneurysm (AAA). Cardiovascular diseases are the main cause of morbidity and mortality worldwide. About 17.5 million people died from CVD in 2005. Among them, 7.6 million deaths were due to CHD and 5.7 million were due to stroke. We should be careful as regards progression of CVD, because about 20 million CVD deaths were estimated in 2015.[1] Many studies suggest that metabolic syndrome (MetS/MS) cases are more liable for future development of CHD and type 2 diabetes mellitus (T2DM).[2]

1.2. Definition of metabolic syndrome

Different definitions of MetS were established. According to National Cholesterol Education Program: Adult Treatment Panel III (NCEP: ATP III), MetS is defined by three or more of the following: waist circumference <_102 cm in men (or >_88 cm in women), triglycerides >_150 mg, high density lipoprotein (HDL) <40 mg/dl in men (or <50 mg/dl in women), fasting plasma glucose >_110 mg/dl, blood pressure >_130/85 mmHg.[3,4] According to the World Health Organization (WHO): Metabolic syndrome is defined by insulin resistance (identified by 1 of the following: T2DM, impaired fasting glucose, impaired glucose tolerance or for those with normal fasting glucose levels (<110 mg/dl), glucose uptake lower than the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions) plus any two of the following parameters: body mass index (BMI) > 30 kg/m^2, waist–hip ratio (WHR) > 0.9 in men (or >0.85 in women), triglycerides >_150 mg/dl, low HDL (<35 mg/dl in men or <39 mg/dl in women), blood pressure >_140/90 mmHg or antihypertensive medication, urinary albumin excretion rate >_20 μg/min or albumin:creatinine ratio >_30 mg/g.[5] Metabolic syndrome can be defined (according to the International Diabetes Federation (IDF)) by obesity, given as waist circumference <_94 cm in men (or <_80 cm in women) for Europeans, plus at least two of the following parameters: triglycerides <_150 mg/dl or treatment for hypertriglyceridemia, HDL < 40 mg/dl in men (or <50 in women) or treatment for this lipid abnormality, fasting plasma glucose (mg/dl) > 100 or diagnosis of diabetes mellitus, blood pressure <_130/85 mmHg or treatment for hypertension.[3] It should be noted that a lot of cases of metabolic syndrome are asymptomatic. They only present lately by symptoms of diabetes.[6]

1.3. Low density lipoprotein subclasses, phenotypes, reference values and methods of measurement

Some studies have shown that the use of hypolipidemic agents reduces CVD risk through the modification of Low density lipoprotein (LDL) particle size; however, the use of statins was associated with reduction rates of CVD less than 30%. To get better reduction rates, we should concentrate on the "**beyond cholesterol**" concept.

Low density lipoprotein particles include three subclasses (LDL I–III), LDL I (large buoyant LDL), LDL II (intermediate density LDL), and LDL III (smaller dense LDL). Different laboratory procedures can be used to separate LDL subclasses. Among them ultracentrifugation and electrophoresis have been mostly used for determining LDL subclasses**.** However, none of these methods has been established as a "gold standard" one.[7,8]

In fact, Gradient Gel electrophoresis (GGE) was considered as an important criteria of CHD risk. However, there is inadequate evidence that LDL subclassification by GGE improves outcomes in patients with CV disease.

Besides, as regards Density Gradient Ultracentrifugation (DGU), the Vertical Auto Profile (VAP) test measures the relative distribution of cholesterol within various lipoprotein subfractions, quantifying the cholesterol content in the VLDL, IDL, LDL, lipoprotein(a) and HDL subclasses. It includes LDL density and other components (i.e.pattern A versus pattern B).[9]

Concerning Nuclear Magnetic Resonance Spectroscopy (NMR), FDA clearance of NMR does not mean the test has clinical importance.[9] However, according to Mehta et al., measuring sdLDL by NMR were shown to be a strong predictor of CV events.[10]

