

[ORIGINAL ARTICLE]

Treatment of Hepatitis C Virus Infection with Direct-acting Antiviral Agents Elevates the Serum Small-dense Low-density Lipoprotein Cholesterol Level

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Abstract:

Objective The low-density lipoprotein cholesterol (LDL) level is known to increase following the treatment of hepatitis C virus (HCV) infection using direct-acting antiviral agents (DAAs). This study aimed to investigate the changes in the lipid profiles, including small-dense LDL cholesterol (sdLDL), in HCV patients treated with DAAs.

Patients We retrospectively assessed 67 HCV patients who achieved sustained virological response with DAA administration and were observed for more than 2 years, of whom 32 were on daclatasvir/asunaprevir, 14 were on sofosbuvir/ledipasvir, and 21 were on sofosbuvir/ribavirin.

Methods We evaluated the lipid profiles, including sdLDL, every 6 months until 2 years after the start of treatment and analyzed the factors related to changes in the sdLDL level.

Results The median sdLDL value at baseline was 12.8 mg/dL, which increased to 19.5 mg/dL at 6 months ($p < 0.001$) and remained elevated at 25.4 mg/dL at 2 years later ($p < 0.001$). The Kaplan-Meier curve indicated that patients with high values of LDL, albumin, muscle attenuation and visceral to subcutaneous adipose tissue area ratio were at increased risk for elevation of sdLDL over 35 mg/dL (log-rank test: $p < 0.001$; $p = 0.008$, $p = 0.002$ and $p = 0.042$, respectively). A multivariate analysis performed on the factors contributing to elevation of sdLDL 2 years after DAA treatment (≥ 35.0 mg/dL) revealed pretreatment LDL (≥ 91.0 mg/dL) and muscle attenuation (≥ 33.7 HU) as significant factors ($p = 0.007$ and $p = 0.032$, respectively).

Conclusion SdLDL increased continuously after DAA treatment, and high LDL levels and low intramuscular fat deposition before treatment contributed to elevated sdLDL levels after treatment.

Key words: hepatitis C virus, direct-acting antiviral agents, intramuscular fat deposition, small dense low-density lipoprotein cholesterol

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Introduction

Hepatitis C virus (HCV) infection is one of the most common chronic diseases worldwide and a major cause of liver cirrhosis and hepatocellular carcinoma (HCC) (1).

Chronic HCV infection is also associated with metabolic disorders, such as fatty liver, diabetes, and dyslipidemia (2). Recently, interferon-free regimens composed of direct-acting antiviral agents (DAA) were developed (3-5). DAA treatment for patients with HCV infection has been shown to induce a sustained virological response (SVR) in many cases.

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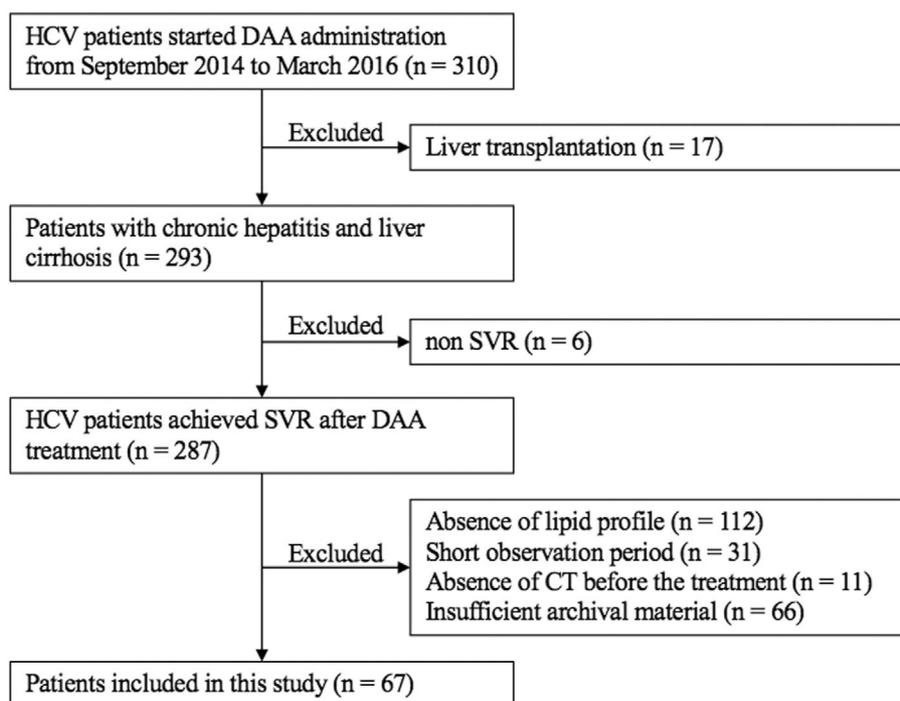


Figure 1. Patients enrolled in this study. CT: computed tomography, DAA: direct-acting antiviral agents, HCV: hepatitis C virus, SVR: sustained virological response

Similar to interferon therapy, SVR induced by DAAs is associated with a reduction in the HCC risk (6).

