Obesity Facts

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Relationship between Lipoprotein Lipase Derived from Subcutaneous Adipose Tissue and Cardio-Ankle Vascular Index in Japanese Patients with Severe Obesity

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Keywords
Cardio-ankle vascular index · Obesity · Lipoprotein lipase · Subcutaneous adipose tissue · Laparoscopic sleeve gastrectomy

Abstract
Introduction: Cardio-ankle vascular index (CAVI) is an arterial stiffness index that correlates inversely with body mass index (BMI) and subcutaneous fat area. Lipoprotein lipase (LPL) that catalyzes the hydrolysis of serum triglycerides is produced mainly in adipocytes. Serum LPL mass reflects LPL expression in adipose tissue, and its changes correlate inversely with changes in CAVI. We hypothesized that LPL derived from subcutaneous adipose tissue (SAT) suppresses the progression of arteriosclerosis and examined the relationship of LPL gene expression in different adipose tissues and serum LPL mass with CAVI in Japanese patients with severe obesity undergoing laparoscopic sleeve gastrectomy (LSG). ***Methods:*** This study was a single-center retrospective database analysis. Fifty Japanese patients who underwent LSG and had 1-year postoperative follow-up data were enrolled (mean age 47.5 years, baseline BMI 46.6 kg/m^2, baseline HbA1c 6.7%). SAT and visceral adipose tissue (VAT) samples were obtained during LSG surgery. LPL gene expression was analyzed by real-time PCR. Serum LPL mass was measured by ELISA using a specific monoclonal antibody against LPL. ***Results:*** At baseline, LPL mRNA expression in SAT correlated positively with serum LPL mass, but LPL mRNA expression in VAT did not. LPL mRNA expression in SAT was correlated, and serum LPL mass tended to correlate inversely with the number of metabolic syndrome symptoms, but LPL mRNA expression in VAT did not. LPL mRNA expression in SAT and CAVI tended to correlate inversely in the group with visceral-to-subcutaneous fat ratio of 0.4 or higher, which is considered metabolically severe. Serum LPL mass increased 1 year after LSG. Change in serum LPL mass at 1 year after LSG tended to be an independent factor

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inversely associated with change in CAVI. ***Conclusions:*** Serum LPL mass reflected LPL mRNA expression in SAT in Japanese patients with severe obesity, and LPL mRNA expression in SAT was associated with CAVI in patients with visceral obesity. The change in serum LPL mass after LSG tended to independently contribute inversely to the change in CAVI. This study suggests that LPL derived from SAT may suppress the progression of arteriosclerosis.

Introduction

Arterial stiffness is mainly recognized as an indicator of arteriosclerosis and a predictor of cardiovascular events. Cardio-ankle vascular index (CAVI) is an arterial stiffness index, which is essentially derived from the stiffness parameter β and therefore independent of blood pressure at the time of measurement [1, 2]. Increased CAVI is observed in persons with cardiovascular disease and risk factors such as diabetes, hypertension, and dyslipidemia [2, 3]. Obesity is also considered a risk factor for atherosclerosis, and its association with CAVI has been reported. In many studies, CAVI was correlated with visceral fat area (VFA) measured by X-ray computed tomography (CT) in patients with obesity [2, 4]. CAVI was higher in patients with obesity and type 2 diabetes, accompanied by VFA accumulation, and decreased after weight loss treatment [5]. A body shape index (ABSI) is an abdominal obesity index calculated by dividing waist circumference by an allometric regression of weight and height, and it reflects metabolic disorders and CAVI [6]. Replacing high waist circumference with high ABSI in the diagnosis of metabolic syndrome (MetS) promoted the identification of patients with MetS and increased CAVI in a cross-sectional study of Japanese population [7]. Therefore, while it is clear that CAVI is higher in patients with abdominal obesity, the relationship between CAVI and obesity remains controversial. An inverse relationship was demonstrated between CAVI and body mass index (BMI) in healthy Japanese subjects [8]. Park et al. [4] also reported that CAVI was related negatively to subcutaneous fat area (SFA) in Korean asymptomatic individuals. We hypothesize that subcutaneous adipose tissue (SAT) may express a factor inhibiting rather than promoting atherosclerosis.