In addition, the Ion-Mobility Analysis measures both the size and concentration of lipoprotein particle subclasses on the basis of gas-phase differential electric mobility.[9]

According to LDL particle size and density, the human lipid profile can be classified into two phenotypes: pattern A and pattern B. Pattern A is characterized by predominance of large buoyant LDL (LDL > 25.5 nm) and pattern B is characterized by predominance of small dense LDL (LDL $\leq$ 25.5 nm).[1,11,12]

Small dense low density lipoprotein (sdLDL) phenotype is expressed in adulthood as a result of genetic and environmental factors. Dyslipidemia, obesity and insulin resistance lead to expression of phenotype B.[4,12] For a given triglyceride level, women were found to have less sdLDL than men. On the other side, Korean males have a greater tendancy to develop a sdLDL phenotype than their Western counterparts.[13]

2. Atherogenic properties of small dense low density lipoprotein

Many experimental studies have explained the atherogenic properties of sd-LDL particles. Small dense low density lipoprotein particles have small size which enables them to penetrate easily into the arterial wall. They have also a high affinity for proteoglycans in the arterial wall, leading to prolonged residency in the subendothelial space.[4,8,14,15] Besides, the affinity of sd-LDL for LDL receptors is lower than larger LDL particles and its clearance from plasma is delayed.[4,14–17] Small dense low density lipoprotein particles are deficient in vitamin E and are highly susceptible to oxidization.[4,7,8,14,15] All these features explain the increased atherogenicity of small LDL subclasses.[1,7,8,13,18–20]

Table 1
Small dense low density lipoprotein as a predictor for cardiovascular disease.

Investigator/type of the study	Duration	Sample size	Results	Advantages	Limitations	Conclusion
Nishikura et al. Prospective cohort study[20]	7 years	258 males, 70 females (with angiographically documen-ted CAD)	– Those who experienced cardiovascular events had significantly higher sd-LDL level – Patients with sdLDL-C>/=35 mg/dl had significantly poorer prognosis (P = 0.012) (no significant difference was found when LDL > 100)	– Acceptable sample size – Acceptable duration of follow up	– Methode of measurment (MM) (heparin Mg precipitation) may affect the results – Confounding factors (hypertention, diabetes) may affect the results – Limited age group (between 54 and 76 years old) – Selection bias cannot be excluded	sdLDL is a promising biomarker to predict future cardiovas-cular events in the secondary prevention of stable CAD
Korean health and genome study (KHGS) Prospective cohort study[22]	8 years	626 participants of the Korean rural population	– Diabetes Mellitus (odds ratio 4.244, 95% confidence interval 1.693–10.640, P = 0.002) was the only predictive factor of CVD	– Participants were matched by age and sex to controls – Acceptable duration of follow up	– MM (TGE) may affect the results – Limited population – Samples had been kept at −70 C for several years; therefore we cannot exclude some degree of protein and/or membrane degradation – Limited age group (between 40 and 69 years old) – Data on the use of lipid-lowering agents are lacking	– Results should be confirmed by larger prospective cohort studies and randomized controlled trials, with better metho-dology

In 43 patients with diabetes, Woodman et al. related LDL size and the presence of oxidized LDL to **endothelial function** as assessed by the response in forearm blood flow to acetylcholine, bradykinin, and sodium nitroprusside. The acetylcholine response was positively associated with LDL size and negatively correlated with the plasma level of oxidized LDL.[13]

However, antioxidant strategies failed to prevent and to limit the atherogenesis in humans. This raised questions about the role of oxidative modification of LDL in atheromatosis.[1]

Another proposed mechanism suggest that: sd-LDL may induce the stimulation of plasminogen-activator-inhibitor 1 and accelerate thromboxane A2 synthesis.[7]

3. Small dense low density lipoprotein as a predictor for cardiovascular disease

Small dense low density lipoprotein is considered an important emerging risk factor for CVD.[1,8,21]

