The Value of Small Dense Low-Density Lipoprotein Cholesterol in Predicting the Risk and Severity of Coronary Heart Disease in Patients with Type 2 Diabetes Mellitus

Juan Huang
Peking University International Hospital
Jun-Xu Gu
Peking University People's Hospital
Hui-Zhang Bao
Peking University People's Hospital
Shan-Shan Li
Peking University People's Hospital
Xiao-Qin Yao
Peking University International Hospital
Ming Yang
Peking University International Hospital
Yang Li
Peking University International Hospital
Ai-Min Zhang
Peking University People's Hospital
Yue Yin
Peking University People's Hospital
Na Zhang
Peking University People's Hospital
Mei Jia (jiamei00718@sina.com)
https://orcid.org/0000-0002-8270-2297

Original investigation

Keywords: small density low – density lipoprotein, coronary heart disease, type 2 diabetes mellitus

Posted Date: June 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-33374/v1

Abstract

Background: Elevated small density low – density lipoprotein cholesterol (sdLDL-C) particles are hallmarks of atherogenic dyslipidemia in patients with type 2 diabetes mellitus (T2DM), which is hypothesized to drive atherosclerotic risk. The present study aims to investigate the association between serum sdLDL-C level and the presence and severity of coronary heart disease (CHD).

Method: A total of 3684 consecutive patients with T2DM who received selective coronary angiography (CAG) were enrolled. The patients were subsequently divided into CHD and non-CHD groups according to results of CAG. The severity of CHD was evaluated by the number of stenotic, and the Gensini Score (GS).The patients were subsequently divided into four groups by the quartiles of sdLDL-C and evaluate the risk and severity of sdLDL-C and CHD.

Results: The sdLDL-C levels in CHD group were significantly higher than non-CHD group [0.80 (0.49) mmol/L vs 0.70 (0.30) mmol/L, P < 0.001]. The results from CHD subgroup analysis indicated that the patients with multiple-vessel disease and high GS had higher sdLDL-C levels compared with those in their matched subgroups (P < 0.05). By adjusting the confounding factors and analyzing by the multiple logistic regression, sdLDL-C had independent correlation with the presence and severity of CHD [CHD: OR = 2.757, 95%, CI = 1.662 - 5.364, P = 0.023; multiple-vessel disease: OR = 3.788, 95%, CI = 1.866 - 7.685, P = 0.026; High GS: OR = 3.054, 95%, CI = 1.944 - 5.699, P = 0.022].

Conclusion: In T2DM patients, the increase of sdLDL-C is related to the increase the prevalence and the severity of CHD. After adjustment for other risk factors, sdLDL-C was found to be an independent risk factor for CHD. Therefore, measuring sdLDL-C may allow for T2DM patients to predict the presence and severity of CHD.

Introduction

Coronary heart disease (CHD) is one of the most common diseases in the world and is associated with very high rates of morbidity and mortality[1–3]. Over the past decades, a large number of studies have examined the modifiable risk factors such as diabetes, hypertension, dyslipidemia, and smoking for the early evaluation of cardiovascular risks[4, 5]. Type 2 diabetes mellitus (T2DM) is a common metabolic disorder characterized by hyperglycemia and insulin resistance[6]. Dyslipidaemia in T2DM may exist alone or associate with metabolic syndrome, and thus increases cardiovascular risk[7, 8]. The typical pattern of diabetic dyslipidaemia consists of elevated low density lipoprotein cholesterol (LDL-C) triglycerides, low high density lipoprotein cholesterol (HDL-C)[9].

Plasma LDL-C is composed of a series of granules with different sizes, densities and chemical compositions[10]. In general, LDL-C with smaller particles and higher density is named as small dense low density lipoprotein cholesterol (sdLDL-C). On the contrary LDL-C with larger particles and smaller density is defined as large and light LDL-C; and the subcomponent between them is medium density LDL-C. Compared with LDL-C, sdLDL-C is thought to be more atherogenic[11, 12]. Evidences from basic and

clinical studies have shown that sdLDL-C is a pro-atherogenic risk factor for atherosclerosis and elevated levels of sdLDL-C may promote the development of CHD[13, 14]. However, the role of sdLDL-C in stable CHD patients, especially in patients with special disease status such as T2DM, has not been fully determined. Therefore, the aim of this study is to determine the relationship between sdLDL-C and the presence and severity of coronary heart disease in Chinese patients with T2DM.