Lipoprotein lipase (LPL) that catalyzes the hydrolysis of triglycerides in the blood is produced mainly in adipocytes and skeletal muscle cells [9, 10]. LPL activity and LPL mass in the blood have been generally measured using plasma after a heparin injection [11]. Development of a sensitive immunoassay system using a specific monoclonal antibody against LPL allows the detection of LPL mass in serum without heparin injection [12, 13]. The serum level of LPL mass correlates negatively with the severity of MetS, type 2 diabetes [14, 15], and coronary atherosclerosis [16]. Furthermore, insulin and troglitazone increase LPL mass in patients with type 2 diabetes [17]. These findings suggest that serum LPL mass reflects insulin sensitivity in adipose tissue [14]. Recently, we reported that in Japanese patients with severe obesity, weight loss after laparoscopic sleeve gastrectomy (LSG) increased serum LPL mass [18]. Changes in CAVI correlate negatively with changes in serum LPL levels after drug treatments, suggesting that serum LPL mass may be related to CAVI. Although LPL is expressed in both SAT and visceral adipose tissue (VAT), it remains unclear whether serum LPL mass concentration primarily reflects LPL expression in SAT or in VAT in severely obese patients and whether adipose tissue LPL has antiatherosclerotic effects. We hypothesized that LPL derived from SAT is a factor suppressing the progression of arteriosclerosis. To clarify whether serum LPL and LPL expression in adipose tissue are influencing factors in patients with severe obesity, we examined LPL gene expression in SAT and VAT samples obtained from Japanese patients with severe obesity undergoing LSG and its relationship with serum LPL mass concentration, CAVI, and metabolic parameters.

Methods

This study was a single-center retrospective database analysis. In the present study, 50 (27 males and 23 females with a mean age of 47.5 years) Japanese patients who underwent LSG at the Toho University Sakura Medical Center between February 2019 and September 2020, who had 1-year postoperative follow-up data were enrolled. The criterion for surgical indication was BMI higher than 35 kg/m^2 with type 2 diabetes, dyslipidemia, hypertension, and/or sleep apnea syndrome. The definition and diagnostic criteria for MetS in Japanese [19] were applied to the diagnosis of MetS in this study. The diagnostic criteria of MetS require the presence of abdominal obesity: waist circumference ≥0.85 m in men or ≥0.90 m in women and at least 2 of the following abnormalities: (1) hyperlipidemia: serum triglyceride concentration ≥150 mg/dL, serum HDL-cholesterol concentration <40 mg/dL and/or receiving anti-hyperlipidemic medication; (2) hypertension: systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg and/or receiving antihypertensive medication; and (3) high fasting glucose: serum glucose concentration ≥110 mg/dL and/or receiving antidiabetic medication.

Table 1. Clinical parameters at baseline

	All patients	V/S <0.4	V/S ≥0.4	*p* value
	mean ± SD	mean ± SD	mean ± SD	
Age, years	47.5±10.2	45.4±7.9	50.2±12.3	0.101
Gender (male/female)	27/23	14/14	13/9	0.126
Height, cm	165.9±9.2	165.3±8.3	166.6±10.4	0.630
Body weight, kg	128.7±30.6	134.4±33.7	121.5±25.1	0.141
BMI, kg/m^2	46.6±10.2	49.1±12.1	43.5±6.2	0.053
Systolic blood pressure, mm Hg	140.7±20.4	142.6±21.2	138.5±19.5	0.485
Diastolic blood pressure, mm Hg	87.2±14.8	86.6±16.2	87.9±13.2	0.767
FBG, mg/dL	135.9±58.9	129.2±43.5	144.5±74.3	0.369
HbA1c, %	6.7±1.2	6.5±1.0	7.0±1.4	0.199
Serum CPR, ng/mL	8.3±14.6	10.2±19.2	5.8±3.3	0.845
TC, mg/dL	199.4±37.6	189.4±31.5	212.1±41.6	0.032
TG, mg/dL	181.1±95.4	158.6±88.3	209.8±98.3	0.059
HDL-C, mg/dL	48.8±11.1	48.7±10.3	49.0±12.4	0.909
AST, IU/L	43.7±31.3	41.4±27.0	46.7±36.4	0.555
ALT, IU/L	31.6±17.5	27.7±12.4	36.6±21.7	0.074
γ-GTP, IU/L	47.1±32	42.9±30.5	52.5±33.9	0.297
Cr, mg/dL	0.7±0.3	0.7±0.2	0.8±0.3	0.637
Uric acid, mg/dL	6.7±1.7	6.9±1.7	6.6±1.7	0.584
Urine albumin, mg/gCr	161.3±537.7	105.2±218.9	232.6±776.8	0.411
Hemoglobin, g/dL	14.8±1.9	14.6±1.8	15.1±2.0	0.331
VFA, cm^2	187.3±95.7	128.0±64.2	262.7±73.5	<0.001
Subcutaneous fat area, cm^2	496.3±210.8	538.6±253.0	442.5±126.4	0.110
Visceral-to-subcutaneous fat ratio	0.41±0.26	0.2±0.1	0.6±0.2	<0.001
Skeletal muscle mass, kg	61.5±18.7	36.8±7.4	36.0±8.1	0.726
Body fat mass, kg	36.5±7.6	66.3±20.3	55.7±15.0	0.054
Serum LPL mass, ng/mL	83.1±35.2	91.3±37.1	72.7±30.3	0.057
CAVI	7.2±1.3	7.0±1.2	7.6±1.3	0.062

