**Aims:** Abnormal compositional changes in low-density lipoprotein (LDL) particles, such as triglyceride (TG) enrichment and size reduction, are common in patients with diabetes. Several cohort studies have demonstrated that LDL-TG and sdLDL-cholesterol (C) are sensitive biomarkers for predicting atherosclerotic cardiovascular diseases beyond LDL-C. Although sdLDL has been extensively studied, little is known about the properties of LDL-TG. We investigated similarities or differences between LDL-TG and sdLDL-C.

**Methods:** Fasting plasma was obtained from 1,085 patients with type 2 diabetes who were enrolled in the diabetes regional cohort study (ViNA Cohort). LDL-TG and sdLDL-C concentrations were measured using a homogeneous assay established by us. In a subset of subjects, LDL-TG and sdLDL-C levels were measured postprandially or after treatment with lipid-lowering drugs.

**Results:** In a quartile analysis, higher LDL-TG quartiles were associated with higher frequency of female and fibrate users, whereas sdLDL-C quartiles were associated with frequency of men, drinking, and metabolic syndrome-related measurements. Higher quartiles of LDL-TG/LDL-C were associated with smoking, drinking, fibrate users, and statin users. LDL-TG was significantly correlated with TG, LDL-C, sdLDL-C, and apolipoprotein (apo) B, with apoB being the primary determinant. LDL-TG correlated to high sensitive C-reactive protein (CRP) independently of other lipids. Mean LDL-TG did not change with fasting/non-fasting. Statin treatment reduced LDL-TG, whereas fibrates increased it, but these drugs reduced sdLDL-C equally.

**Conclusions:** LDL-TG levels were more tightly regulated by the number of LDL particles than plasma TG levels were. SdLDL-C was closely associated with metabolic syndrome-related factors, whereas LDL-TG was associated with low-grade systemic inflammation.

**Key words:** LDL triglycerides, Small dense LDL-cholesterol, Diabetes, Metabolic syndrome, Apolipoprotein B

**Abbreviations:** TG: triglycerides, C: cholesterol, LDL: low-density lipoprotein, sdLDL: small dense low-density lipoprotein, lbLDL: Large buoyant LDL, VLDL: very-low-density lipoprotein, HDL: high-density lipoprotein, TRL: triglyceride-rich lipoprotein, Apo: Apolipoprotein, HsCRP: high sensitive C-reactive protein, HL: hepatic lipase, LPL: lipoprotein lipase, Lp(a): Lipoprotein (a), CHD: coronary heart disease, CVD: cerebrovascular disease, ASCVD: atherosclerotic cardiovascular disease, UAR: urinary albumin ratio, CETP: cholesterylester transfer protein

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**Introduction**

Diabetes is a major cause of atherosclerotic cardiovascular disease (ASCVD), and diabetes-related dyslipidemia is closely associated with high prevalence of ASCVD, independent of hyperglycemia. Diabetic dyslipidemia is characterized by elevated triglycerides (TGs), lowered high-density lipoprotein (HDL)-cholesterol (C), and the preponderance of small dense low-density lipoproteins (sdLDL). In addition,
patients with diabetes preferentially have TG-enriched lipoproteins across all lipoprotein spectra, including LDL \(^3,4\). It is well recognized that sdLDL particles are more atherogenic than large buoyant (lb) LDL particles\(^3-6\). Our group has established a fully automated assay kit for quantifying sdLDL-C levels\(^5\), and this assay system was adopted in famous cohort studies such as in the community atherosclerosis risk (ARIC) study and Hisayama study\(^8,9\). All studies have consistently demonstrated that sdLDL-C is superior to LDL-C in predicting ASCVD. Recently, our group has established a fully automated LDL-TG assay kit\(^10\). Using this kit, Saeed et al.\(^11\) reported that LDL-TG was a sensitive marker for predicting coronary heart disease (CHD) and cerebrovascular disease (CVD) in the ARIC study. They also found that the predictive power of LDL-TG was superior to that of remnant-like particles (RLP)-C, which represent atherosclerotic TRL remnants\(^11\). There are several other studies that have already indicated that LDL-TG levels can predict ASCVD beyond LDL-C\(^12,13\). Atherosclerosis is considered to be chronic inflammation of blood vessels, and high sensitive C-reactive protein (hsCRP) is a sensitive biomarker of systemic inflammation. Interestingly, some studies have pointed out that LDL-TG levels are more closely associated with the inflammatory marker C-reactive protein (CRP) than with LDL-C\(^11,12\).

SdLDL is produced from TG-rich LDL by the action of hepatic lipase (HL)\(^15\). Therefore, LDL-TG may have a precursor–product relationship with sdLDL\(^16\). Although SdLDL-C has been extensively studied, properties of LDL-TG are not well understood.

In this study, we investigated the correlation between LDL-TG and various metabolic and lipid parameters in a large number of patients with type 2 diabetes to clarify the similarities or differences between LDL-TG and sdLDL-C.