In an observational cohort study (details shown in Table 1), patients who developed cardiovascular events had higher sd-LDL level, sd-LDL/LDL ratio, LDL/HDL ratio & greater HbA1c. **Cardiovascular events** were death caused by CVD, onset of acute coronary syndrome (ACS), need for peripheral arterial and coronary revascularization, hospitalization for surgical procedure for any CVD, hospitalization for heart failure and/or for stroke. Those who experienced cardiovascular events were older, had higher prevalence of hypertension (HT) and diabetes mellitus (DM), significant higher Gensini coronary atherosclerosis scores. In conclusion, these results confirmed that **sdLDL is a very promising biomarker to predict future cardiovascular events in the secondary prevention of stable coronary artery disease (CAD)**.[20] However, **the Korean Health and Genome Study** (**KHGS**, a prospective cohort study) reported that **DM was the only independent predictive factor of CVD**.[22] ***The KHGS was conducted on a larger sample size and for a longer duration, compared to the study conducted by Nishikura et al. However, the KHGS study was limited to the Korean population, the samples might be altered and data on the use of lipid lowering agents were lacking. Therefore, the results should be confirmed by larger prospective cohort studies and randomized controlled trials (RCTs), with a better methodology. The results of these studies are further discussed in*** Table 1**.**

Also, according to a meta-analysis of twelve RCTs, a residual risk of major cardiovascular events was demonstrated despite usage of hypolipemic agents (statins).[23] ***This raises the question about the role of fibrates which target specifically the sdLDL.***

Besides, according to a longitudinal observational study, Small dense LDL cholesterol is a cardiovascular risk factor in several chronic inflammatory diseases.[24]

4. Clinical significance of small dense low density lipoprotein in coronary heart disease

Low Density Lipoprotein-Cholesterol (LDL-C) concentration is not always elevated in patients with ACS.[16]

Studies have shown that a **predominance of sd-LDL is closely associated with CAD**. Also, sd-LDL-cholesterol (small density LDL-cholesterol) concentrations are high in individuals **at a high risk for CAD, including patients with T2DM and MS**. Therefore, sd-LDL concentration is considered as a surrogate marker for CAD and is accepted as a risk factor for cardiovascular events by the (NCEP III).[7,8,12,15,25] Similar results were found in case-control and prospective studies.[11]

In a case-control study, the serum sdLDL was detected in 146 CAD patients + 207 control group using the heparin-Mg precipitation method. The 26.8% of CAD patients with LDL-C < 2.59 mmol/l have serum sdLDL-C > 0.62 mmol/l, and they are characteristic of higher total cholesterol, triglycerides and lower HDL-C. They concluded that the measurement of serum sd-LDL is valuable in explaining the residual cardiovascular risk in patients with CAD, especially those with DM.[26]

A case-control study was conducted on 194 consecutive patients with chest pain (which is considered of low to intermediate risk for significant coronary stenosis) who were referred for elective coronary angiography. The proportion of sdLDL was a

Table 2
Clinical significance of small dense low density lipoprotein in CHD.