V/S, visceral-to-subcutaneous fat ratio; BMI, body mass index; CPR, C-peptide immunoreactivity; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; γ-GTP, γ-glutamyl transpeptidase; Cr, creatinine; LPL, lipoprotein lipase; CAVI, cardio-ankle vascular index.

The following preoperative (baseline) data were collected from medical records: age, anthropometric measurements, VFA, SFA, skeletal muscle mass, blood pressure, glycated hemoglobin (HbA1c), fasting blood glucose, fasting serum C-peptide, lipid markers, liver function, renal function, serum LPL mass, and CAVI. Body weight was measured, and a blood sample was collected in the morning after 12 h of fasting. VFA was determined using CT, which was performed within normal medical practice for screening prior to LSG. The CT scan was performed at the umbilical level with the subject resting in a supine position. SFA was calculated by subtracting VFA from the total fat area. Skeletal muscle mass was measured by bioelectrical impedance analysis using InBody 720 (InBody Japan Co., Ltd., Tokyo, Japan) [9]. CAVI was measured with a VaSera CAVI instrument (Fukuda Denshi Co., Ltd., Tokyo, Japan) by methods described previously [20]. Serum LPL mass was measured by a sandwich enzyme-linked immunosorbent assay using a specific monoclonal antibody against LPL (Daiichi Pure Chemicals, Japan), as described by Kobayashi et al. [12]. The linearity and coefficient of variation for this assay have been described in our previous report [21]. Anthropometric data, blood test data, skeletal muscle mass, VFA, and SFA were measured before and 1 year after LSG surgery.

Abdominal SAT and VAT samples as residual tissue were obtained during normal surgical procedures for LSG. The excised material was dissected accurately to ensure only pure adipose tissue was used in subsequent steps. One part of the freshly excised adipose tissue was immediately dissected, cut into small pieces suitable for rapid penetration by the RNAlater RNA Stabilization Reagent (Qiagen GmbH, Hilden, Germany), and submerged according to the manufacturer's protocol. The remaining surgical samples were flash frozen and stored at −80°C until analysis. Total RNA was isolated with the RNeasy Lipid Tissue Mini kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. After DNase treatment, RNA was reverse transcribed into cDNA using the PrimeScript RT reagent kit (Qiagen GmbH, Hilden, Germany). Quantitative real-time PCR was performed using Probe qPCR mix (Takara Bio Inc., Shiga, Japan). Relative mRNA expression level of LPL

was calculated using the comparative CT method and normalized to 18S rRNA. The sequences of the primers used were LPL: forward 5′-GAGAGAACCAGACTCCAATGTCA-3′, reverse 5′-AGGGTAGTTAAACTCCTCCTCCA-3′; 18S rRNA: forward 5′-GCTCTTTCTCGATTCCGTGGG-3′, reverse 5′-CATGCCAGAGTCTCGTTCGTTA-3′.

The results are expressed as mean ± SD. The statistical software SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used in all statistical analyses. For comparisons between groups, parametric data were analyzed with the Student's *t* test, and non-parametric data were analyzed with the Mann-Whitney U-test. To compare paired samples, parametric data were analyzed using the paired *t* test, and non-parametric data were analyzed using the Wilcoxon signed-rank test. Fisher's exact test was used to identify any significant difference between proportions. Correlation coefficients were calculated using the Pearson correlation coefficient and Spearman's rank correlation coefficient, as appropriate. Comparisons between multiple groups were conducted using one-way ANOVA followed by post hoc Bonferroni tests. Multiple regression was used to analyze the association of independent variables with the change in CAVI at 1 year after LSG. A two-sided *p* value of 0.05 was considered statistically significant.