Changes in the lipid profiles after DAA administration have been reported in recent years. The life cycle of HCV is closely related to the lipid metabolism (2, 7). In 2015, antiviral therapy using sofosbuvir (SOF) and ribavirin (RBV) was reported to increase the serum low-density lipoprotein cholesterol (LDL) level in patients infected with the HCV genotype 1 by week 4 and sustained at week 24 (end of treatment) until week 36 (8). Subsequently, changes in the lipid profiles were also reported after the administration of mainly daclatasvir (DCV)/asunaprevir (ASV), SOF/ledipasvir (LDV), and SOF/RBV (9-13).

LDL contains fractions of large buoyant particles and small-dense particles (14). Small-dense LDL (sdLDL) particles have a low-binding affinity to LDL receptors, tend to penetrate the arterial wall, and are susceptible to oxidative stress. A simple precipitation assay for selective and direct measurement of serum sdLDL was developed in 2003 (15). Recently, using this quantitative method, sdLDL was found to be a predictive factor of coronary artery diseases (CADs) (16-20).

Previous reports have indicated that the sdLDL level, measured after HCV eradication using DAAs, is associated with carotid intima-media thickness (IMT) (21), liver steatosis, and dyslipidemia (22). However, to our knowledge, no studies have so far investigated the long-term outcomes of DAAs and factors that influence the relationship between DAA treatment and LDL profiles, including sdLDL, over a one-year period. Thus, this study aimed to investigate changes in lipid profiles, including sdLDL, in HCV patients

treated with DAAs and to analyze the factors related to sdLDL changes.

Materials and Methods

Study participants

A total of 310 HCV patients with chronic hepatitis and liver cirrhosis were started on an interferon-free treatment at a university hospital and medical center from September 2014 to March 2016. Chronic HCV infection was diagnosed by detecting the positivity of anti-HCV antibody and HCV-ribonucleic acid (RNA). Cases were included if they could be followed for >2 years from the start of treatment and sdLDL could be measured from conserved serum every 6 months. The exclusion criteria were 1) patients who underwent liver transplantation (n=17), 2) patients who did not achieve SVR (n=6), and 3) insufficient data, such as a short observation period and the absence of lipid profile data and computed tomography (CT) analysis (n=220). Finally, a total of 67 patients were eligible for inclusion in this retrospective study (Fig. 1).

Treatment regimen

A combination therapy of DCV (Daklinza[®], Bristol-Myers Squibb, New York, USA) (60 mg, once daily) and ASV (Sunvepra[®], Bristol-Myers Squibb) (100 mg, twice daily) was taken orally for 24 weeks, SOF (400 mg, once daily) and LDV (90 mg, once daily) (Harvoni[®], Gilead Sciences, Foster City, USA) for 12 weeks, and SOF (Sovaldi[®], Gilead Sciences) (400 mg once daily) and RBV (600 mg, 800 mg,

or 1,000 mg daily according to body weight) for 12 weeks. DCV/ASV and SOF/LDV were administered to patients infected with HCV genotype 1b, and SOF/RBV was administered to patients infected with HCV genotype 2a/2b. The SVR was determined by confirming the negativity of HCV-RNA at 12 weeks after DAA administration.

Study design

Lipid profiles, including sdLDL, were evaluated at baseline, 0.5, 1, 1.5, and 2 years after the start of treatment. sdLDL levels were measured from the conserved serum at the same blood sampling date. The sdLDL increase rate after the 2-year treatment was compared according to DAAs and HCV genotypes. Patients were divided into two groups by the sdLDL levels at 35 mg/dL 2 years after the treatment, and the factors contributing to elevated sdLDL levels were analyzed.