Investigator/type of the study	Duration	Sample size	Results	Advantages	Limitations	Conclusion
Quebec study St-Pierre et al. Prospective cohort study[1,13,20,27]	13 Years	2072 men (French population of Quebec)	sdLDL: sdLDL (LDLc < 225A) is a strong and independent predictor of IHD in the first seven years of follow up. RR = 3.1(P < 0.001)	– Large sample size – Sex discrepancy was avoided – Acceptable duration of follow up	– MM (GGE) may affect the results – The association between sdLDL and IHD was attenuated after multivariate adjustment – Genetic and environmental variation	sdLDL is a very strong biomarker of IHD
Framingham Study Ai et al. Prospective cohort[7,28]		– 1680 female participants – 1508 male participants	In women: sdLDL was higher in patients with CHD (P = 0.0015) In men: sdLDL/LDL ratio was higher in patients with CHD (P = 0.0019)	– The study taked into account the gender difference and the difference between pre-menopausal and post-menopausal females – Acceptable duration of follow up	– The use of lipid-lowering agents may affect the results – MM may affect the results	– sdLDL is a very strong predictor of CHD in women – sdLDL/LDL ratio is a very strong predictor of CHD in men
Biracial ARIC Hoogeveen et al. Prospective cohort[29]	11 years	– 10,000 men and women – Include smokers, MetS, DM	sdLDL-C was associated with incident CHD. HR = 1.61; 95% CI. (P < 0.001)	– Large sample size – Acceptable duration of the study	– MM (new homogenous essay) may affect the results – Confounding factors in these patients	– sdLDL is very strongly correlated with CHD

strong univariate predictor of significant coronary artery stenosis evaluated by both methods: invasive coronaryangiography & CT based techniques. It was concluded that sdLDL particles may play a role in risk classification of patients with suspected angina pectoris.[19]

Findings from the **Quebec Cardiovascular Study c**onfirmed that sdLDL (LDLc < 255 Å) is a strong and independent predictor of CHD in the first seven years of follow up.[1,13,20,27]

Ai et al. quantified sd-LDL-C in 1680 female participants of the **Framingham Offspring Study** with or without CHD. Mean sd-LDL-C levels were higher in those with CHD compared to those without CHD (0.83 vs. 0.68 mmol/L, P = 0.0015) although they had the similar mean LDL-C levels (3.53 vs. 3.46 mmol/L, P = 0.543). Thus, sd-LDL-C measurement helps in the management of high-risk patients with CAD whose total LDL-C levels are not elevated. Unlike women, 1508 men with or without CHD in the same study had similar levels of mean sd-LDL-C (0.83 vs. 0.84 mmol/L, P = 0.609). However, the percentage of sd-LDL-C to total LDL-C was higher in those with CHD than in those without CHD (26.1% vs. 23.7%, P = 0.0019). This could be explained by the fact that men generally had more confounding factors than women, the ratio of sd-LDL-C to total LDL-C may be more valuable than the absolute concentration of sd-LDL-C.[7,28]

In a prospective cohort study, (the biracial ARIC study) plasma sdLDL-C levels were strongly correlated with an atherogenic lipid profile and were higher in diabetic patients than non-diabetic patients (49.6 versus 42.3 mg/dL; P < 0.0001). Even in individuals considered to be at low cardiovascular risk based on their LDL-C levels, the sdLDL-C was associated with incident CHD in atherosclerosis risk in communities (ARIC) study participants.[29] ***All of the previous studies confirmed the role of sdLDL as a predictor of CHD. However, The Framingham Offspring study showed that sdLDL /LDL ratio is a very strong predictor of CHD in men***; ***this might be attributed to the fact that men had more confounding factors. These studies are further discussed in*** Table 2***, taking into account the sample size, the gender, the duration of the study, the method of measurement, other possible confounding factors and the P value of the results.*** Besides, lipoprotein profiles that are relatively rich in sd-LDL particles are associated with up to a **3-fold greater risk** of myocardial infarction than those that mainly consist of large buoyant (lb)-LDL particles.[1,17]

5. Clinical significance of small dense low density lipoprotein in cerebrovascular strokes

Acute ischemic stroke (AIS) is an important cause of morbidity and mortality worldwide. In fact, logistic regression analysis showed that i**ncreased sdLDL was an important predictor for AIS onset** even when the other CVD risk factors were taken into consideration. Thus, it was concluded that measuring LDL particle size alone is not sufficient for accurate assessment of AIS risk.[15,30]

Zeljkovic et al. reported, according to Landray et al. study, a greater proportion of smaller LDL subfractions in cases with carotid atherosclerosis than in those with normal carotid arteries. Also, smaller LDL particles were associated with risk for carotid atherosclerosis.[15,31]