Methods

Study population

One thousand eight hundred and forty-two Chinese Han patients (2152 males, 1532 females) from Peking University International Hospital and Peking University People's Hospital were sequentially enrolled between October 2015 to October 2019. All patients who were diagnosed with T2DM, which was defined according to the American Diabetes Association (ADA) criteria: 1) self-reported history of T2DM, 2) under current treatment of insulin or oral hypoglycemic medicine, 3) repeated fasting plasma glucose (FPG) 7.0 mmol/L, 4) glycated hemoglobin A1c (HbA1c) 6.5%.

The diagnostic criteria for patients with CHD are coronary angiography (CAG) performed in our institution and at least one major coronary artery occlusion or stenosis is found to be more than 75% and the severity of CHD was evaluated by Gensini score (GS) system. The diabetic patients were divided into non-CHD group and CHD group based on the results of CAG. The diabetic patients with CHD were classified into the GS tertiles: low GS (GS $\leq$ 25), intermediate GS (GS: 26–40) and high GS (GS $\geq$ 41).

Exclusion criteria included: 1) any known inflammatory or infectious disease, or confirmed or suspected cancer, 2) acute coronary syndrome within the previous six months, 3) percutaneous coronary intervention within the previous three months, 4) history of coronary artery bypass operation, 5) chronic heart failure, cardiomyopathy, valvular heart disease, 6) pulmonary heart disease, or 7) severe liver and kidney dysfunction.

Conventional clinical and laboratory indicator tests

Blood samples were collected in the morning after overnight fasting for at least 12 h. All measurements were performed within 6 h. FBG, homocysteine (HCY), hypersensitive C-reactive protein (hs-CRP), serum lipid profiles, including triglycerides (TG), total cholesterol (TC), LDL-C and HDL-C were determined on a Beckman AU5832 analyzer (Beckman Coulter Inc., USA). Apolipoproteins A-1 (apoA1), and B (apoB) were measured by immunoturbidimetry (Daiichi Pure Chemicals Co., Ltd., Tokyo). Lp(a) in the serum samples was measured using latex enhanced immunoturbidimetry Lp(a) kit (Roche Inc., Germany). Direct quantitative determination of sdLDL-C assay was done using sdLDL-C reagent kits (Denka Seiken Co., Ltd. Japan). Hemoglobin A1c (HbA1c) was measured using high-performance liquid chromatography technology (Trinity Biotech Inc., USA).

Statistical analyses

The distributions of all quantitative variables were analysed using the one-sample Kolmogorov-Smirnov test. Normally distributed data are reported as means ± standard deviations, and the differences between various groups were compared using the Analysis of Variance. Non-normally distributed continuous data were reported as medians (inter-quartile ranges), and the differences between various groups were compared using the Kruskal-Wallis test. Categorical data was presented as percentage (%) and compared by Chisquare test. Mantel-Haenszel test for linear trend was used to detect whether sdLDL-C levels was positively correlated with the CHD. The association of sdLDL-C with the presence and severity of CHD was analyzed by multivariate logistic regression adjusted for age, gender, BMI, glucose, HbA1c, ApoB, ApoA1, TC, TG, HDL-C, LDL-C, Lp(a), hs-CRP, and HCY. All data analyses were performed using SPSS version 22.0 for Windows (IBM Corp., USA). $P < 0.05$ was considered to be statistically significant.

Results

Study population characteristics

A total of 3684 participants were enrolled in this study, including 2220 CHD patients and 1464 non-CHD patients. Table 1 shows clinical characteristics and risk factors of all participants, including age, gender, glucose, HbA1c, blood-lipid indicators, Lp(a), hs-CRP, HCY and sdLDL-C. Levels of ApoB, LDL-C, hs-CRP, HCY, and sdLDL-C in CHD group were higher than those in non-CHD group. The CHD group had a significantly lower apoA1 and HDL-C levels compared with non-CHD group. There were no significant differences of other variables between the two groups ($P > 0.05$).