Results

Relationship between LPL mRNA Expression in SAT and Baseline Clinical Variables

At baseline, the mean age was 47.5 years, BMI was 46.6 kg/m^2, blood pressure was 140.7/87.2 mm Hg, HbA1c was 6.7%, VFA was 187.3 cm^2, SFA was 496.3 cm^2, serum LPL mass was 83.1 ng/mL, and CAVI was 7.2. Other background parameters are shown in Table 1. Table 2 shows univariate correlation analysis between LPL mRNA expression in SAT and clinical variables at baseline. LPL mRNA expression in SAT correlated significantly and positively with serum C-peptide immunoreactivity, creatinine, and serum LPL mass, and negatively with VFA, visceral-to-subcutaneous fat ratio, and skeletal muscle mass. In contrast, no correlation was observed between LPL mRNA expression in VAT and any of the baseline clinical variables including serum LPL mass (data not shown).

Table 2. Univariate correlation analysis between LPL mRNA expression in SAT and clinical variables at baseline

Variables	Subcutaneous LPL mRNA expression	
	r	*p* value
Body weight	−0.230	0.109
BMI	−0.112	0.437
Systolic blood pressure	−0.269	0.061
Diastolic blood pressure	−0.003	0.986
FBG	−0.016	0.910
HbA1c	−0.174	0.227
Serum CPR	0.297	0.036
TC	−0.030	0.837
TG	−0.273	0.055
HDL-C	0.030	0.838
AST	−0.005	0.972
ALT	−0.070	0.629
γ-GTP	−0.088	0.545
Cr	0.289	0.042
Uric acid	−0.221	0.937
Urine albumin	−0.011	0.123
Hemoglobin	−0.279	0.050
VFA	−0.415	0.003
Subcutaneous fat area	−0.156	0.280
Visceral-to-subcutaneous fat ratio	−0.280	0.049
Skeletal muscle mass	−0.414	0.004
Body fat mass	−0.173	0.245
Serum LPL mass	0.296	0.037

BMI, body mass index; CPR, C-peptide immunoreactivity; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; γ-GTP, γ-glutamyl transpeptidase; Cr, creatinine; LPL, lipoprotein lipase.

Relationship between Symptoms of MetS and LPL Levels

We have previously reported that the serum level of LPL mass correlates negatively with the severity of MetS [14]. In this study, the serum level of LPL mass correlated negatively with the number of MetS symptoms in patients with severe obesity (Fig. 1c). Interestingly, LPL mRNA expression in SAT tended to correlate negatively with the number of MetS symptoms (Fig. 1a). On the other hand, LPL mRNA expression in VAT did not correlate with the number of symptoms (Fig. 1b).

Relationship between LPL mRNA Expression in SAT and CAVI

We classified the subjects into visceral fat obesity group and subcutaneous fat obesity group using a cutoff visceral-to-subcutaneous fat ratio (V/S ratio) of 0.4 [22]. Table 1 shows that total cholesterol, VFA, and visceral-to-subcutaneous fat ratio were significantly higher in the group with V/S ratio of 0.4 or higher. Serum LPL mass tended to be lower ($p < 0.057$) and CAVI tended to be higher ($p < 0.062$) in the group with V/S ratio of 0.4 or higher. To test the hypothesis that

