Carotid Intima-media Thickness and Small Dense Low-density Lipoprotein Cholesterol Increase after One Year of Treatment with Direct-acting Antivirals in Patients with Hepatitis C Virus Infection

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Abstract:
Objective Direct-acting antivirals (DAAs) for treating hepatitis C virus (HCV) infection exert a significantly high sustained viral response (SVR), and patients experience a rebound increase in low-density lipoprotein cholesterol (LDL) and total cholesterol levels. Carotid intima-media thickness (IMT) is a highly reproducible and non-invasive parameter for assessing the atherosclerotic process, and the small dense (sd) LDL level is useful for clinically evaluating the atherogenic risk.

Methods A total of 48 patients with chronic HCV infection were treated with DAAs. All patients exhibited an SVR 24 weeks later. We compared the metabolic profiles of the patients, including the sdLDL and IMT values, at the start of DAA treatment with those after one year of treatment. We verified whether the HCV clearance after the administration of DAAs is associated with the development of atherosclerosis.

Results The sdLDL, %sdLDL (sdLDL/LDL), and LDL values were exacerbated after a year of treatment; however, the triglyceride level, glycated hemoglobin level, insulin resistance, and body weight remained unaltered. The max-IMT was increased after a year compared to that at the start of treatment. Differences in the max-IMT (dmax-IMT) were greater in men than in women; however, no correlation was observed between the max-IMT and genotype, fibrosis, hypertension, hyperlipidemia, diabetes, obesity, and dialysis status. The %sdLDL at the start and a year later was positively correlated with the dmax-IMT. No correlation was observed among various factors including the LDL, triglyceride, body mass index, insulin resistance and dmax-IMT. In uni- and multivariate analyses, a significant correlation was observed between %sdLDL≥16% at the start of treatment and the sex and dmax-IMT.

Conclusion Because the sdLDL and IMT values were exacerbated after a year of DAA treatment, atherosclerosis must be evaluated in patients achieving an SVR.

Key words: hepatitis C virus, direct-acting antivirals, intima-media thickness, small dense low-density lipoprotein cholesterol

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The recent introduction of direct-acting antivirals (DAAs) has changed hepatitis C virus (HCV) infection treatment. Daclatasvir/asunaprevir (DCV/ASV) (1) and sofosbuvir/ledipasvir (SOF/LDV) (2) for HCV 1B infection and sofosbuvir/ribavirin (SOF/RBV) for HCV 2A/2B infection (3) are common DAA treatments in Japan. These treatments result in significantly high sustained viral response (SVR) rates (85-100%) after a short treatment course (12-24 weeks) without any severe adverse effects. As a result of DAA treatment for HCV infection, the rate of hepatocellular carcinoma occurrence or recurrence is not markedly different between patients achieving an SVR after receiving DAA and those achieving an SVR after receiving interferon-based therapy (4). In addition, the wait time for liver transplantation for HCV infection complicated by decompensated cirrhosis has decreased by over 30% due to the advent of DAA therapy (5).

It has been reported that SVR induced by interferon-based therapy resolves HCV-related extrapathologic disorders and reduces the overall mortality due to hepatic and non-hepatic pathologies as well as the risk of cardiovascular events and bacterial infections (6). SVR causes a two-thirds reduction in the risk of type 2 diabetes mellitus development in HCV-positive patients treated with interferon-based therapy (7). Interferon-based treatment is also associated with a lower risk of end-stage renal disease, acute coronary syndrome, and ischemic stroke (8). HCV-infected patients exhibit increased rates of insulin resistance, diabetes, and atherosclerosis, which may lead to increased cardiovascular morbidity and mortality (9).

The serum lipid profile is a prediction factor for SVR (10), and a significant proportion of patients successfully treated with interferon experience a rebound increase in low-density lipoprotein cholesterol (LDL) and total cholesterol to levels associated with an increased risk of coronary artery disease (10, 11). Similarly, interferon-free DAA treatments increase serum LDL levels during and after DAA treatment (12-15). LDL is considered one of the most important risk factors for cardiovascular diseases (16). Therefore, monitoring the lipid levels in the body is important in patients receiving antiviral therapy (11).