Table 1
baseline characteristics in type 2 diabetic patients

Variables	Total	CHD group	Non-CHD group	*P* value
N (%)	3684	2220 (60.26%)	1464 (39.74%)	–
Age (years)	58.61 ± 9.32	59.48 ± 9.62	56 89 ± 8.98	0.296
Male (%)	2152 (58.41%)	1324 (59.64%)	828 (56.56%)	0.422
BMI (kg/m^2)	26.16 ± 3.6	26.51 ± 3.2	25.81 ± 3.3	0.203
Glucose (mmol/L)	7.56 ± 2.10	7.85 ± 2.12	7.37 ± 2.08	0.082
HbA1c (%)	7.42 ± 1.33	7.61 ± 1.42	7.35 ± 1.35	0.089
ApoB (mg/dL)	82.78 ± 28.70	88.15 ± 29.87	74.65 ± 27.39	< 0.001
ApoA1 (mg/dL)	140.24 ± 32.67	116.83 ± 29.67	175.83 ± 35.04	< 0.001
Total cholesterol (mmol/L)	4.44 (1.33)	4.46 (1.72)	4.41 (0.98)	0.737
Triglycerides (mmol/L)	1.32 (0.88)	1.32 (0.82)	1.32 (0.94)	0.987
HDL-C (mmol/L)	1.02 (0.46)	0.86 (0.29)	1.31 (0.39)	< 0.001
LDL-C (mmol/L)	2.71 (0.95)	2.87 (1.35)	2.61 (0.61)	< 0.001
Lp(a) (nmol/L)	39.25 (39.75)	39.71 (48.37)	38.09 (33.46)	0.576
hs-CRP (mg/L)	2.10 (2.31)	3.10 (2.90)	1.63 (1.56)	0.028
HCY (umol/L)	11.06 (7.74)	11.99 (10.22)	9.55 (5.53)	< 0.001
sdLDL-C (mmol/L)	0.74 (0.37)	0.80 (0.49)	0.70 (0.30)	< 0.001
Data are reported as means ± SD or n(%), median (interquartile ranges). SD: Standard deviation				
BMI: body mass index; HbA1c: Hemoglobin A1c; apoB : apolipoprotein B ; apoA1 : apolipoprotein A1; HDL-C: high density lipoprotein cholesterol; LDL-C : low density lipoprotein cholesterol ; Lp(a) : lipoprotein (a); HsCRP : hypersensitive C-reactive protein; HCY : homocysteine ; sdLDL-C : small dense low-density lipoprotein cholesterol.				
Statistical analysis was performed with the ANOVA or Kruskal – Wall test and and with Chi-square test for categorical variables.				

Relation of sdLDL-C levels and severity of CHD

Based on the CAG results of each individual, the diabetic patients with CHD were further divided into the following subgroups including multiple-vessel disease group, and high GS group for the purpose of intensively evaluating the relation of sdLDL-C to the severity of CHD (Table 2 and Table 3).

Table 2
baseline characteristics in type 2 diabetic patients with multiple-vessel disease of coronary heart disease patients

Variables	1 vessel	2 vessels	≥ 3 vessels	*P* value
N (%)	576 (25.95%)	656 (29.55%)	988 (44.50%)	–
Age (years)	58.67 ± 10.72	59.79 ± 11.21	59.28 ± 9.88	0.700
Male (%)	336 (58.3%)	384 (58.5%)	604 (61.1%)	0.661
BMI (kg/m^2)	26.23 ± 2.9	26.57 ± 3.2	27.54 ± 3.5	0.156
Glucose (mmol/L)	8.07 ± 2.32	7.61 ± 2.09	7.51 ± 2.11	0.095
HbA1c (%)	7.77 ± 1.47	7.53 ± 1.39	7.59 ± 1.41	0.212
ApoB (mg/dL)	67.65 ± 21.74	85.22 ± 20.72	101.77 ± 29.43	< 0.001
ApoA1 (mg/dL)	111.87 ± 31.49	115.85 ± 30.24	118.87 ± 26.41	0.071
Total cholesterol (mmol/L)	4.35 (1.62)	4.51 (1.70)	4.68 (1.85)	0.037
Triglycerides (mmol/L)	1.32 (0.82)	1.38 (0.83)	1.30 (0.78)	0.723
HDL-C (mmol/L)	0.89 (0.32)	0.85 (0.30)	0.82 (0.27)	0.537
LDL-C (mmol/L)	2.68 (1.05)	2.83 (1.00)	2.99 (1.34)	0.014
Lp(a) (nmol/L)	37.80 (40.61)	41.51 (49.94)	39.47 (45.54)	0.189
hs-CRP (mg/L)	5.60 (8.03)	4.41 (7.12)	3.10 (6.57)	0.002
HCY (umol/L)	11.60 (8.14)	12.69 (10.37)	12.00 (11.53)	0.078
sdLDL-C (mmol/L)	0.72 (0.24)	0.80 (0.24)	0.85 (0.52)	0.003
Data are reported as means ± SD or n(%), median (interquartile ranges). SD: Standard deviation				
BMI: body mass index; HbA1c: Hemoglobin A1c; apoB : apolipoprotein B ; apoA1 : apolipoprotein A1; HDL-C: high density lipoprotein cholesterol; LDL-C : low density lipoprotein cholesterol ; Lp(a): lipoprotein (a); HsCRP : hypersensitive C-reactive protein; HCY : homocysteine ; sdLDL-C : small dense low-density lipoprotein cholesterol.				
Statistical analysis was performed with the ANOVA or Kruskal – Wall test and and with Chi-square test for categorical variables.				