Demographic data and laboratory measurements

The demographic data including age, sex, medical history, body mass index (BMI), and laboratory data before the treatment were collected. BMI was calculated by dividing patients' weight (kg) by the square of their height (m). Laboratory data included alanine 2-oxoglutarate aminotransferase (ALT), serum albumin, LDL, high-density lipoprotein cholesterol (HDL), TG, and alpha-fetoprotein (AFP). The fibrosis-4 (FIB-4) index was calculated using the following equation: $[\text{age (years)} \times \text{aspartate 2-oxoglutarate aminotransferase (U/L)}] / [\text{platelet count (} 10^4/\mu\text{L)} \times 10 \times \text{ALT (U/L)}]^{1/2}$. Hypertension and diabetes mellitus were determined by the medical history, using of medications, and the diagnostic criteria. Hypertension was defined as blood pressure $\geq 140/90$ mmHg (23). Diabetes mellitus was defined as a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c $\geq 6.5\%$ (23). SdLDL was measured using a homogeneous assay (sd LDL-EX, Denka Seiken, Tokyo, Japan). Biochemistry tests including those for sdLDL were performed on BioMajesty JCA-BM6070 (JEOL, Tokyo, Japan).

CT analyses of body composition variables

CT was performed within 1 month before or after screening for HCC prior to DAA treatments. CT images of the third lumbar vertebra (L3) were analyzed using Slice-O-Matic software (version 5.0; Tomovision, Montreal, Canada) to determine both the skeletal muscle and adipose tissue areas. Each tissue was demarcated using previously reported Hounsfield unit (HU) thresholds (24). The skeletal muscle was identified at -29 to +150 HU. Subcutaneous adipose tissue (SAT) was defined as -190 to -30 HU and visceral adipose tissue (VAT) as -150 to -50 HU. The skeletal muscle was normalized by dividing the area by the square of the height, and called the skeletal muscle index (SMI) (25). To evaluate the quality of skeletal muscle and intramuscular fat deposition, the CT attenuation value of the skeletal muscle in the L3 region was measured, the average of which was called muscle attenuation (MA). In addition, the visceral to

subcutaneous adipose tissue area ratio (VSR) was calculated to assess abdominal adipose tissue distributions.

Statistical analysis

The data were analyzed using the Stata software program version 15 (StataCorp, College Station, USA). Continuous data were expressed as medians [interquartile range (IQR)]. Changes in the LDL, sdLDL, HDL, and TG levels were compared using the Wilcoxon signed-rank test. The sdLDL increase rates in the 2-year treatment according to DAAs and genotypes were compared using the Kruskal-Wallis test. The Mann-Whitney U test was used to compare two groups, divided based on the sdLDL value at 35 mg/dL 2 years after the treatment. Multinomial variables were compared with chi-square tests. In patients divided into the two groups, the cumulative incidence of the increase in sdLDL ≥ 35 mg/dL was estimated by the Kaplan-Meier method and assessed using the log-rank test. Laboratory data were dichotomized with the median value at baseline. Body composition variables were divided by the cut-off points (SMI, MA, and VSR) determined by analyzing the receiver operating characteristic (ROC) curve. The Cox regression analysis was used to identify risk factors of sdLDL increase. Age, sex, and variables with $p < 0.20$ were selected for the multiple regression model. Values of $p < 0.05$ were considered to be statistically significant.

Ethical consideration

Informed consent was obtained from each patient, and the study protocol was approved by the ethical committee of each hospital and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Results

Baseline characteristics

The baseline characteristics of the patients are shown in Table 1. The median age was 70.0 years. There were 27 (40.3%) men and 40 (59.7%) women. 32 patients received DCV/ASV, 14 received SOV/LDV, and 21 received SOF/RBV. The median LDL level at baseline was 91.0 (IQR 79-110) mg/dL, HDL was 57.0 (IQR 45-65) mg/dL, TG was 100.0 (IQR 76-131) mg/dL, and sdLDL was 12.8 (IQR 9-19) mg/dL. Four patients (6.0%) were treated with statins.

Changes in serum lipid profiles

The boxplots of the changes of each lipid profile are illustrated in Fig. 2. The median LDL level increased from 91.0 to 112.0 (IQR 98-132) mg/dL in 6 months after treatment ($p < 0.001$) and remained elevated at 114.0 (IQR 91-133) mg/dL at 2 years after treatment ($p < 0.001$). The median sdLDL level also increased from 12.8 to 19.5 (IQR 14-26) mg/dL at 6 months after treatment ($p < 0.001$) and remained elevated at 25.4 (IQR 20-36) mg/dL 2 years after treatment ($p < 0.001$). The median HDL levels at 6 months

Table 1. Baseline Characteristics of Patients.