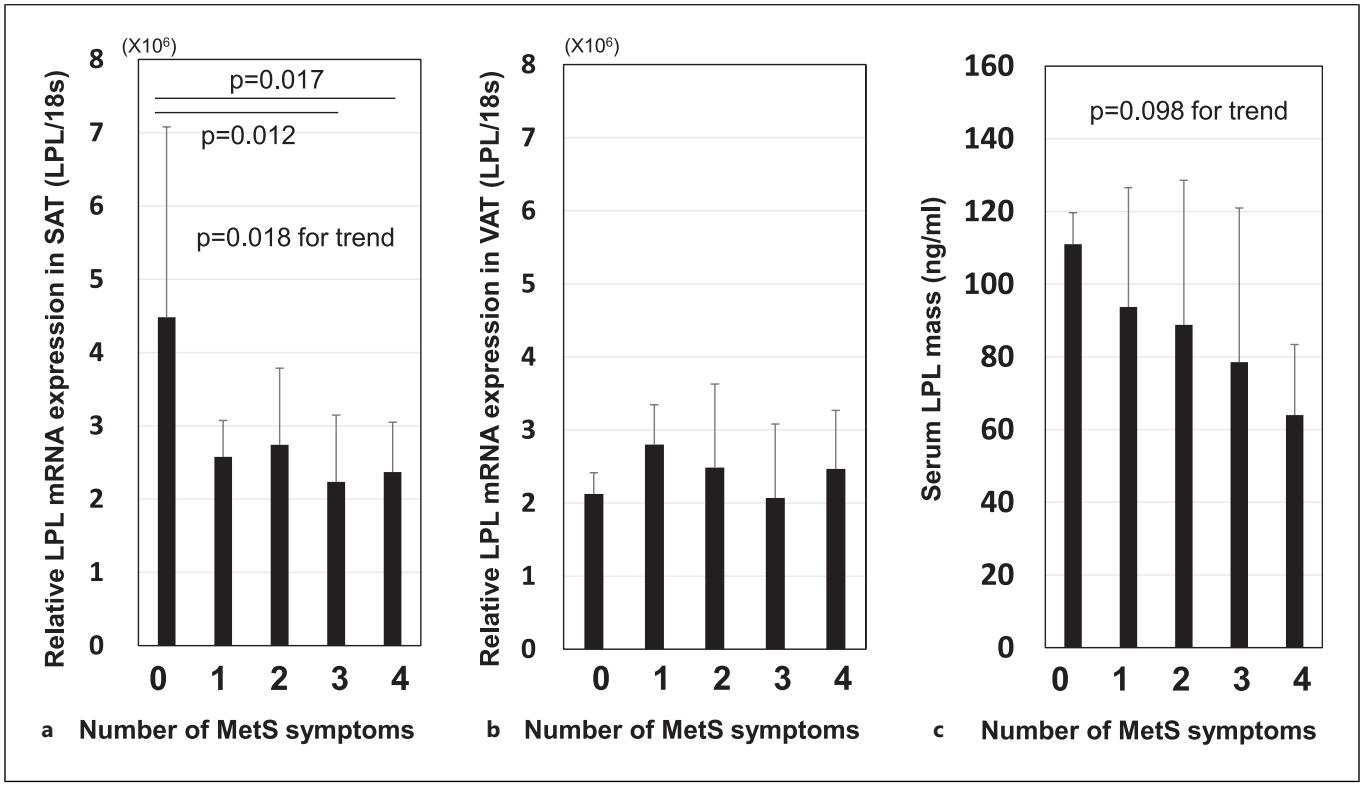

Fig. 1. Relationship between the number of symptoms of MetS and LPL mRNA expression in SFA (**a**), LPL mRNA expression in VFA (**b**), and serum LPL mass level (**c**). Comparison among multiple groups was conducted using one-way ANOVA followed by a post hoc Bonferroni test. LPL, lipoprotein lipase; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; MetS, metabolic syndrome.

SAT-derived LPL may be a factor that suppresses the progression of atherosclerosis, we examined the relationship between LPL mRNA expression in SAT and CAVI in the two groups. LPL mRNA expression in SAT was not associated with CAVI in the group with V/S ratio less than 0.4 (Fig. 2a) but tended to be negatively associated with CAVI in the group with V/S ratio of 0.4 or higher (Fig. 2b). On the other hand, LPL mRNA expression in VAT was not related to CAVI at all, regardless of the V/S ratio (data not shown).

Changes in Serum LPL Mass at 1 Year after LSG

One year after LSG, serum LPL mass increased, and the increase was significantly greater in the group with V/S ratio of 0.4 or higher (Fig. 3). Table 3 shows the univariate correlation analysis between the changes in clinical variables and change in CAVI at 1 year after LSG. Change in CAVI was related to the changes in skeletal muscle mass, body fat mass, and serum LPL mass. We examined the factors associated with the change in CAVI using multiple regression analysis (Table 4). The variables that were significantly associated with changes in CAVI in univariate analysis, i.e., changes in skeletal muscle mass, body fat mass, and serum LPL mass, were selected as variables for the multiple regression model. The change in serum LPL mass at 1 year after LSG tended to be an independent factor associated inversely with the change in CAVI.