Table 3
baseline characteristics in type 2 diabetic patients with Gensini score of coronary heart disease patients

Variables	Low GS	Intermediate GS	High GS	*P* value
N (%)	724 (32.62%)	768 (34.59%)	728 (32.79%)	–
Age (years)	59.65 ± 10.02	60.11 ± 10.43	58.72 ± 8.91	0.776
Male (%)	420 (58.01%)	464 (60.42%)	440 (60.44%)	0.744
BMI (kg/m2)	26.46 ± 3.28	26.26 ± 3.19	26.89 ± 3.47	0.540
Glucose (mmol/L)	8.11 ± 2.31	7.72 ± 2.02	7.64 ± 2.10	0.181
HbA1c (%)	7.81 ± 1.48	7.55 ± 1.42	7.57 ± 1.39	0.197
ApoB (mg/dL)	82.17 ± 26.06	86.67 ± 22.58	90.78 ± 30.37	0.006
ApoA1 (mg/dL)	115.25 ± 29.75	113.02 ± 31.57	117.03 ± 26.89	0.412
Total cholesterol (mmol/L)	4.37 (1.40)	4.49 (1.41)	4.73 (1.83)	0.012
Triglycerides (mmol/L)	1.32 (0.76)	1.25 (0.66)	1.37 (0.83)	0.332
HDL-C (mmol/L)	0.88 (0.33)	0.86 (0.30)	0.84 (0.24)	0.698
LDL-C (mmol/L)	2.77 (1.04)	2.89 (1.07)	3.09 (1.45)	0.026
Lp(a) (nmol/L)	38.54 (40.71)	40.09 (45.17)	41.17 (51.39)	0.664
hs-CRP (mg/L)	3.40 (7.08)	4.55 (11.32)	4.06 (8.39)	0.476
HCY (umol/L)	11.35 (10.15)	12.27 (9.29)	12.69 (11.79)	0.045
sdLDL-C (mmol/L)	0.71 (0.29)	0.80 (0.27)	0.91 (0.53)	< 0.001
Data are reported as means ± SD or n(%), median (interquartile ranges). SD: Standard deviation				
BMI: body mass index; HbA1c: Hemoglobin A1c; apoB : apolipoprotein B ; apoA1 : apolipoprotein A1; HDL-C: high density lipoprotein cholesterol; LDL-C : low density lipoprotein cholesterol ; Lp(a) : lipoprotein (a); HsCRP : hypersensitive C-reactive protein; HCY : homocysteine ; sdLDL-C : small dense low-density lipoprotein cholesterol.				
Statistical analysis was performed with the ANOVA or Kruskal – Wall test and and with Chi-square test for categorical variables.				

The patients with diabetes and CHD were then classified into single-vessel (n = 576), two-vessel (n = 656), and multiple-vessel disease (n = 988) groups (Table 2). We found a significant increase in sdLDL-C levels in patients with multiple-vessel diseases group [0.72 (0.24) mmol/L vs. 0.80 (0.24) mmol/L vs. 0.85 (0.52) mmol/L, P = 0.003]. At the same time, these patients were divided into three groups according to the tertiles of GS: low GS (≤ 25, n = 724), intermediate GS (26–40, n = 768) and high GS (≥ 41, n = 728) group (Table 3). It can be seen from the results that the serum sdLDL-C levels in the high GS group was

significantly higher than that in the other two groups [0.71 (0.29) mmol/L vs. 0.80 (0.27) mmol/L vs. 0.91 (0.53) mmol/L, P < 0.001].