Characteristics	n (interquartile range, %)
Age, years	70.0 (62-77)
Sex, male/female	27/40
BMI	22.5 (21-24)
Genotype 1B/2A/2B	46/17/4
DAA DA/SL/SR	32/14/21
HCV-RNA (log IU/mL)	6.20 (5.6-6.6)
Alb (g/dL)	4.10 (3.7-4.3)
ALT (IU/L)	40.0 (26-70)
Fib-4 index	3.60 (2.4-7.6)
AFP (ng/mL)	5.90 (3.3-12.0)
LDL (mg/dL)	91.0 (79-110)
HDL (mg/dL)	57.0 (45-65)
TG (mg/dL)	100.0 (76-131)
sdLDL (mg/dL)	12.8 (9-19)
Statin use, n (%)	4 (6.0)
Hypertension, n (%)	31 (44.3)
Diabetes, n (%)	8 (11.9)
Body composition variable	
SMI (cm ² /m ²)	40.6 (35-48)
MA (HU)	30.8 (28-35)
VSR	0.511 (0.39-0.84)

Results are expressed as median (interquartile range) or frequency (%). AFP: alpha fetoprotein, Alb: serum albumin, ALT: alanine aminotransferase, BMI: body mass index, DA: daclatasvir/asunaprevir, DAA: direct acting antiviral, FIB-4: fibrosis-4, HCV: hepatitis C virus, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, MA: muscle attenuation, sdLDL: small dense low-density lipoprotein cholesterol, SL: sofosbuvir/ledipasvir, SMI: skeletal muscle index, SR: sofosbuvir/tribavirin, TG: triglyceride, VSR: visceral to subcutaneous adipose tissue area ratio

and 1.5 years from baseline were higher than those at baseline ($p=0.004$ and $p=0.006$, respectively). However, HDL levels at 1 and 2 years from the start of treatment did not significantly increase compared with the baseline levels. Similarly, the TG level did not significantly increase compared with its baseline level. Finally, the median sdLDL level increased from 12.8 mg/dL to 25.4 mg/dL, and the increase in ratio in 2 years was 2.06 (IQR 1.4-2.9) (Fig. 3).

We divided the patients into two groups based on the sdLDL levels at 35 mg/dL 2 years after the treatment. In previous reports, patients with sdLDL ≥ 35 mg/dL had significantly more cardiovascular events than those with lower sdLDL levels (19, 20). There were 19 patients in the high sdLDL group and 48 in the low sdLDL group (Table 2). The LDL levels at baseline were significantly higher in the high sdLDL group than in the low sdLDL group ($p<0.001$).

Kaplan-Meier event-free survival analysis

The Kaplan-Meier event-free survival curves for patients divided at the median levels of LDL and albumin, presence or absence of hypertension, and at the cut-off points of SMI, MA, and VSR, as determined by analyzing the ROC curve, are illustrated in Fig. 4. We excluded two patients whose

sdLDL exceeded 35 mg/dL at baseline and therefore analyzed 65 patients. The cumulative incidence of the increase in sdLDL ≥ 35 mg/dL was evaluated. Events influencing the increase in sdLDL level ≥ 35 mg/dL were observed in 20 patients. Patients with high median levels of LDL and albumin, and MA and VSR levels above the target level were at increased risk for events that lead to an sdLDL increase ≥ 35 mg/dL (log-rank test: $p<0.001$, $p=0.008$, $p=0.002$ and $p=0.042$, respectively). No statistical differences were observed regarding the existence of hypertension and above or below the target levels of SMI.

Cox regression analysis

Hazard ratios (HR) with a 95% confidence interval (CI) of each risk factor for the increase in sdLDL ≥ 35 mg/dL was estimated by the Cox proportional hazard model (Table 3). According to a univariate analysis, LDL and albumin above the median value; MA above the cut-off point, determined by the ROC curve were associated with an increased risk of a sdLDL increase. According to a multivariate Cox regression analysis, LDL (≥ 91.0 mg/dL, HR 4.768, 95%CI 1.524-14.919, $p=0.007$) and MA (≥ 33.7 HU, HR 2.735, 95%CI 1.092-6.848, $p=0.032$) were independent risk factors of an elevated sdLDL level.

Discussion

The direct quantification method of sdLDL was recently used in many cohort studies. In the Suita study, a cohort study conducted in Japan, the increase in sdLDL was identified as a significant risk factor for cardiovascular disease (17). This method was used in two clinical trials in the United States (16, 18). Our group showed that a significant correlation was observed between sdLDL and carotid IMT after DAA treatment (21).

When the sdLDL level at 2 years from the administration of DAAs was divided into two groups based on a level ≥ 35 mg/dL, the LDL levels tended to be high in the sdLDL ≥ 35 mg/dL group, and the Kaplan-Meier event-free survival analysis showed that patients with high values of LDL, albumin, MA and VSR were at increased risk of events that increase sdLDL ≥ 35 mg/dL. Patients with sdLDL level ≥ 35 mg/dL have been reported to develop more cardiovascular events than those with lower sdLDL levels (19, 20), as a result, the eradication of HCV by DAA treatments may increase the incidence of CAD in the future. According to a Cox regression analysis, a high LDL level and high CT attenuation of skeletal muscles before treatment were associated with an increase in sdLDL after DAA treatment. The higher the LDL levels, the higher the sdLDL levels (16, 17). Our results also confirmed the positive correlation between LDL and sdLDL levels at baseline and 2 years after treatment (Supplementary material 1). This association, shown in the multivariate analysis, was considered to be physiological.