**Methods**

**Subjects**

Subjects of this study \((n=1,085)\) were participants in the “ViNA” cohort study. The ViNA cohort study began on October 1, 2019 and will carry out regular tests, assessment of diabetic complications, and prognostic surveys within the next 2, 4, and 6 years. The subjects were diabetic patients aged 30–89 who had been treated at the Ebina General Hospital Diabetes Center for over a year. Exclusion criteria were patients with malignancies currently being treated, patients with severe liver, endocrine, and respiratory disorders, and patients undergoing hemodialysis. In this study, we used baseline blood and urine samples collected from October 1, 2019 to September 30, 2020. Subject characteristics were listed in a part of Table 1. Two hundred thirty-two (21%) patients were insulin users. Most subjects with type 2 diabetes \((n=884)\) were treated with the following hypoglycemic agents alone or in combination: a sulfonylurea, metformin, pioglitazone, dipeptidyl peptidase-4 inhibitor, sodium-glucose co-transporter-2 inhibitor, a-glucosidase inhibitor, and glucagon-like peptide-1 receptor agonist. The majority of hypertensive patients \((n=645)\) used antihypertensive drugs such as calcium channel blockers, angiotensin II receptor blockers, diuretics, and beta blockers alone or in combination. Subjects with hyperlipidemia were treated with statins \((n=598)\), ezetimibe \((n=74)\), fibrates \((n=75)\), or omega-3 fatty acids \((n=39)\) alone or in combination. All patients are taught an appropriate diet proposed by the Japan Diabetes Foundation by a dietitian.

A subset of subjects \((n=44)\) was retrospectively investigated for lipid levels in non-fasting plasma on another day when fasting blood samples were collected. Breakfast was taken between 6:00 am and 8:00 am, and blood was drawn at the hospital from 8:00 am to 10:00 am. Therefore, postprandial samples were collected 1–4 hours after breakfast. The interval between the two blood draws was 1 to 4 months. Another subset of subjects retrospectively investigated fasting lipid levels before and 2–4 months after treatment with either statins \((n=12)\) or fibrates \((n=11)\). The statins were pitavastatin \((1 \text{ mg / d, } n=9)\) and rosuvastatin \((2.5 \text{ mg / d, } n=3)\), and the fibrates were pemafibrate \((0.2 \text{ mg / d})\) only. In a preliminary study, we measured TG and cholesterol concentrations in LDL subfractions obtained from 10 healthy volunteers.

**Measurements**

Plasma samples were taken in the morning after overnight fasting. LDL-TG and sdLDL-C concentrations were measured directly in plasma by the homogeneous method established by our group (Denka Co., Ltd., Tokyo). All blood samples, including
LDL-TG and sdLDL-C, were immediately measured using an automated analyzer without storage in the refrigerator. The principles of these assays were fully explained previously. Of note is that the direct LDL-TG and LDL-C assays measure LDL, densities (d) = 1.019–1.063 g/ml, and the direct sdLDL-C assays measure LDL, d = 1.044–1.063 g/ml. lbLDL-C was calculated by subtracting sdLDL-C from LDL-C.

Table 1. Measurements stratified by LDL-TG quartile in subjects with diabetes

| Quartile | Total | Q1 | Q2 | Q3 | Q4 |
|---------|-------|----|----|----|----|
| LDL-TG (mg/dl) | 14.5 (6.7-59.7) | 10.2 (6.7-11.8) | 13.3 (11.9-14.4) | 15.8 (14.5-17.3) | 20.4 (17.4-59.7) |
| Number | 1085 | 266 | 272 | 276 | 271 |
| p trend | <0.0001 | | | | |