After dividing diabetic patients with CHD into four groups according to quartiles of sdLDL-C levels, The results show that there is a linear correlation between the level of sdLDL-C and the multiple-vessel disease group and the high GS group. With the increase of serum sdLDL-C, the degree of CHD obstruction is more serious. (Table 4) (P < 0.001).

Table 4
Linear relationship between small dense low-density lipoprotein cholesterol levels and severity of coronary heart disease

sdLDL-C (mmol/L)	1 vessel	2 vessel	≥ 3 vessels	*P*	Low GS	Intermediate GS	High GS	*P*
0.12–0.58	215	160	173	< 0.001	267	161	124	< 0.001
0.58–0.80	147	203	212		180	256	160	
0.81–1.07	103	151	296		129	189	210	
1.07–2.31	111	142	307		146	162	234	
sdLDL-C: small dense low-density lipoprotein cholesterol; GS: Gensini Score.								
Statistical analysis was performed with the Mantel-Haenszel test for linear trend.								

Table 5
Odd ratios of CHD, multiple-vessel disease and high GS in relation to quartiles of small dense low-density lipoprotein

Variables	sdLDL-C, mmol/L			
	< 0.58	0.58–0.74	0.75–0.95	> 0.95
CHD				
Model 1 [a]				
Odds ratio (95% CI)	1.00 (Ref.)	2.168 (1.062–5.364)	3.668 (1.260–8.166)	3.015 (2.014–5.878)
P value	–	0.225	0.129	0.019
Model 2 [b]				
Odds ratio (95% CI)	1.00 (Ref.)	1.996 (1.226–5.926)	2.087 (1.398–6.876)	2.705 (1.617–5.645)
P value	–	0.398	0.198	0.042
Model 3 [c]				
Odds ratio (95% CI)	1.00 (Ref.)	1.926 (1.162–4.964)	2.242 (1.401–6.564)	2.757 (1.662–5.364)
P value	–	0.341	0.143	0.023
Multiple-vessel disease				
Model 1 [a]				
Odds ratio (95% CI)	1.00 (Ref.)	2.152 (1.298–4.312)	3.911 (2.127–9.113)	4.281 (2.468–6.561)
P value	–	0.156	0.078	< 0.001
Model 2 [b]				

sdLDL-C: small dense low-density lipoprotein cholesterol; GS: Gensini Score; CHD: coronary heart disease; CI: Confidence interval.

[a] Univariate model.

[b] Adjusted for age, sex, and body mass index.

[c] Additionally adjusted for Hemoglobin A1c, apolipoprotein B, apolipoprotein A1, high density lipoprotein cholesterol, low density lipoprotein cholesterol, lipoprotein (a), hypersensitive C-reactive protein, and homocysteine.

Variables	sdLDL-C, mmol/L			
	< 0.58	0.58–0.74	0.75–0.95	> 0.95
Odds ratio (95% CI)	1.00 (Ref.)	2.412 (1.353–4.003)	3.677 (1.708–9.542)	3.961 (1.786–6.986)
P value	–	0.107	0.129	0.014
Model 3 [c]				
Odds ratio (95% CI)	1.00 (Ref.)	2.302 (1.310–4.212)	3.558 (1.801–7.145)	3.788 (1.866–7.685)
P value	–	0.121	0.009	0.026
High GS				
Model 1 [a]				
Odds ratio (95% CI)	1.00 (Ref.)	1.907 (1.145–5.920)	3.465 (2.050–5.637)	3.391 (2.131–5.557)
P value	–	0.101	0.045	< 0.001
Model 2 [b]				
Odds ratio (95% CI)	1.00 (Ref.)	2.172 (1.210–6.812)	2.958 (1.602–8.331)	3.122 (1.901–5.721)
P value	–	0.199	0.171	0.028
Model 3 [c]				
Odds ratio (95% CI)	1.00 (Ref.)	1.902 (1.010–5.412)	2.902 (1.619–7.912)	3.054 (1.944–5.699)
P value	–	0.191	0.121	0.022

sdLDL-C: small dense low-density lipoprotein cholesterol; GS: Gensini Score; CHD: coronary heart disease; CI: Confidence interval.