However, Zeljkovic et al. reported in a prospective cohort study analysis (including 200 patients and 162 controls) that patients who experienced strokes had a higher level of sdLDL **(P < 0.001).** It also reported that **early AIS mortalities had significantly higher amount of sdLDL particles (P < 0.05), underlining the importance of sdLDL during disease exacerbation**. An AIS patient with elevated level of sdLDL had 5.5-fold higher risk of dying during hospitalization, even when other confounding factors were adjusted. The limitations of this study were that: cases and controls weren't matched by the age and the sex, the number of cases of mortality was limited and the population was limited (Serbian population).[15]

So, sdLDL is an independent very strong predictor of incidence of cerebrovascular strokes. Also, it's a strong predictor of mortality by cerebrovascular strokes.

Furthermore, sdLDL-C may be a useful predictor in the assessment of CA-IMT in Chinese population: there was significant association between them after adjustment of traditional CVD risk factors. In addition, sdLDL was considered a better lipid variable than other standard parameters in assessing the risk of CVD using CA-IMT in healthy population. The limitations of this study were that**:** the cohort was relatively small and included only the healthy

subjects. Subjects with coronary risk factors or CVD are required. Finally, it is not possible to determine a cause and effect relationship between sdLDL-C concentrations and CA-IMT as this study was a cross-sectional one. Therefore, further studies are needed.[32]

6. Metabolic syndrome: an important target population

MetS is considered a major risk factor for CVD.[4] According to the American Association of Clinical Endocrinologists (AACE), patients with metabolic syndrome are at increased risk of cardiovascular disease.[33]

6.1. Risk assessment

The **10-year risk of fatal cardiovascular disease** (death caused by any arterial disease) can be estimated using the Systematic Coronary Risk Evaluation (SCORE) system**.** According to the **European Society of Cardiology (ESC)**, the **2012 guidelines** for cardiovascular prevention established that patients can be classified into four major groups: low risk (with a SCORE rating less than 1%, corresponding to a 10-year probability of cardiovascular mortality of less than 1%), moderate risk (with a SCORE greater or equal to 1% and less than 5%), high risk (subjects with markedly elevated one risk factor, as well as subjects with diabetes, moderate chronic kidney disease, or a SCORE rating greater or equal to 5% and less than 10%) and very high risk (those with documented cardiovascular disease, severe chronic kidney disease, diabetes associated with one (or more) cardiovascular risk factor(s), diabetes with eGFR (estimated glomerular filtration rate) less than 60 mL/min/1.73 m^2 or subjects with a SCORE rating greater or equal to 10%).[21]

6.2. Formation & significance of small dense low density lipoprotein in metabolic syndrome

Studies have demonstrated that pattern B lipid profile is associated with a **dyslipidaemic syndrome** (ALP: atherogenic lipid profile) which is characterized by elevated levels of **large triglyceride-rich** very low density lipoproteins (**VLDL**), **low HDL** levels, **high** levels of **small dense LDL**, and high hepatic lipase activity. The overproduction or the decreased clearance of VLDL is the key metabolic feature of the generation of sdLDL. These features are common in patients with diabetes and metabolic syndrome.[3,13]

Patients with **insulin resistance (IR) and central obesity** exhibit increased lipolysis and elevated levels of free fatty acids. This is the main feature in the pathophysiology of metabolic syndrome.[3]

Triglyceride levels and obesity are important factors that affect LDL particle size. In case of **hypertriglyceridemia**, Triglycerides are transferred from VLDL to HDL, then to LDL; while cholesterol is eliminated from LDL. This leads to the formation of **smaller denser LDL**.[12]

The generation of sdLDL particles seems to be related to the insulin resistance and hypertriglyceridemia; this can contribute to the significance of sdLDL in patients with the metabolic syndrome.[34]