| Male | 680 (63%) | 192 (72%) | 172 (63%) | 169 (61%) | 147 (54%) |
| Age (y) | 67.0 (11.1) | 67.5 (10.2) | 67.0 (10.7) | 66.5 (12.0) | 66.9 (11.4) |
| Current smoker | 183 (17%) | 35 (13%) | 46 (17%) | 53 (19%) | 49 (18%) |
| Alcohol drinker | 382 (35%) | 94 (35%) | 89 (33%) | 96 (35%) | 103 (38%) |
| Coronary heart disease | 117 (11%) | 32 (12%) | 33 (12%) | 29 (11%) | 23 (8%) |
| Cerebralvascular disease | 91 (8%) | 22 (8%) | 20 (7%) | 26 (9%) | 23 (8%) |
| Type 1 diabetes | 27 (3%) | 8 (3%) | 5 (2%) | 6 (2%) | 8 (3%) |
| Insulin | 232 (21%) | 54 (20%) | 54 (20%) | 65 (24%) | 59 (22%) |
| insulin dose (U) | 23 [15-33] | 22 [14-34] | 23 [16-32] | 24 [16-32] | 22 [16-32] |
| Hypotensive drugs | 645 (59%) | 157 (59%) | 164 (60%) | 154 (56%) | 170 (63%) |
| Hypolipidemic drugs | 681 (63%) | 158 (59%) | 189 (69%) | 161 (58%) | 173 (64%) |
| Statins | 597 (55%) | 149 (56%) | 176 (65%) | 140 (51%) | 132 (49%) |
| Fibrates | 75 (7%) | 5 (2%) | 10 (4%) | 19 (7%) | 41 (15%) |
| SBP (mmHg) | 132 (14) | 130 (14) | 131 (13) | 133 (15) | 134 (14) |
| BMI (Kg/m²) | 25.2 (4.2) | 24.4 (3.7) | 25.2 (4.0) | 25.5 (4.3) | 25.7 (4.7) |
| Fatty liver* | 130 (49%) | 21 (37%) | 33 (49%) | 37 (52%) | 39 (55%) |
| VFA (cm²) | 159.2 (81.2) | 148.1 (63.6) | 156.1 (80.6) | 157.5 (82.0) | 174.9 (94.8) |
| ALT (U) | 20 [15-30] | 18 [15-25] | 22 [16-32] | 20 [15-29] | 21 [15-32] |
| GTP (U) | 25 [17-42] | 21 [16-32] | 25 [18-40] | 25 [17-42] | 30 [18-58] |
| HbA1c (%) | 7.4 (0.9) | 7.3 (0.7) | 7.4 (0.9) | 7.5 (0.9) | 7.4 (1.0) |
| TC (mg/dL) | 182 (31) | 172 (27) | 174 (28) | 185 (23) | 195 (26) |
| TG (mg/dL) | 104 [76-149] | 87 [66-121] | 104 [78-151] | 106 [74-153] | 117 [93-177] |
| %LDL-TG/TG | 13.9 [9.5-19.6] | 11.6 [8.2-15.3] | 12.6 [8.9-16.8] | 14.9 [10.5-21.2] | 18.2 [12.1-22.7] |
| LDL-C (mg/dL) | 102 (24) | 93 (22) | 98 (21) | 105 (23) | 112 (26) |
| %LDL-TG/LDL-C | 14.4 [11.9-18.0] | 11.0 [9.2-12.9] | 13.5 [11.7-15.7] | 15.1 [13.1-17.7] | 19.0 [16.2-23.2] |
| HDL-C (mg/dL) | 54 (14) | 56 (14) | 53 (14) | 55 (15) | 53 (14) |
| NonHDL-C (mg/dL) | 127 (28) | 115 (23) | 121 (24) | 130 (26) | 142 (31) |
| lbLDL-C (mg/dL) | 71 (27) | 69 (18) | 74 (21) | 73 (23) | 70.9 (4.2) |
| sdLDL-C (mg/dL) | 28.0 [21.3-38.1] | 23.5 [18.2-30.8] | 27.7 [20.7-34.5] | 28.9 [22.2-37.0] | 35.5 [25.0-50.1] |
| TRL-C (mg/dL) | 23 [18-29] | 21 [17-25] | 22 [17-28] | 23 [18-30] | 27 [20-35] |
| apoB (mg/dl) | 87 (18) | 78 (15) | 84 (15) | 89 (16) | 99 (21) |
| apoCIII (mg/dl) | 10.4 (3.3) | 7.8 (2.4) | 9.3 (3.1) | 10.0 (3.2) | 11.2 (3.1) |
| apoE (mg/dl) | 4.1 (1.3) | 3.8 (1.2) | 3.9 (1.1) | 4.1 (1.2) | 4.6 (1.4) |
| Lp (a) (mg/dl) | 13.1 [6.2-24.8] | 11.7 [5.7-22.6] | 15.0 [6.6-25.5] | 17.2 [6.2-23.1] | 12.8 [6.1-31.6] |
| cGFR (ml/min/1.73m²) | 70.9 (20.0) | 71.0 (18.3) | 70.1 (20.8) | 72.1 (19.5) | 70.2 (21.3) |
| UAR (mg/g) | 16.2 [6.8-51.7] | 13.8 [5.4-49.9] | 16.5 [7.2-54.0] | 14.0 [6.1-36.4] | 19.9 [8.2-74.4] |
| WBC | 6583 (1714) | 6131 (1567) | 6590 (1513) | 6654 (1785) | 6950 (1871) |
| hsCRP (ng/L) | 0.06 [0.03-0.13] | 0.03 [0.02-0.07] | 0.05 [0.03-0.12] | 0.07 [0.03-0.15] | 0.09 [0.04-0.21] |

*1 The p trend was estimated by Cochran-Armitage trend test for categorical variables or Jonckheere-Terpstra trend test for continuous variables.
*2 Total 267 subjects were measured Fatty liver.
*3 Total 195 subjects were measured VFA.
nonHDL-C was calculated by subtracting HDL-C from TC; and TG-rich lipoprotein (TRL)-C was calculated by subtracting LDL-C and HDL-C from total-C (TC). The distribution of TG and cholesterol in the lbLDL (d = 1.019–1.043) and sdLDL (d = 1.044–1.063) fractions was preliminarily examined separately in the plasma by ultracentrifugation (n = 10). Fatty liver was diagnosed based on the CT scan image by the radiologists, and the visceral fat area (VFA) was measured from the same image using the fat scan program (Fujifilm, Tokyo). Apolipoproteins, Lipoprotein (Lp) (a), hsCRP, C-peptide, and albumin were measured using commercially available test kits. Albumin in urine was corrected by urinary creatinine and represented as the urinary albumin ratio (UAR).

Differences between groups were examined using either Student’s t-test or Mann–Whitney U test. Significance was evaluated using Wilcoxon signed-rank test. The chi-squared test of association was used to discover whether there was a relationship between two categorical variables. The p trend was estimated using the Cochran–Armitage trend test for categorical variables or the Jonckheere–Terpstra trend test for continuous variables. Correlations between variables were evaluated using Spearman’s correlation analysis. Multivariate linear regression was employed to analyze the effects of LDL-TG, sdLDL-C or hsCRP on other related factors. A p-value less than 0.05 was considered statistically significant. Analyses were performed using JMP software version 15 (SAS Institute, Cary, NC, USA).