[a] Univariate model.

[b] Adjusted for age, sex, and body mass index.

[c] Additionally adjusted for Hemoglobin A1c, apolipoprotein B, apolipoprotein A1, high density lipoprotein cholesterol, low density lipoprotein cholesterol, lipoprotein (a), hypersensitive C-reactive protein, and homocysteine.

For exploring the role of sdLDL-C in CHD, univariate and multivariate regression analyses were also performed in our study. All participants were divided into four quartiles of sdLDL-C levels, and the present and severity of CHD in individuals with different sdLDL-C levels was assessed. Through univariate

logistic regression, sdLDL-C levels were associated with the presence and severity of CHD (CHD group vs. non–CHD group: OR = 3.015, 95% CI: 2.014–5.878, P = 0.019; multiple-vessel disease group vs. single-vessel disease group: OR = 4.281, 95% CI: 2.468–6.561, P < 0.001; high GS group vs. low GS group: OR = 3.391, 95% CI: 2.131–5.557, P < 0.001). The multiple-factor logistic regression was applied to adjust for age, gender, BMI, glucose, HbA1c, ApoB, ApoA1, TC, TG, HDL-C, LDL-C, Lp(a), hs-CRP, and HCY, sdLDL-C levels remained to be independently associated with the presence and severity of CHD (CHD group vs. non–CHD group: OR = 2.757, 95% CI: 1.662–5.364, P = 0.023; multiple-vessel disease group vs. single-vessel disease group: OR = 3.788, 95% CI: 1.866–7.685, P = 0.026; high GS group vs. low GS group: OR = 3.054, 95% CI: 1.944–5.699, P = 0.022).

Discussion

sdLDL-C is a distinct LDL-C subclass, which is associated with raised TG and decreased HDL-C levels in adiposity and diabetes, playing a distinct metabolic role in atherosclerosis[15–18]. In this study including patients with T2DM, we found that there was an independent association between sdLDL-C and CHD. Briefly, the patients with more severe coronary stenosis had higher sdLDL-C levels and sdLDL-C was independently associated with the presence and severity of angiography-proven CHD presented as GS multiple-vessel disease in patients with T2DM. These findings provide evidence that the measurement of serum sdLDL-C is clinically valuable for estimating the future onset of CHD beyond the predefined cardiovascular risks[19, 20].

Many studies have confirmed the high concentrations of sdLDL-C may be a risk factor for CHD[21–24]. Several studies in different populations using various sdLDL-C measurements suggested that the sdLDL-C was related to the carotid intima thickness and in association with progression of carotid artery plaque[25]. In an 11-year follow-up study involving 11419 men and women, 1158 participants who developed CHD showed average sdLDL-C concentrations of 43.5 mg/dL[26]. Moreover, the increased sdLDL-C concentrations were correlated with a higher propensity for diabetes, arterial hypertension, increase in body mass index (BMI) and hs-CRP values. In the Multi-Ethnic Study of Atherosclerosis (MESA), a higher concentration of sdLDL-C was associated with the development of CHD among overall study participants, but the association was not statistically significant among patients with T2DM[27]. Our result was inconsistent with this finding. The reasons for this discrepancy are not entirely clear, but the conflict between the results of the study may be caused by a variety of confounding factors, such as different population characteristics, study design, disease status, confounding variables, or sdLDL-C measurement method. Therefore, the inconsistent effect of sdLDL-C on CHD in patients with T2DM may also mean that the role of sdLDL-C in heart metabolic diseases is complex and needs to be studied carefully[28]. That's why we used a large Chinese cohort for this study. In our study, we found that the level of sdLDL-C in T2DM patients was related to the presence of angiographically confirmed CHD. In addition, in order to further study the relationship between sdLDL-C and CHD severity in diabetic patients, we used GS system to conduct multiple subgroup analysis.

There are several limitations in the present study. Firstly, there are only two centers for this study, which might result in selective biases. Secondly, we were able to measure the serum sdLDL-C level and other risk factors only once at baseline. We were also unable to obtain information about medical treatment during the follow-up period. Finally, although there is statistical significance between the level of sdLDL-C and CHD in patients with T2DM, CHD is a complex disease with many pathogenic factors, which also requires more research to confirm our findings.