6.3. Small dense low density lipoprotein as a predictor for cardiovascular disease in patients with metabolic syndrome

Accumulating evidence has shown that sd-LDL levels are increased in atherosclerotic disorders, including diabetes, dyslipidemia, MetS and cardiovascular disease.[1,7,8,16,18]

In a prospective 2-year follow-up study, conducted on subjects with metabolic syndrome and without overt CAD, sdLDL was found as a feature of the metabolic syndrome and an independent predictor for future cardio- and cerebro-vascular events. These findings may have potentially important consequences on the assessment and management of atherogenic dyslipidemia in this category of **high-risk patients** but should be confirmed by future prospective studies with larger sample size.[25]

According to the **Framingham Heart Study**, small LDL particle concentration augmented with the number of metabolic syndrome features and patients with the metabolic syndrome were more prone to cardiovascular events. However, it didn't succeed to prove a significant association between the concentration of small LDL and risk of cardiovascular disease. The discrepancy of this result with that in the **Quebec study** may be attributed to the loss of the discriminatory power of sdLDL in this group of high-risk subjects.[13,35] However, another study revealed that LDL particle size is rarely a significant and independent predictor of CAD risk in patients without MetS.[4]

Also, Packard et al. reported that, according to a multivariate analysis conducted by Berneis et al., **LDL size** is the variable **most strongly linked to the presence of CHD and to a positive carotid intima media thickness (IMT) measurement** (>1-mm thickness).[13,36] Similar results were reported by Gerber et al.[34] ***Therefore, the previous studies confirmed the role of sdLDL as a component of metabolic syndrome cases, as a predictor for insulin resistance, IMT and cardiovascular events in patients with MetS. However, the duration of these studies might be insufficient, selection bias cannot be excluded and the results should be confirmed by larger prospective cohort studies, and RCTs. Details are shown in*** Table 3**.**

In an observational study including 185 patients from South of Spain, it was reported that LDL particle size was smaller in males than females and that LDL particle size was **smaller in patients with MetS than in patients without MetS**. According to this study, predominance of sdLDLc was associated with an increased risk of CAD.[4]

Many studies have demonstrated an increased cardiovascular risk in patients with MS even before the development of overt hyperglycemia. An increase in sdLDL particles is strongly associated with an increased cardiovascular risk, both in patients with and without diabetes or metabolic syndrome, even when the traditional risk factors were taken into consideration.[34]

Besides, in a case-control study, the serum **sdLDL-C in the patients with CAD and T2DM is significantly higher** than that in the CAD without T2DM, 0.48 mmol/l versus 0.42 mmol/l, $p < 0.05$). It was concluded that the detection of serum sd-LDL could help in understanding the residual cardiovascular risk in patients with CAD, particularly when associated with DM.[26]

Similar results were found in a prospective cohort study: sdLDL level was measured in the biracial ARIC study using a new developed homogenous assay. Plasma **sdLDL-C** levels were strongly correlated with the **dyslipidemic syndrome** and were higher in patients with diabetes mellitus than non-diabetes mellitus (49.6 versus 42.3 mg/dL; $P < 0.0001$).[29] Furthermore, Hirayama et al. reported, according to Toledo et al.'s study, that cases with type 2 diabetes (associated to moderate or severe hepatic steatosis) had 25% and 72% higher sd-LDL concentrations than those without hepatic steatosis.[7,37]

Moreover, patients with metabolic syndrome or type 2 diabetes have an increased cardiovascular risk **despite optimal control** of other risk factors as **LDL-C**.[34] In addition, Inukai et al. study found that the strongest predictor of carotid artery IMT in 27 diabetic and 12 control subjects was the concentration of small LDL, independent of LDL size distribution, LDL cholesterol, HDL cholesterol or triglyceride.[13] Similar results were found by a prospective cohort study.[34]

In addition, a group of reports described the associations of **sdLDL with many metabolic disorders**, such as endocrine diseases, including growth hormone (GH) deficiency, polycystic ovary syn-

Table 3
SdLDL as a predictor for CVD in patients with metabolic syndrome.