**Results**

**Table 1** illustrates characteristics of the subjects and measured values of the subjects as a whole and values stratified by the LDL-TG quartile (Q). The higher quartiles were more frequent in females (less males). In fact, LDL-TG levels were higher in females than in males in total subjects (15.9 ±0.2 vs. 14.7 ± 0.2 mg/dl, p < 0.0001, data not presented). CHD and CVD prevalence did not change in different quartiles. There was no significant difference in the use of hypoglycemic agents among the four groups (data not presented). Two hundred thirty-two (21%) patients were insulin users. The number of insulin users, insulin dose, and rate of type 1 diabetes did not change at LDL-TG quartiles. Fibrate use increased, but statin use decreased with higher quartiles. Systolic blood pressure (SBP), body mass index (BMI), and the presence of fatty liver increased slightly at higher quartiles. Gamma-GTP and C-peptide increased, but glucose and hemoglobin A1c did not change at higher quartiles. The higher quartiles of LDL-TG were significantly associated with higher levels of TC, TG, LDL-C, nonHDL-C, sdLDL-C, TRL-C, apo B, apo CIII, apo E, and lbLDL-C. The LDL-TG/LDL-C and LDL-TG/plasma TG percentages also increased with the higher quartiles of LDL-TG. The estimated glomerular filtration rate (eGFR) or UAR did not change with higher quartiles. White blood cell count (WBC) and hsCRP increased significantly with higher LDL-TG quartiles.

**Table 2** illustrates the various measurements layered by the quartile of the LDL-TG/LDL-C (%). The higher LDL-TG/LDL-C quartiles were significantly associated with the frequency of females, smokers, and CHD. The higher the quartile, the higher the number of statin, fibrate, and insulin users. Metabolic syndrome-related factors such as BMI and VFA did not change between quartiles. The LDL-TG/LDL-C quartile was significantly associated with high concentrations of TC, TG, LDL-C, NonHDL-C, lbLDL-C, sdLDL-C, and TRL-C. ApoB was inversely correlated with the higher quartiles of LDL-TG/LDL-C. UAR, WBC, and hsCRP increased with higher LDL-TG/LDL-C quartiles.

**Table 3** lists the various measurements stratified by the sdLDL-C quartile. Higher sdLDL-C quartiles were significantly associated with younger, more frequent males, more drinkers, CHD, higher insulin dose, and less frequent type 1 diabetes and insulin users. The higher the quartile, the larger the number of fibrate users and the smaller the number of statin users. Metabolic syndrome-related factors such as SBP, fatty liver, VFA, C-peptide, and blood glucose levels increased significantly with higher quartiles. The higher the quartile of sdLDL-C, the higher are TC, TG, LDL-C, and non-HDL-C and the lower are HDL-C, TRL-C, apoB, apo CIII, and apo E; this is in contrast with lbLDL-C or Lp(a). WBC and hsCRP mildly increased as the sdLDL-C quartile increased.

**Table 4** presents the univariate and multivariate correlations between LDL-TG or sdLDL-C and plasma lipid parameters. Similarly to quartile analysis, LDL-TG was significantly correlated with many lipid parameters in the linear regression analysis. In particular, apoB was highly correlated with LDL-TG.
Correlated with sdLDL-C. The multivariate analysis revealed that apoB, log-TG, and apo CIII were independently associated with sdLDL-C.

Table 5 presents the relationship between hsCRP levels and various measurements. HsCRP levels were high in CVD subjects and low in type 1 diabetes. HsCRP was associated with metabolic syndrome-related factors such as SBP, BMI, VFA, C-peptide, hyperglycemia, and dyslipidemia, and kidney...

(r=0.449). In multivariate analysis, LDL-C, log-
sdLDL-C, or log-TG lost their association with
LDL-TG when apo B was entered as the independent
variable. When apoCIII and E were added to this
multivariate analysis, apoB and apoE were
independently positively correlated with LDL-TG.

SdLDL-C was significantly correlated with all
lipid parameters. ApoB (r=0.76), apo CIII (r=0.61),
nonHDL-C (r=0.69), and TG (r=0.62) were highly
correlated with sdLDL-C. The multivariate analysis
revealed that apoB, log-TG, and apo CIII were
independently associated with sdLDL-C.

Table 5 presents the relationship between hsCRP
levels and various measurements. HsCRP levels were
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Table 3. Measurements stratified by sdLDL-cholesterol quartile in subjects with diabetes