Conclusion

In conclusion, our study indicates that the increase of sdLDL-C is an independent predictor of CHD, and is related to the severity of CHD. These findings suggest that sdLDL-C is a crucial biomarker for the prediction of the occurrence and severity of CHD complicated with T2DM.

Declarations

Acknowledgements

The authors thank all the staff and participants of this study for their important contributions.

Conflict of interest

There are no conflict of interest.

Funding Sources

This study was supported by the Beijing Science and Technology Plan (Z181100001718156).

Author contributions

Juan Huang, Jun-Xu Gu, Mei Jia: the conception and design of the study. Hui-Zhang Bao, Shan-Shan Li, Xiao-Qin Yao, Ming Yang, Yang Li, Ai-Min Zhang, Yue Yin, Na Zhang: acquisition of data, analysis and interpretation of data. Juan Huang, Jun-Xu Gu, Mei Jia: drafting the article and revising it critically for important intellectual content. Juan Huang, Mei Jia: final approval of the version to be submitted.

Availability of data and materials

The datasets used and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request

Ethics approval and consent to participate

The present study complied with the Declaration of Helsinki and was approved by the Hospital Research Ethics Committee, and written informed consent was obtained from all patients.

Consent for publication

Not applicable.

References

1. Collaborators GBDCoD: **Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017**. *Lancet* 2018, **392**(10159):1736-1788.
2. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE *et al*: **2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines**. *Journal of the American College of Cardiology* 2019, **73**(24):e285-e350.
3. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J: **Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries**. *Circulation* 2016, **134**(6):441-450.
4. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN *et al*: **Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association**. *Circulation* 2020, **141**(9):e139-e596.
5. Pletcher MJ, Moran AE: **Cardiovascular Risk Assessment**. *The Medical clinics of North America* 2017, **101**(4):673-688.
6. Grant PJ, Cosentino F: **The 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: New features and the 'Ten Commandments' of the 2019 Guidelines are discussed by Professor Peter J. Grant and Professor Francesco Cosentino, the Task Force chairmen**. *European heart journal* 2019, **40**(39):3215-3217.
7. Jin JL, Cao YX, Liu HH, Zhang HW, Guo YL, Wu NQ, Zhu CG, Xu RX, Gao Y, Sun J *et al*: **Impact of free fatty acids on prognosis in coronary artery disease patients under different glucose metabolism status**. *Cardiovascular diabetology* 2019, **18**(1):134.
8. Jin JL, Zhang HW, Cao YX, Liu HH, Hua Q, Li YF, Zhang Y, Wu NQ, Zhu CG, Xu RX *et al*: **Association of small dense low-density lipoprotein with cardiovascular outcome in patients with coronary artery disease and diabetes: a prospective, observational cohort study**. *Cardiovascular diabetology* 2020, **19**(1):45.