Discussion

We hypothesized that LPL derived from SAT may be a factor that suppresses the progression of arteriosclerosis and examined LPL gene expression in adipose tissues of Japanese patients with severe obesity undergoing LSG and its relationship with serum LPL mass and CAVI. LPL mRNA expression in SAT correlated positively with serum LPL mass. Moreover, both serum level of LPL mass and LPL mRNA expression in SAT correlated negatively with the number of MetS symptoms. These findings indicate that serum level of

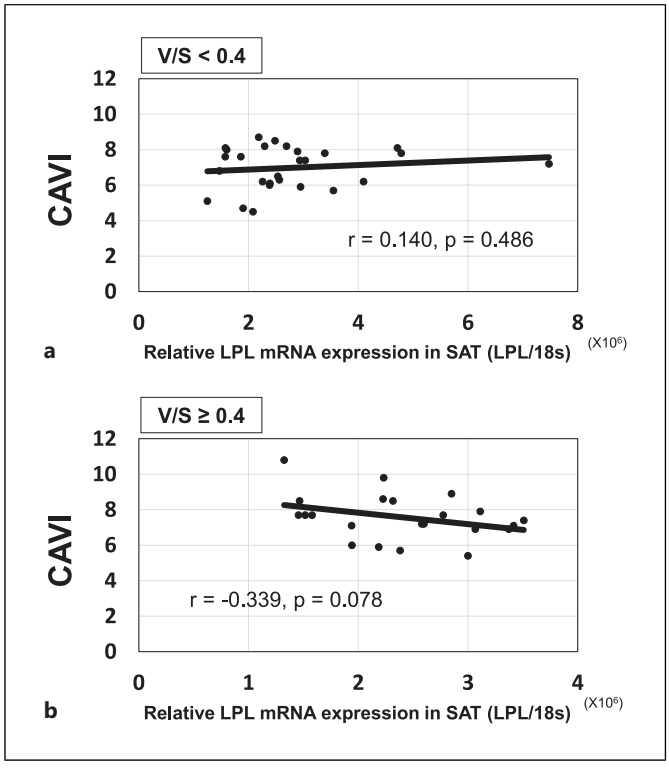

Fig. 2. Correlation between LPL mRNA expression in SAT and CAVI in patients with visceral-to-subcutaneous fat ratio <0.4 (**a**) and ≥0.4 (**b**). LPL, lipoprotein lipase; SAT, subcutaneous adipose tissue; V/S, visceral-to-subcutaneous fat ratio; CAVI, cardio-ankle vascular index.

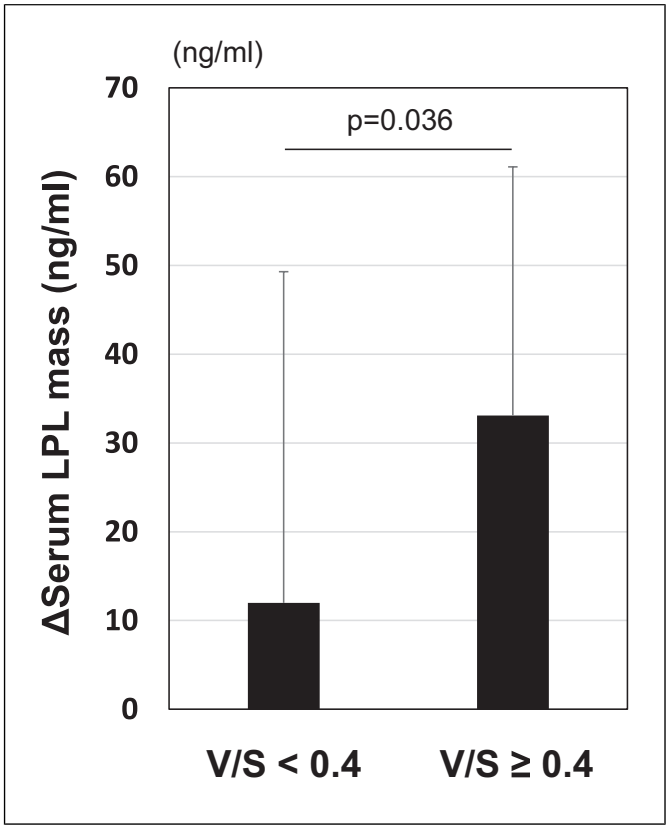

Fig. 3. Change in serum LPL mass level from baseline to 1 year after LSG in patients with visceral-to-subcutaneous fat ratio <0.4 and ≥0.4. LPL, lipoprotein lipase; LSG, laparoscopic sleeve gastrectomy; V/S, visceral-to-subcutaneous fat ratio.

LPL mass reflects LPL mRNA expression in SAT in Japanese patients with severe obesity. In addition, LPL mRNA expression in SAT and CAVI correlated inversely in the group with V/S ratio of 0.4 or higher, which is considered metabolically severe. This finding suggests that LPL mRNA expression in SAT may have a suppressive effect on the elevated CAVI associated with visceral obesity through a direct or indirect mechanism. Finally, the change in serum LPL mass at 1 year after LSG tended to be an independent factor associated negatively with the change in CAVI, suggesting that LPL mass, a marker of LPL mRNA expression in SAT, reflects changes in vascular function in a potentially reversible manner.