| Quartile  | Q1 (8.5-21.3) | Q2 (21.4-28.0) | Q3 (28.1-38.0) | Q4 (38.1-117.6) | p trend*1 |
|-----------|---------------|---------------|---------------|-----------------|-----------|
| sdLDL-C (mg/dl) | 17.5 | 24.6 | 32.4 | 48.7 | 0.0041 |
| Number | 276 | 270 | 268 | 271 | 0.0041 |
| Male | 166 (60%) | 151 (56%) | 174 (65%) | 189 (70%) | 0.0041 |
| Age | 68 (11) | 67 (11) | 68 (11) | 65 (12) | 0.0014 |
| Current smoker | 46 (17%) | 38 (14%) | 42 (16%) | 57 (21%) | ns |
| Alcohol drinker | 86 (31%) | 82 (30%) | 91 (34%) | 123 (45%) | 0.0004 |
| Coronary heart disease | 43 (16%) | 30 (11%) | 23 (9%) | 21 (8%) | 0.0019 |
| Cerebrovascular disease | 26 (9%) | 24 (9%) | 22 (8%) | 19 (7%) | ns |
| Type 1 diabetes | 13 (5%) | 7 (3%) | 5 (2%) | 2 (1%) | 0.0027 |
| Insulin | 71 (26%) | 61 (23%) | 57 (21%) | 43 (16%) | 0.0054 |
| insulin dose | 20 [14-30] | 24 [16-33] | 21 [11-31] | 28 [20-40] | ns |
| Hypolipidemic agents | 177 (64%) | 171 (63%) | 170 (63%) | 163 (60%) | ns |
| Statins | 162 (59%) | 150 (56%) | 153 (57%) | 132 (49%) | 0.0347 |
| Fibrates | 13 (5%) | 18 (7%) | 14 (5%) | 30 (11%) | 0.0102 |
| Hypotensive agents | 166 (60%) | 160 (59%) | 154 (57%) | 165 (61%) | ns |
| SBP (mmHg) | 130 (15) | 131 (13) | 134 (13) | 133 (14) | 0.0452 |
| BMI (Kg/m²) | 24.3 (4.3) | 25.2 (4.3) | 25.1 (3.7) | 26.2 (4.3) | <0.0001 |
| Fatty liver*2 | 17 (25%) | 27 (50%) | 39 (58%) | 47 (61%) | <0.0001 |
| VFA (cm²)*3 | 105 (59) | 157 (71) | 170 (77) | 203 (82) | <0.0001 |
| ALT (U) | 16 [13-23] | 20 [15-29] | 21 [16-30] | 26 [17-39] | <0.0001 |
| γ-GTP (U) | 19 [14-28] | 24 [16-37] | 25 [18-38] | 37 [22-66] | <0.0001 |
| Hba1c (%) | 7.3 (0.8) | 7.3 (0.8) | 7.4 (0.9) | 7.5 (1.0) | ns |
| Glucose (mg/dL) | 141 (40) | 149 (35) | 150 (37) | 157 (44) | <0.0001 |
| C-peptide (mg/dL) | 1.0 [0.7-1.6] | 1.2 [0.8-1.8] | 1.3 [0.9-1.9] | 1.6 [1.1-2.2] | <0.0001 |
| TC (mg/dL) | 159 (24) | 180 (26) | 186 (27) | 202 (30) | <0.0001 |
| TG (mg/dL) | 73 [57-96] | 93 [71-121] | 115 [91-151] | 166 [120-227] | <0.0001 |
| LDL-C (mg/dL) | 83 (17) | 101 (19) | 107 (21) | 118 (24) | <0.0001 |
| LDL-TG (mg/dL) | 13.2 [10.6-16.0] | 14.2 [11.6-16.5] | 14.6 [12.3-17.0] | 16.6 [13.8-20.9] | <0.0001 |
| HDL-C (mg/dL) | 57 (15) | 57 (15) | 54 (14) | 50 (12) | <0.0001 |
| Non-HDL-C (mg/dL) | 102 (18) | 123 (20) | 132 (21) | 152 (26) | <0.0001 |
| lbLDL-C (mg/dL) | 66 (16) | 76 (19) | 74 (21) | 66 (24) | ns |
| TRI-C (mg/dL) | 19 [15-23] | 22 [17-27] | 24 [19-30] | 32 [24-41] | <0.0001 |
| apoB (mg/dL) | 70 (10) | 83 (11) | 91 (12) | 106 (17) | <0.0001 |
| apoCIII (mg/dL) | 8.2 [6.9-9.9] | 9.6 [8.2-11.2] | 11.1 [9.3-13.0] | 13.8 [11.2-16.6] | <0.0001 |
| apoE (mg/dL) | 3.6 (1.1) | 3.9 (1.0) | 4.0 (1.1) | 4.9 (1.4) | <0.0001 |
| Lp (a) (mg/dL) | 14.3 [7.1-28.7] | 14.4 [6.6-26.4] | 11.8 [5.9-20.9] | 11.9 [5.6-24.0] | 0.0119 |
| eGFR (ml/min/1.73m²) | 70 (21) | 70 (18) | 72 (20) | 72 (21) | ns |
| UAR (mg/g) | 18.3 [6.6-54.3] | 13.7 [5.7-40.8] | 16.5 [7.3-45.9] | 19.3 [7.5-73.8] | ns |
| WBC | 6301 (1762) | 6419 (1682) | 6701 (993) | 6919 (1046) | <0.0001 |
| hsCRP (ng/L) | 0.05 [0.02-0.11] | 0.06 [0.03-0.14] | 0.05 [0.03-0.11] | 0.08 [0.04-0.17] | <0.0001 |

Dysfunction. LDL-TG had the strongest association with hsCRP among lipid parameters. By contrast, sdLDL-C lost its correlation with hsCRP in the multivariate analysis.

Fig. 1 illustrates the difference in lipid levels between fasting and postprandial conditions on different days of the same individual. Mean levels of TG increased in postprandial samples, but mean levels of non-fasting LDL-C, non-HDL-C, LDL-TG, and sdLDL-C were similar to those at fasting.

Fig. 2 illustrates the differences (d) in TG, LDL-
We examined the correlation between LDL-TG and various parameters in more than 1,000 diabetic patients to find the metabolic properties of this new risk factor for ASCVD. Given that sdLDL is produced from TG-rich LDL\textsuperscript{18}), it is not surprising that there is a significant correlation between LDL-TG and sdLDL-C. However, despite the proposed precursor–product relationships between them\textsuperscript{17}), these risk factors were found to have different properties. SdLDL-C was strongly correlated with metabolic syndrome-related factors such as increased VFA, SBP, blood glucose, fatty liver, and hyper-TG/low HDL-C. By contrast, LDL-TG had a limited association with these measurements. SdLDL is preferentially produced from the large TG-rich VLDL (VLDL\textsubscript{1}), and VLDL\textsubscript{1} production is enhanced by the presence of insulin.