9. Ikezaki H, Furusyo N, Yokota Y, Ai M, Asztalos BF, Murata M, Hayashi J, Schaefer EJ: **Small Dense Low-Density Lipoprotein Cholesterol and Carotid Intimal Medial Thickness Progression**. *Journal of atherosclerosis and thrombosis* 2020.
10. Witte DR, Taskinen MR, Perttunen-Nio H, Van Tol A, Livingstone S, Colhoun HM: **Study of agreement between LDL size as measured by nuclear magnetic resonance and gradient gel electrophoresis**. *Journal of lipid research* 2004, **45**(6):1069-1076.
11. Alizadeh-Fanalou S, Nazarizadeh A, Alian F, Faraji P, Sorori B, Khosravi M: **Small dense low-density lipoprotein-lowering agents**. *Biological chemistry* 2019.
12. Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM: **Low-density lipoprotein subclass patterns and risk of myocardial infarction**. *Jama* 1988, **260**(13):1917-1921.
13. Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM, Pradhan AD: **Triglyceride-Rich Lipoprotein Cholesterol, Small Dense LDL Cholesterol, and Incident Cardiovascular Disease**. *Journal of the American College of Cardiology* 2020, **75**(17):2122-2135.
14. Talebi S, Bagherniya M, Atkin SL, Askari G, Orafai HM, Sahebkar A: **The beneficial effects of nutraceuticals and natural products on small dense LDL levels, LDL particle number and LDL particle size: a clinical review**. *Lipids in health and disease* 2020, **19**(1):66.
15. Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN: **Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases**. *Oxidative medicine and cellular longevity* 2017, **2017**:1273042.
16. Santos HO, Earnest CP, Tinsley GM, Izidoro LFM, Macedo RCO: **Small dense low-density lipoprotein-cholesterol (sdLDL-C): Analysis, effects on cardiovascular endpoints and dietary strategies**. *Progress in cardiovascular diseases* 2020.
17. Soltanmohammadi E, Piran S, Mohammadi A, Hosseni B, Naseri F, Shabani M, Najafi M: **Serum sdLDL-C and Cellular SREBP2-dependent Cholesterol Levels; is there a Challenge on Targeting PCSK9?** *Journal of medical biochemistry* 2016, **35**(4):410-415.
18. Saeed A, Feofanova EV, Yu B, Sun W, Virani SS, Nambi V, Coresh J, Guild CS, Boerwinkle E, Ballantyne CM *et al*: **Remnant-Like Particle Cholesterol, Low-Density Lipoprotein Triglycerides, and Incident Cardiovascular Disease**. *Journal of the American College of Cardiology* 2018, **72**(2):156-169.
19. Schulte DM, Paulsen K, Turk K, Brandt B, Freitag-Wolf S, Hagen I, Zeuner R, Schroder JO, Lieb W, Franke A *et al*: **Small dense LDL cholesterol in human subjects with different chronic inflammatory diseases**. *Nutrition, metabolism, and cardiovascular diseases : NMCD* 2018, **28**(11):1100-1105.
20. Dansinger ML, Williams PT, Superko HR, Schaefer EJ: **Effects of weight change on apolipoprotein B-containing emerging atherosclerotic cardiovascular disease (ASCVD) risk factors**. *Lipids in health and disease* 2019, **18**(1):154.
21. Sakai K, Koba S, Nakamura Y, Yokota Y, Tsunoda F, Shoji M, Itoh Y, Hamazaki Y, Kobayashi Y: **Small dense low-density lipoprotein cholesterol is a promising biomarker for secondary prevention in older men with stable coronary artery disease**. *Geriatrics & gerontology international* 2018, **18**(6):965-972.

22. Ai M, Otokozawa S, Asztalos BF, Ito Y, Nakajima K, White CC, Cupples LA, Wilson PW, Schaefer EJ: **Small dense LDL cholesterol and coronary heart disease: results from the Framingham Offspring Study**. *Clinical chemistry* 2010, **56**(6):967-976.
23. Meyer BC, Hemmen TM, Jackson CM, Lyden PD: **Modified National Institutes of Health Stroke Scale for use in stroke clinical trials: prospective reliability and validity**. *Stroke* 2002, **33**(5):1261-1266.
24. Kathiresan S, Otvos JD, Sullivan LM, Keyes MJ, Schaefer EJ, Wilson PW, D'Agostino RB, Vasan RS, Robins SJ: **Increased small low-density lipoprotein particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study**. *Circulation* 2006, **113**(1):20-29.
25. Albers JJ, Slee A, Fleg JL, O'Brien KD, Marcovina SM: **Relationship of baseline HDL subclasses, small dense LDL and LDL triglyceride to cardiovascular events in the AIM-HIGH clinical trial**. *Atherosclerosis* 2016, **251**:454-459.
26. Hoogeveen RC, Gaubatz JW, Sun W, Dodge RC, Crosby JR, Jiang J, Couper D, Virani SS, Kathiresan S, Boerwinkle E *et al*: **Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study**. *Arteriosclerosis, thrombosis, and vascular biology* 2014, **34**(5):1069-1077.
27. Tsai MY, Steffen BT, Guan W, McClelland RL, Warnick R, McConnell J, Hoefner DM, Remaley AT: **New automated assay of small dense low-density lipoprotein cholesterol identifies risk of coronary heart disease: the Multi-ethnic Study of Atherosclerosis**. *Arteriosclerosis, thrombosis, and vascular biology* 2014, **34**(1):196-201.
28. Peradze N, Farr OM, Perakakis N, Lazaro I, Sala-Vila A, Mantzoros CS: **Short-term treatment with high dose liraglutide improves lipid and lipoprotein profile and changes hormonal mediators of lipid metabolism in obese patients with no overt type 2 diabetes mellitus: a randomized, placebo-controlled, cross-over, double-blind clinical trial**. *Cardiovascular diabetology* 2019, **18**(1):141.