Recent data suggest that the "metabolically healthy obesity" phenotype is not a cardiometabolically benign condition [23], and the European Commission classifies obesity as a chronic disease [24]. On the other hand, it has been reported that CAVI inversely correlates with BMI and SFA [4]. In this study, baseline CAVI was higher in the group with V/S ratio of 0.4 or higher, consistent with many studies showing that CAVI correlates positively with visceral obesity. In patients with MetS and patients with type 2 diabetes and obesity, weight reduction using a calorie restriction diet reduced CAVI [5, 25]. On the other hand, the mean CAVI also did not change at 1 year after LSG in this study (data not shown). A Japanese multi-institutional retrospective study reported that subcutaneous fat mass was reduced to a greater extent than visceral fat mass after LSG [26]. These findings may be explained by the inverse relationship between CAVI and SFA [4]. However, the mechanism by which subcutaneous fat accumulation decreases CAVI remains unclear.

According to several studies, serum LPL mass levels reflect insulin sensitivity in adipose tissue and increase with weight loss after LSG [15, 17, 18, 21, 27]. As shown in Figure 3, serum LPL mass increased 1 year after LSG in this study, especially in the group with a V/S ratio of 0.4 or higher. The mechanism by which

bariatric surgery increases serum LPL levels is not fully understood. Previous studies have demonstrated that enlarged adipocytes are associated with substantial changes in adipokines [28, 29]. Enlarged adipocytes are the result of the process of adipogenic differentiation, mainly through activation of PPARγ [30, 31]. LPL, an adipokine that catalyzes the hydrolysis of triglycerides in the blood, is produced mainly in adipocytes by insulin action [9, 10] and is transported to the surface of endothelial cells [11, 32]. We have reported that LPL expression in cultured adipocytes decreases with excessive increase in adipocyte size via the endogenous renin-angiotensin system [33]. Extrapolating these findings, it is possible that reduced adipocyte size as a result of weight loss after LSG may have increased LPL expression in adipocytes. On the other hand, Ohira et al. [18] reported that the increase in serum LPL mass after LSG was associated with LSG per se, independent of the decrease in BMI. LSG may increase serum LPL mass by mechanisms beyond simply weight loss, such as via changing gut microbiota and increasing serum bile acid levels. Further investigations are required.

Table 3. Univariate correlation analysis between the change in CAVI and the changes in clinical variables from baseline to 1 year after LSG

Variables	ΔCAVI	
	rs	*p* value
ΔBody weight	0.005	0.971
ΔBMI	−0.077	0.594
ΔSystolic blood pressure	0.312	0.703
ΔDiastolic blood pressure	0.109	0.477
ΔFBG	−0.114	0.445
ΔHbA1c	0.079	0.595
ΔSerum CPR	−0.203	0.171
ΔTC	0.007	0.962
ΔTG	0.179	0.229
ΔHDL-C	0.009	0.954
ΔAST	0.067	0.653
ΔALT	0.054	0.716
Δγ-GTP	0.200	0.178
ΔCr	0.407	0.050
ΔUric acid	−0.015	0.918
ΔUrine albumin	0.259	0.078
ΔHemoglobin	0.234	0.114
ΔVFA	0.334	0.252
ΔSubcutaneous fat area	−0.027	0.860
ΔSkeletal muscle mass	−0.340	0.022
ΔBody fat mass	0.337	0.091
ΔSerum LPL mass	−0.320	0.028

CAVI, cardio-ankle vascular index; BMI, body mass index; CPR, C-peptide immunoreactivity; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; γ-GTP, γ-glutamyl transpeptidase; Cr, creatinine; LPL, lipoprotein lipase.

In this study, serum LPL mass and CAVI correlated inversely in the group with V/S ratio of 0.4 or higher, suggesting that LPL mRNA expression in adipose tissue may have a suppressive effect on the elevated CAVI associated with visceral obesity. Several clinical reports have described an association between serum LPL levels and CAVI. Nagayama et al. [27, 34] reported that administration of a 5-hydroxytryptamine2A receptor antagonist and statins increased serum LPL, which correlated significantly with a decrease in CAVI. Yamaguchi et al. [35] reported that an LPL enhancer bezafibrate reduced CAVI in hypertriglyceridemic patients with type 2 diabetes. In these three studies, there was no change in body weight or BMI during the study period. LPL is a key regulator of TG, hydrolyzing TG to glycerol and free fatty acids in TG-rich lipoproteins, and is thought to lower the risk of cardiovascular disease. These findings suggest that an increase in serum LPL mass, that is, an increase in LPL mRNA expression in SAT, may have a direct CAVI-lowering effect.