Several mechanisms associated with an elevated LDL

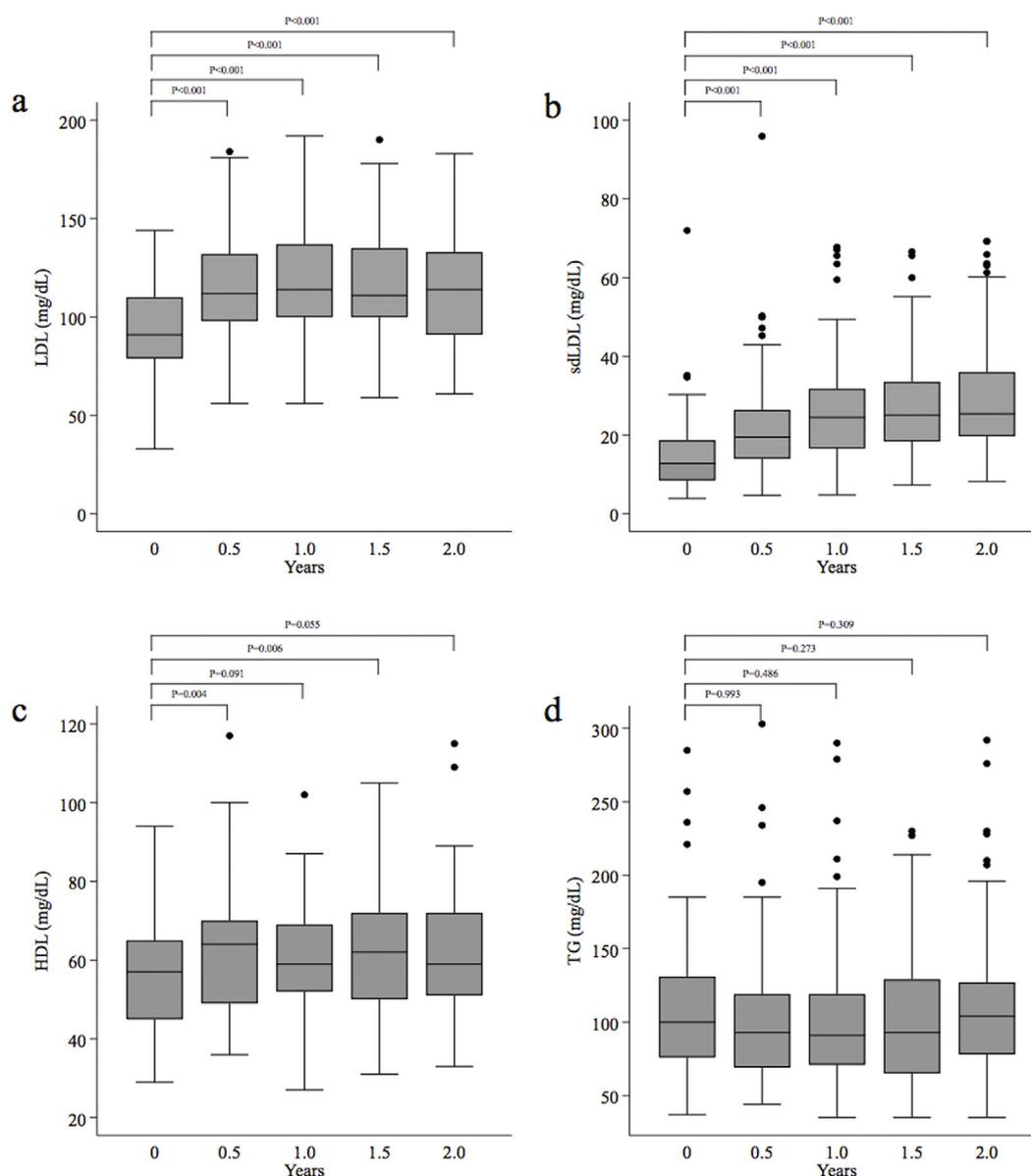


Figure 2. Boxplots of the longitudinal changes in each lipid profile after the administration of DAAs. (a) LDL, (b) sdLDL, (c) HDL, and (d) TG at baseline, 0.5 years, 1 year, 1.5 years, and 2 years after the start of DAA treatment. The line within the box represents the median value, the box height is the interquartile range (first to third quartile), the lower and upper whiskers represent minimum and maximum values, respectively, and dots are outliers. Wilcoxon's signed-rank test was performed for comparisons. DAA: direct-acting antiviral agents, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, sdLDL: small-dense low-density lipoprotein cholesterol, TG: triglyceride