### Table 4. Correlations between LDL-TG or sdLDL-C and lipoprotein parameters

|              | Univariate LDL-TG | Univariate sdLDL-C |
|--------------|-------------------|--------------------|
|              | Spearman’s rs     | p                  | Spearman’s rs     | p                  |
| TC           | 0.2930            | <0.0001            | TC                | 0.5315            | <0.0001            |
| TG           | 0.2305            | <0.0001            | TG                | 0.6222            | <0.0001            |
| LDL-C        | 0.3040            | <0.0001            | LDL-C             | 0.5495            | <0.0001            |
| HDL-C        | -0.0749           | 0.0136             | HDL-C             | -0.1902           | <0.0001            |
| Non-HDL-C    | 0.3739            | <0.0001            | Non-HDL-C         | 0.6901            | <0.0001            |
| lbLDL-C      | 0.1165            | 0.0001             | lbLDL-C           | 0.0085            | ns                 |
| sdLDL-C      | 0.3245            | <0.0001            | LDL-TG            | 0.3245            | <0.0001            |
| TRL-C        | 0.2407            | <0.0001            | TRL-C             | 0.5050            | <0.0001            |
| apoB         | 0.4493            | <0.0001            | apoB              | 0.7612            | <0.0001            |
| apoCIII      | 0.1382            | <0.0001            | apoCIII           | 0.6197            | <0.0001            |
| apoE         | 0.2504            | <0.0001            | apoE              | 0.4030            | <0.0001            |

|              | Multivariate log_LDL-TG | R2=0.263 | apoB | 0.8978 | <0.0001 |
|--------------|--------------------------|----------|------|--------|---------|
|              | log_TG                   | β        | p    |        |         |
| R2=0.301     | log_LDL-TG               | 0.0945   | ns   |        |         |
| apoB         | 0.9457                   | <0.0001  |      |        |         |
| LDL-C        | -0.5507                  | <0.0001  |      |        |         |
| log_TG       | -0.0243                  | ns       |      |        |         |
| apoB         | 1.0325                   | <0.0001  |      |        |         |
| log_apoCIII  | -0.2858                  | <0.0001  |      |        |         |
| apoE         | 0.0974                   | 0.0016   |      |        |         |

C, LDL-TG, and sdLDL-C concentrations before and after treatment with statins or fibrates. As expected, TG was reduced by fibrate treatment, and LDL-C was reduced by statin treatment. LDL-TG was increased by fibrates but reduced by statins. Both lipid-lowering drugs reduced sdLDL-C to the same extent. D-LDL-TG was significantly correlated with d-lbLDL-C but not with d-TG or d-sdLDL-C. This result suggested that fibrates increased LDL-TG through an increase in lbLDL, but it was not clear how much LDL-TG was distributed in the lbLDL or sdLDL fraction. Then, we preliminarily measured the distribution of TG and cholesterol in the lbLDL and sdLDL fractions of plasma separated by ultracentrifugation. The median concentration of lbLDL-TG was 10 mg/dl, and sdLDL-TG was 4 mg/dl, indicating that lbLDL-TG was more than twice as high as sdLDL-TG (Supplementary Table 1).

**Discussion**

We examined the correlation between LDL-TG and various parameters in more than 1,000 diabetic patients to find the metabolic properties of this new risk factor for ASCVD. Given that sdLDL is produced from TG-rich LDL\textsuperscript{18}), it is not surprising that there is a significant correlation between LDL-TG and sdLDL-C. However, despite the proposed precursor–product relationships between them\textsuperscript{17}), these risk factors were found to have different properties. SdLDL-C was strongly correlated with metabolic syndrome-related factors such as increased VFA, SBP, blood glucose, fatty liver, and hyper-TG/low HDL-C. By contrast, LDL-TG had a limited association with these measurements. SdLDL is preferentially produced from the large TG-rich VLDL (VLDL\textsubscript{1}), and VLDL\textsubscript{1} production is enhanced by the presence of insulin.
### Table 5. High sensitive C-reactive protein (hsCRP) levels and associations with various measurements

|                                   | Yes           | No            | p             |
|-----------------------------------|---------------|---------------|---------------|
| Male                              | 0.05 (0.03-0.12)* | 0.07 (0.03-0.15) | ns**          |
| Current smoker                    | 0.06 (0.03-0.14) | 0.06 (0.03-0.13) | ns            |
| Alcohol drinker                   | 0.06 (0.03-0.14) | 0.06 (0.03-0.13) | ns            |
| Coronary heart disease            | 0.05 (0.02-0.11) | 0.06 (0.03-0.14) | ns            |
| Cerebrovascular disease           | 0.08 (0.04-0.24) | 0.06 (0.03-0.13) | 0.0012        |
| Type 1 diabetes                   | 0.02 (0.02-0.07) | 0.06 (0.03-0.13) | 0.0089        |
| Insulin                           | 0.06 (0.03-0.15) | 0.06 (0.03-0.13) | ns            |
| Hypotensive drugs                 | 0.06 (0.03-0.14) | 0.05 (0.02-0.12) | 0.0004        |
| Hypolipidemic drugs               | 0.05 (0.03-0.13) | 0.06 (0.03-0.14) | ns            |
| Statins                           | 0.05 (0.02-0.12) | 0.07 (0.03-0.15) | 0.0004        |
| Fibrates                          | 0.08 (0.04-0.16) | 0.06 (0.03-0.13) | 0.0195        |
| Fatty liver                       | 0.11 (0.05-0.22) | 0.05 (0.02-0.13) | <0.0001       |