Investigator/type of the study	Duration	Sample size	Results	Advantages	Limitations	Conclusion
Rizzo et al. Prospective cohort study[25]	2 years	732 cases of MetS, without overt CAD	sdLDL is a feature of MetS, and an independent predictor for future cardiovascular and cerebrovascular events (P < 0.0001)	– Large sample size – No age or gender was excluded	-MM (GGE) may affect the results. – Selection bias cannot be excluded – Results should be confirmed by larger prospective cohort studies and RCTs	sdLDL is a very promising screening tool of cardiovascular events in patients with MetS
Berneis et al. Prospective cohort study[13,36]	2 years	59 predia-betic patient (the majority of whom will have MetS+) men	sdLDL predicts the IMT (P = 0.003) and insulin resistance (IR) (P < 0.05)	Sex discrepancy (as a confounding factor was avoided)	– Limited sample size – MM (GGE) may affect the results – Selection bias cannot be excluded	sdLDL is a stong predictor of IMT and IR in patients with MetS
Sancho-Rodiguez et al. Observational study[4]	1 year	185 MetS cases + 72 controls from South Spain	– LDL particle size was significantly smaller in MetS patients (P > 0.001) – Predominance of sdLDL was associated with an increased risk of CAD	– Acceptable sample size – Male: Female ratio = 1:1	– The number of controls was less than cases – Genetic variation – Short duration	sdLDL is an important component of MetS, and a predictor of CAD in MetS cases
Framingham heart study Prospective cohort study [13,35]	1 year	112 CHD cases, from the Japanese Population	– MetS cases had a higher level of sdLDL (P = 0.042), and a higher rate of cardiovascular events (P = 0.0202: for stable angina, P = 0.0893: for acute coronary syndrome) – However, there was no discernable association between the abundance of sdLDL and the risk of MCV	Acceptable sample size	– Short duration – Genetic variation – Abdominal circumference wasn't measured – 60% received lipid lowering agents	– Results should be confirmed by further investigations taking into account the modified Japanese criteria of the definition of MetS

drome (PCOS), chronic kidney disease (CKD), liver diseases and human immunodeficiency virus (HIV) infection.[7]

However, the various study documented that **elevated LDL-C and increased ratio of LDL/HDL** is the most valuable lipid parameter making those individuals at risk for atherosclerosis.[1]

7. Conclusion

Small dense low density lipoprotein is a new emerging risk factor for cardiovascular diseases because it is more atherogenic than LDL. It can be used as a predictor of future cardiovascular events and in secondary prevention of stable coronary artery disease. sd-LDL can also predict mortality from AIS. It was found that patients with AIS who had elevated sd-LDL had 5.5-fold higher risk of dying during hospitalization. Several genetic and environmental factors affect LDL particle size, among these environmental factors dyslipidemia, obesity and insulin resistance, all lead to increased level of sd-LDL. Also production of sd-LDL is increased in metabolic syndrome .This can be explained by the presence of insulin resistance which is the key for pathogenesis of MetS.

8. Recommendations

- Small dense low density lipoprotein is a valuable screening tool of CVD in patients with MetS. Its use in early screening is admonished.
- Role of sdLDL in the risk assessment & the prevention of CVD must be confirmed by larger prospective cohort studies and RCTs.
- More studies are needed to assess the inclusion of the reference values of sdLDL in the new guidelines which defines the metabolic syndrome.
- Extensive researches are recommended to evaluate the predictive role of sdLDL in other metabolic disorders such as liver disease, polycystic ovary syndrome, growth hormone deficiency, chronic kidney disease and obstructive sleep apnea syndrome.
- The standardization of the methods of measurement of sdLDL must be investigated by further studies taking into account the availability & the cost of the test.

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