level after DAA treatment have been reported. One of the causes of the increase in serum cholesterol after HCV eradication is thought to be the excess lipids in the blood due to the loss of function of the HCV life cycle, which uses the lipid metabolism in hepatocytes, such as the formation of lipoviral particles by connecting with lipoproteins (2, 7). We also evaluated the associations between serum protein convertase subtilisin/kexin 9 (PCSK9), microRNA (miR) 122, and an elevation of LDL levels after treatment of HCV genotype 1b infection with DCV/ASV (26). PCSK9 plays a role in promoting the lysosomal degradation of the LDL re-

ceptor by preventing it from recycling to the plasma membrane of hepatocytes, which causes the increase in the plasma LDL levels (27). The antagonism of miR122 induces the suppression of HCV replication and cholesterol synthesis (28). Thus, the upregulation of miR122 in hepatocytes may strengthen lipogenesis and elevate the serum LDL levels.

To the best of our knowledge, this is the first report to investigate the relationship between hyperlipidemia after DAA treatment of HCV and body composition. Liver disease is considered to be a representative disease of secondary sarco-

penia, and the Japan Society of Hepatology has proposed the criteria for diagnosing sarcopenia in liver disease (29). Obesity is also associated with chronic liver diseases, and patients with liver cirrhosis may develop loss of skeletal muscle and gain of adipose tissue. The concurrence of sarcopenia and obesity is called sarcopenic obesity (30). Additionally, when the cells of skeletal muscle are depleted, fatty infiltration into the muscles is often present, which is called myosteatosis. In previous reports, the survival rates of sarco-

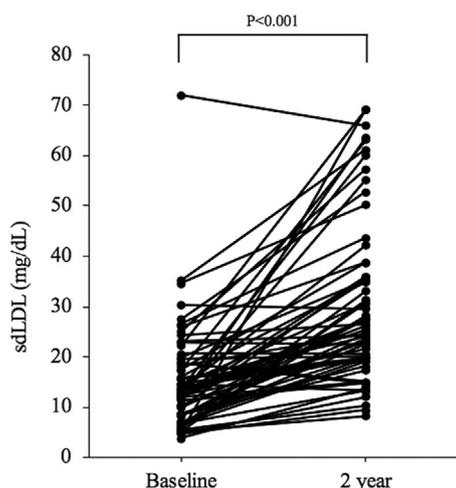


Figure 3. Change in sdLDL from baseline to 2 years after treatment. Changes in sdLDL levels in individual patients from baseline to 2 years after the DAA treatment. Wilcoxon's signed-rank test was performed for comparisons. DAA: direct-acting antiviral agents, sdLDL: small-dense low-density lipoprotein cholesterol

penia, sarcopenic obesity, and myosteatosis groups in cirrhosis and HCC patients were lower than those in patients without muscular abnormalities (25, 30). Additionally, intramuscular fat deposition has been reported to be related to the glucose metabolism and increased total cholesterol (31). Contrary to previous reports, our study showed that the group with low intramuscular fat deposition had higher sdLDL levels after DAA treatment. The apparent cause of the association between elevated sdLDL and high CT values of skeletal muscle is unknown. LDL was also a factor contributing to sdLDL elevation after treatment, and sdLDL tended to increase above 35 mg/dL in the high albumin and VSR group. After the eradication of HCV, the quality of life of HCV patients is expected to improve; oral intake will increase and weight gain and obesity are attained, leading to hyperlipidemia. Our results suggest that HCV patients who have good nutritional status, good muscle quality, and higher LDL cholesterol levels tended to have increased levels of sdLDL with treatment. These patients may develop CAD after SVR and have a poor prognosis by the DAA treatment.

In this study, the sdLDL level increased approximately twice in the 2 years after treatment with DAAs. No patients were treated for elevated LDL levels during the observation period in this study. However, CAD are expected to increase in these patients, treatment for the hyperlipidemia should be actively considered. Although the therapeutic agents for sdLDL have not yet been investigated sufficiently, statins and sodium-glucose co-transporter-2 inhibitors have been reported to be effective (32, 33).

Patients treated with DCV/ASV had a higher increase rate than patients treated with SOF/LDV or SOF/RBV (Supplementary material 2). However, no significant change was

Table 2. Comparison of Clinical Characteristics between Two Groups Divided by SdLDL Level after DAA Treatment for 2 Years at a Cutoff Value of 35 mg/dL.