LPL has also been suggested to have an indirect vasodilating effect. Two isoforms of nitric oxide synthase (NOS); inducible NOS and endothelial NOS, are present in adipose tissues [36], suggesting the role of nitric oxide (NO) in regulating adipose tissue mass. On the other hand, the NO-releasing reagent hydroxylamine and

Table 4. Multiple regression analysis of the association between the change in CAVI and the changes in clinical variables from baseline to 1 year after LSG

Independent variable	β coefficient	Standard error	*t* value	*p* value
ΔSkeletal muscle mass	−0.296	0.079	−1.672	0.103
ΔBody fat mass	−0.067	0.025	−0.380	0.706
ΔSerum LPL mass	−0.271	0.006	−1.799	0.080

CAVI, cardio-ankle vascular index; LPL, lipoprotein lipase.

NOS substrate L-arginine increased LPL activities, as well as accelerated TG accumulation in cultured pre-adipocytes derived from rat white adipose tissue [37]. Essentially, NO has a role of relaxing the surrounding smooth muscle, thereby dilating the vessels and increasing blood flow. Taken together, these findings may suggest that NO simultaneously promotes vasodilation and adipocyte differentiation in adipose tissue, resulting in increased TG synthesis. In addition, adipocyte LPL can also affect serum lipids such as oxidized low-density lipoprotein (LDL). It is therefore possible that adipocyte LPL and NO may work together to exert an anti-atherosclerotic effect by inhibiting markers of inflammation and oxidative stress such as oxidized LDL. Further studies are needed in another population with residual serum to measure inflammatory markers.

In this study, LPL mRNA expression in VAT was not associated with serum LPL mass, the number of MetS symptoms, or CAVI. However, many studies clearly show that CAVI correlates with VFA in patients with obesity [2, 4]. Nonetheless, no report has examined whether LPL mRNA expression in VAT is associated with CV events or vascular function. One of the limitations of this study is that we could not find an association between LPL mRNA expression in VAT and CAVI. Rather, LPL mRNA expression in SAT tended to be associated negatively with CAVI in the group with higher V/S ratio, and the increase in serum LPL mass after LSG was significantly greater in the group with higher V/S ratio in this study. Although LPL mRNA expression in VAT alone does not affect CAVI, LPL mRNA expression in VAT may interact with that in SAT. This possibility warrants further investigation in the future. One of the strengths of this study is that it is the first study to obtain both gene expression in SAT and CAVI data in patients with severe obesity. In the future, it is expected that new atherosclerosis-inhibiting and atherosclerosis-promoting factors will be identified in SAT.

Conclusion

Serum LPL mass reflected LPL mRNA expression in SAT in Japanese patients with severe obesity, and LPL mRNA expression in SAT was inversely related to CAVI in patients with visceral obesity. The change in serum LPL mass at 1 year after LSG tended to be an independent factor inversely associated with the change in CAVI. This study found that serum LPL reflects LPL expression derived from SAT in patients with severe obesity and suggests that LPL derived from SAT may suppress the progression of arteriosclerosis.

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Statement of Ethics

All procedures and data collection were in accordance with the ethical standards of the Institutional and Japanese National Research Committees or the ethical standards of the Helsinki Declaration of 1975. Details about the study were disclosed on the hospital's website, and the potential participants were given the opportunity to opt-out. This study and consent procedure were reviewed and approved by the Ethics Committee of Toho University Sakura Medical Center, approval number S21056.

Conflict of Interest Statement

The authors have no competing interest to declare.

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Author Contributions

Yuka Takahashi, Shoko Nakamura, Shuhei Yamaoka, Kazuki Abe, Sho Tanaka, Yasuhiro Watanabe, Takashi Yamaguchi, Daiji Nagayama, Masahiro Ohira, Ichiro Tatsuno, and Kohji Shirai contributed to collection and/or assembly of data. Atsuhito Saiki contributed to the research concept and design, collection and/or assembly of data, data analysis, and writing of the article. Takashi Oshiro contributed to data interpretation and critical revision of the manuscript. All authors approved the version to be published.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request. Further inquiries can be directed to the corresponding author.

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