#### Univariate hsCRP

|                                  | Spearman’s rs | p             |
|-----------------------------------|---------------|---------------|
| Age                               | 0.0045        | ns            |
| SBP                               | 0.0696        | 0.0226        |
| BMI                               | 0.3424        | <0.0001       |
| VFA, n = 195                      | 0.3779        | <0.0001       |
| ALT                               | 0.1298        | <0.0001       |
| yGTP                              | 0.3123        | <0.0001       |
| HbA1c                             | 0.1431        | <0.0001       |
| Glucose                           | 0.0899        | 0.0032        |
| C-peptide                         | 0.2426        | <0.0001       |
| TC                                | 0.0762        | 0.0124        |
| TG                                | 0.2451        | <0.0001       |
| LDL-C                             | 0.1446        | <0.0001       |
| LDL-TG                            | 0.2829        | <0.0001       |
| %LDL-TG/TLD-C                     | 0.1482        | <0.0001       |
| HDL-C                             | -0.1689       | <0.0001       |
| Non-HDL-C                         | -0.1831       | <0.0001       |
| lbLDL-C                           | 0.0592        | ns            |
| sdLDL-C                           | 0.1507        | <0.0001       |
| TRL-C                             | 0.1013        | 0.0009        |
| apoB                              | 0.2056        | <0.0001       |
| apoCIII                           | 0.1116        | 0.0002        |
| apoE                              | 0.1427        | <0.0001       |
| Lp (a)                            | 0.0384        | ns            |
| eGFR                              | -0.0515       | ns            |
| UAR                               | 0.0698        | 0.0224        |
| WBC                               | 0.3079        | <0.0001       |

#### Multivariate (adjusted) log hsCRP

|                                  | β             | p             |
|-----------------------------------|---------------|---------------|
| TC                                | 0.0555        | 0.0491        |
| log_TG                            | 0.0372        | ns            |
| LDL-C                             | 0.0716        | 0.0112        |
| HDL-C                             | -0.0358       | ns            |
| Non-HDL-C                         | 0.0805        | 0.0042        |
| log_TRL-C                         | 0.0345        | ns            |
| apoB                              | 0.0782        | 0.0053        |
| log_apoCIII                       | 0.0136        | ns            |
| apoE                              | 0.0565        | 0.0402        |
| log_sdLDL-C                       | -0.0151       | ns            |
| log_LDL-TG                        | 0.1724        | <0.0001       |

Multivariate analysis is adjusted for cerebrovascular disease, type 1 diabetes, hypotensive drugs, statins, fibrates, SBP, BMI, HbA1c, log ALT, log yGTP, glucose, log C-peptide, log UAR, and WBC. *range, **not significant.
Fig. 1. Changes in lipid concentrations between fasting and non-fasting states
TG, LDL-TG, non-HDL-C, LDL-TG, and sdLDL-TG concentrations in fasting and non-fasting plasma (1–4 hours after breakfast) on different days in the same individual (n=44). The interval between the two blood draws was 1 to 4 months. The whiskers of the box plots indicate the central 95% of the distribution. Significance was evaluated using the Wilcoxon signed-rank test. ns = not significant.

Fig. 2. Difference (d) in lipid concentrations before and after treatments with either fibrates or statins (A) and correlations between d-LDL-TG and d-TG, d-LDL-C, or d-sdLDL-C in all treated subjects (B).
The statins are pitavastatin (1 mg/day, n=9) and rosuvastatin (2.5 mg/d, n=3), and the fibrate is pemafibrate (0.2 mg/d, n=11). A: The whiskers of the box plots indicate the central 95% of the distribution. Significance was evaluated using the Wilcoxon rank sum test. The letters “rs” indicate Spearman’s rank correlation coefficient.

resistance in the liver and adipose tissue supplying excess free fatty acids to the liver. VLDL1-TG is a major regulator of LDL particle size. Unlike sdLDL-C, LDL-TG did not strongly correlate with metabolic syndrome-related measurements. This suggests that VLDL1 production does not critically regulate the TG content of LDL. Mechanisms leading to the formation of sdLDL are involved in
cholosterylester transfer protein (CETP) and HL, besides VLDL1 production. CETP promotes the transfer of TG from VLDL to LDL; the resulting TG-rich LDL is the preferred substrate for HL; and increased lipolysis of TG-rich LDL results in the formation of sdLDL. Therefore, an increase in CETP and a decrease in HL produce TG-rich LDL and can increase LDL-TG levels. Silbernagel reported that LDL-TG levels were strongly associated with HL region variation and that LDL-TG-elevating alleles were associated with low HL activity. HL activity has been reported to be enhanced by insulin resistance and increased in type 2 diabetes. Therefore, sdLDL-C, and LDL-TG may have the opposite relationship to HL; that is, low HL activity increases LDL-TG but reduces sdLDL-C. This may in part explain why sdLDL-C is associated with metabolic syndrome-related factors but LDL-TG is not. LDL-TG had higher levels in women than in men. This was already recognized in previous studies. Applebaum reported that administration of ethinyl estradiol significantly suppressed HL activity in postheparin plasma in healthy women. Estrogen-induced suppression of HL may explain high levels of LDL-TG in women.