Factor	sdLDL<35 mg/dL (n=48)	sdLDL≥35 mg/dL (n=19)	p value
Age, years	70.5 (64-78)	68.0 (59-75)	0.150
Sex, male/female	18/30	9/10	0.458
BMI	22.7 (22-24)	22.4 (18-24)	0.160
HCV-RNA (log IU/mL)	6.15 (5.8-6.6)	6.20 (5.3-6.6)	0.671
Alb (g/dL)	4.00 (3.6-4.3)	4.10 (3.8-4.7)	0.077
Fib-4 index	4.28 (2.6-7.6)	2.88 (1.9-6.5)	0.158
AFP (ng/mL)	6.35 (3.3-12.3)	5.00 (3.4-7.1)	0.636
LDL (mg/dL)	87.0 (76-97)	112.0 (91-126)	0.002
HDL (mg/dL)	56.0 (44-63)	59.0 (52-77)	0.081
TG (mg/dL)	101.5 (76-130)	91.0 (71-155)	0.994
Hypertension +/-	25/23	5/14	0.056
Diabetes +/-	5/43	3/16	0.541
SMI (cm ² /m ²)	40.6 (36-48)	41.3 (33-47)	0.559
MA (HU)	30.4 (28-33)	33.7 (26-37)	0.487
VSR	0.490 (0.39-0.82)	0.558 (0.45-0.81)	0.922

Data were collected at baseline. Results are expressed as median (interquartile range) or number. Mann-Whitney U and chi-square tests were performed for comparisons. AFP: alpha fetoprotein, Alb: serum albumin, BMI: body mass index, FIB-4: fibrosis-4, HCV: hepatitis C virus, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, MA: muscle attenuation, SMI: skeletal muscle index, TG: triglyceride, VSR: visceral to subcutaneous adipose tissue area ratio