We found that both LDL-TG and sdLDL-C were closely associated with apoB, but TG was more closely associated with sdLDL-C than with LDL-TG. It is speculated that enhanced production of VLDL simply leads to increased levels of LDL-TG and sdLDL-C, whereas LDL modeling through VLDL-LDL cascade and lipid transfer with other lipoproteins may be more strongly associated with sdLDL formation than with TG-rich LDL formation. It has been suggested that the LDL-TG/LDL-C ratio is superior to LDL-TG levels for detecting the presence of metabolic disorders. As illustrated in Table 2, the higher the ratio of LDL-TG/LDL-C, the higher the prevalence of CHD; this was not observed for LDL-TG levels. This alternative approach has the potential to enhance the predictive power of LDL-TG for ASCVD. In this study, 232 (21%) patients were insulin users, and insulin plays an important role in lipid metabolism. We previously reported that sdLDL-C levels decreased after the introduction of intensive insulin therapy. This was closely associated with the TG-lowering effect of insulin. Consistent with previous studies, sdLDL-C levels were lower in insulin users. By contrast, higher sdLDL-C was positively correlated with C-peptide levels. Because high levels of fasting C-peptide reflect endogenous hyperinsulinenia due to insulin resistance, our result is consistent with the well known notion that insulin resistance is a potent up-regulator of sdLDL levels.

Unlike sdLDL-C, no significant effect of insulin use or C-peptide on LDL-TG was found. However, prospective studies are required to elucidate the effects of insulin on LDL-TG levels.

HsCRP is used as a sensitive biomarker for vascular inflammation. Marz reported for the first time that LDL-TG was strongly associated with hsCRP and WBC, suggesting that the atherogenicity of LDL-TG was due to its inflammatory properties. We observed that the association between LDL-TG and hsCRP was stronger than the association of LDL-C, apo B, or sdLDL-C with hsCRP. Moreover, the multivariate analysis revealed that the correlation coefficient was more than twice as high for LDL-TG (β=0.1724) as that for LDL-C (β=0.0716). Silbernagel speculated that HL was down-regulated by systemic inflammation, leading to elevated LDL-TG levels. Stahlman proposed another speculation that palmitic acid in the TG molecule of LDL particles promoted inflammation. Further research will be required to elucidate the possibility that TG in LDL can cause more inflammation than cholesterol in LDL.

Unlike plasma TG levels, mean LDL-TG levels did not change significantly between fasting and postprandial conditions. These two blood samples were taken on different days when the subject visited the hospital. Therefore, in some samples, LDL-TG changed significantly before and after a meal. Nonetheless, this general clinical approach suggests that fasting/non-fasting is not a critical issue for LDL-TG assessment. This is also true for the sdLDL-C measurement.

We unexpectedly observed an increase in LDL-TG in subjects after treatment with fibrates. This supports our new finding that LDL-TG is not definitively regulated by plasma TG levels. We found that changes in lbLDL-C were positively correlated with changes in LDL-TG. It is well known that fibrates increase LDL size; thus, sdLDL-C decreases, and lbLDL-C increases. Our preliminary study using ultracentrifugation revealed that TG in LDL was twice as much in the lbLDL fraction as that in the sdLDL fraction. Therefore, it was suggested that the increase in lbLDL by fibrates could outweigh the decrease in sdLDL and increase the amount of TG in the total LDL. Fibrates promote TRL lipolysis, which may referentially increase lbLDL production. We have already reported that sdLDL-C decreased to the same extent in fibrates and statins and confirmed this result in the present study. Therefore, it is unlikely that fibrates will increase the overall atherogenicity of LDL.

This study has some limitations. First, laboratory
properties. LDL-TG and sdLDL-C had different metabolic properties. SdLDL-C was closely associated with metabolic syndrome-related factors, whereas LDL-TG was associated with low-grade systemic inflammation.

Conclusions

LDL-TG and sdLDL-C had different metabolic properties. SdLDL-C was closely associated with metabolic syndrome-related factors, whereas LDL-TG was associated with low-grade systemic inflammation.

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Authors’ Contributions

TH designed, conducted this study, analyzed the data, and wrote. RK, YH, NS, EA, MH, and TO collected data. MO conducted an additional study. NS and YI analyzed the data. THa and SK contributed to finalizing the paper. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

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**Supplemental Table 1.** Cholesterol and triglyceride concentrations in ultracentrifugally isolated large buoyant (lb) and small dense (sd) LDL fractions

Percentage composition of total-cholesterol and triglycerides in sdLDL and lbLDL fractions from 10 healthy volunteers after obtaining written informed consent. The LbLDL and SdLDL fractions were separated by ultracentrifugation with densities of 1.019 to 1.043 and 1.044 to 1.063 g/ml, respectively.

| lb LDL (mg/dl) | sd LDL (mg/dl) | lb LDL/sd LDL |
|----------------|----------------|---------------|
| Cho | TG | Cho | TG | Cho | TG |
| 32.4 | 10.4 | 68.2 | 14.1 | 0.5 | 0.7 |
| 61.0 | 9.2 | 39.5 | 4.9 | 1.5 | 1.9 |
| 18.0 | 9.4 | 48.0 | 15.8 | 0.4 | 0.6 |
| 71.3 | 10.7 | 64.0 | 7.9 | 1.1 | 1.4 |
| 82.7 | 11.5 | 40.1 | 4.9 | 2.1 | 2.4 |
| 55.3 | 5.7 | 2.45 | 2.6 | 2.3 | 2.2 |
| 45.5 | 18.7 | 57.8 | 10.5 | 0.8 | 1.8 |
| 62.2 | 12.0 | 26.5 | 4.5 | 2.3 | 2.7 |
| 62.4 | 9.0 | 34.6 | 3.5 | 1.5 | 1.6 |
| 78.2 | 12.7 | 42.8 | 3.7 | 1.8 | 3.5 |

Plasma was obtained from 10 healthy volunteers.
LbLDL fraction: density of 1.019-1.043. SdLDL fraction: density of 1.044-1.063