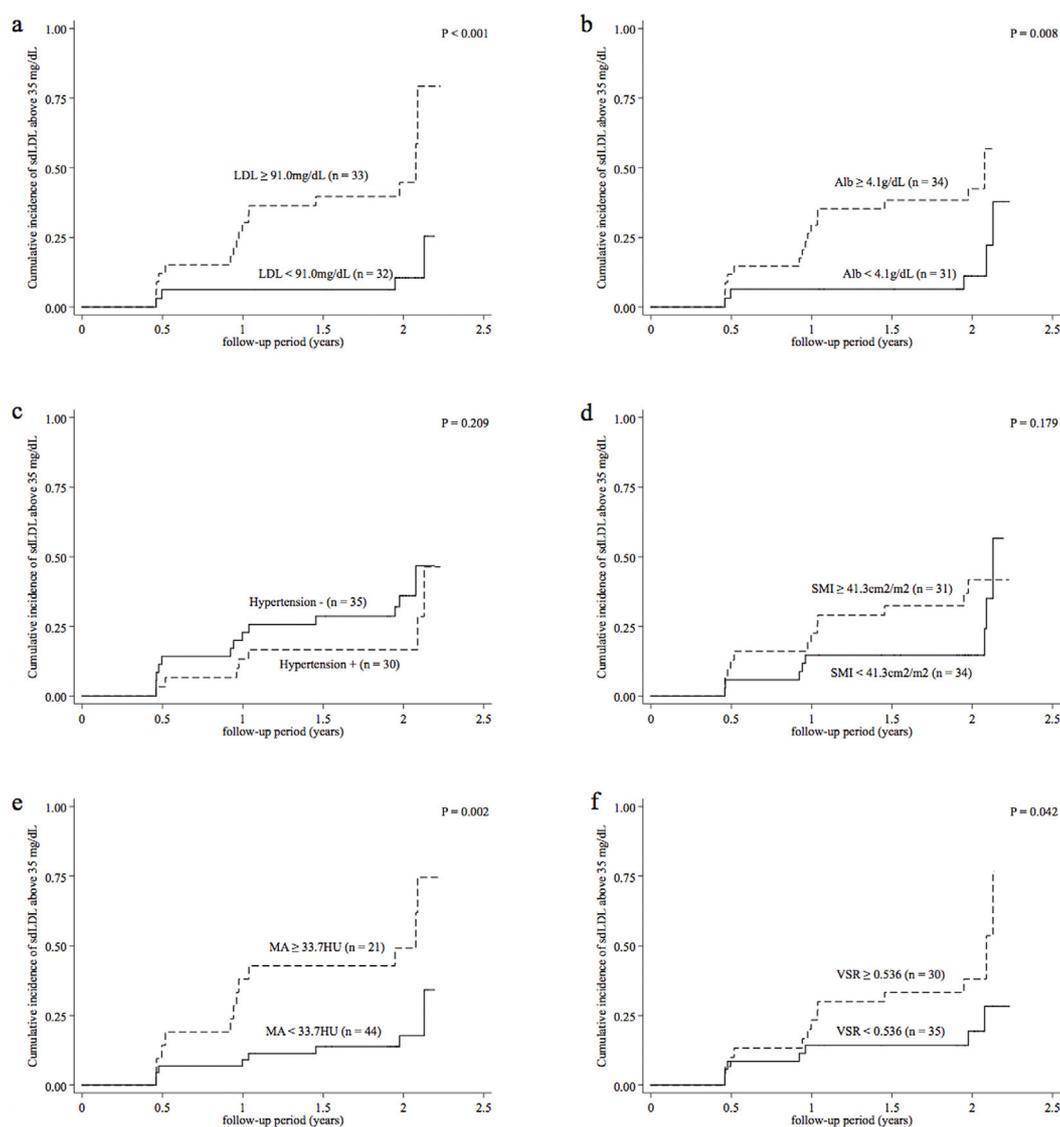


Figure 4. Cumulative incidence curves of the increase in sdLDL ≥ 35 mg/dL according to clinical and body composition variables. The survival rates were analyzed using the Kaplan-Meier method. Two groups were divided at the median levels for (a) LDL and (b) albumin, presence or absence of hypertension (c), and cut-off points of (d) SMI, (e) MA, and (f) VSR, as determined by the ROC curve. Incidence rates were compared using log-rank test. Alb: serum albumin, LDL: low-density lipoprotein cholesterol, MA: muscle attenuation, SMI: skeletal muscle index, VSR: visceral to subcutaneous adipose tissue area ratio

found in the increase rate between HCV genotypes (1b, 2a, and 2b). Similar increases in LDL levels of patients who achieved SVR with interferon therapy were reported (34). Therefore, it is considered that the increase in the LDL levels is derived in part from the clearance of HCV, regardless of the therapy regimen. With regard to the relationship between DAAs and lipid metabolism, SOF/LDV regimen increased the LDL levels rapidly during the treatment period, but DCV/ASV regimen tended to increase the LDL levels greater than those treated with the regimens including SOF after treatment (11, 12). The eradication of HCV was not considered to be the sole factor, and DAAs themselves may therefore induce pharmacological effects on the lipid metabolism.

Our study is associated with some limitations. The sample size was small ($n=67$), and this was a retrospective study. Future studies are therefore required to further analyze the long-term outcomes, including complications, of HCV eradication. In this study, we defined the increase of sdLDL as the events according to a Kaplan-Meier event-free survival analysis and a Cox regression analysis. In fact, the onset of CAD should be defined as an event for these analyses. However, there are few reports with long-term follow-up periods evaluating dyslipidemia more than 2 years after DAA treatment.

In conclusion, the LDL level, including sdLDL, increased from 6 months after the start of DAA treatment and remained high until 2 years later. High LDL levels and low

Table 3. Risk Factors for the Increase in sdLDL Level above 35 mg/dL.

Factors	Univariate			Multivariate		
	Hazard ratio	95%CI	p value	Hazard ratio	95%CI	p value
Age ≥70	0.496	0.197-1.247	0.136			
Male	1.432	0.594-3.451	0.423			
BMI ≥22.5	0.840	0.344-2.051	0.702			
Alb >4.1 g/dL	3.650	1.310-10.169	0.013	2.886	0.976-8.529	0.055
FIB-4 index ≥4.2	0.391	0.150-1.019	0.055			
LDL ≥91.0 mg/dL	5.938	1.923-18.342	0.002	4.768	1.524-14.919	0.007
HDL ≥57.0 mg/dL	1.196	0.495-2.888	0.691			
Hypertension	0.558	0.222-1.405	0.216			
SMI ≥41.3	1.833	0.746-4.505	0.187			
MA ≥33.7	3.831	1.562-9.396	0.003	2.735	1.092-6.848	0.032
VSR ≥0.449	2.525	1.002-6.362	0.05			

95% CI: 95% confidence interval, Alb: serum albumin, BMI: body mass index, FIB-4: fibrosis-4, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, MA: muscle attenuation, SMI: skeletal muscle index, VSR: visceral to subcutaneous adipose tissue area ratio. Each variable was assessed using Cox proportional hazards analysis

intramuscular fat deposition at baseline contributed to the elevated sdLDL levels after 2 years of treatment. Thus, in these patients and in HCV patients, strict lipid level monitoring is required after DAA treatment.

The authors state that they have no Conflict of Interest (COI).

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