The carotid intima-media thickness (IMT) is a highly reproducible and non-invasive parameter for assessing the atherosclerotic process (17). The measurement of small dense (sd) LDL by the current precipitation method is useful for evaluating the atherogenic risk and may be applicable in routine clinical examinations (18). The change in the sdLDL and IMT values in patients with SVR has not been evaluated. We compared the metabolic profiles of patients, including the sdLDL and IMT values, at the start of DAA treatment and one year into treatment and determined whether the HCV clearance after the administration of DAA is associated with the development of atherosclerosis.

### Materials and Methods

Table 1. Clinical Profiles of 48 Patients before DAA Treatment.

| Parameter          | Number or Mean (SD) |
|--------------------|---------------------|
| Women/Men          | 28/20               |
| FIB-4 (≥3.25<3.25) | 21/27               |
| FIB-4              | 3.63 (1.92)         |
| HCV genotype 1B/2A+2B | 40/8               |
| DAA DCV/ASV/SOF/LDV/SOF/RBV | 43/6/8 |
| Age (years)        | 70.1 (11.08)        |
| HCV-RNA (log IU/mL)| 5.8 (1)             |
| ALT (U/L)          | 46.8 (41.12)        |
| Albumin (g/dL)     | 4.3 (0.5)           |
| AFP (ng/mL)        | 9.4 (14.5)          |
| PIVKA-II (mAU/mL)  | 19.8 (7.28)         |
| LDL (mg/dL)        | 107.8 (34.8)        |
| sdLDL (mg/dL)      | 19.8 (10.6)         |
| %sdLDL             | 18 (7.2)            |
| HDL (mg/dL)        | 60.9 (19.4)         |
| TG (mg/dL)         | 107.8 (72.9)        |
| HbA1c (%)          | 5.7 (0.7)           |
| Body weight (kg)   | 53.9 (11)           |
| BMI (kg/m²)        | 22 (3.419)          |
| HOMA-IR            | 2.76 (1.72)         |
| Creatinine eGFR (mL/min/1.73 m²) | 64.9 (23.95) |
| Cystatin eGFR (mL/min/1.73 m²) | 57.23 (24.1) |
| Hypertension +/-   | 26/22               |
| Hyperlipidemia +/- | 43/6                |
| Diabetes +/-       | 44/4                |
| Obesity +/-        | 37/11               |
| Dialysis +/-       | 44/4                |

Normal ranges of clinical parameters in fasting serum were as follows:

ALT 5-40 U/L, albumin 3.8-5.2 g/dL, LDL 70-139 mg/dL, HDL men 40-86 mg/dL, HDL women 40-96 mg/dL, TG 50-149 mg/dL, and HbA1c 4.6-6.2%. All laboratory measurements were conducted after overnight fasting.

FIB-4: fibrosis-4, DAA: direct acting anti-viral, DCV/ASV: Daclatasvir/asunaprevir, SPF/LDV: sofosbuvir/ledipasvir, SOF/RBV: sofosbuvir/ribavirin, ALT: aspartate aminotransferase, AFP: α-fetoprotein, PIVKA: protein induced vitamin K ascept, BMI: body mass index, HOMA-IR: homeostasis model assessment insulin resistance.
The clinical profiles of all patients at the start of DAA treatment are presented in Table 1. Regarding the HCV genotype, 28 patients had HCV 1B, and 20 patients had HCV 2A/2B infections. A total of 28 patients were women. The mean BMI was 22, and 11 patients were obese (BMI > 25). The mean HOMA-IR was 2.76. On average, non-obese patients had insulin resistance at the start of treatment. Patients were not taking any antiplatelet agents or eicosapentaenoic acid orally, and statin was the only medication given for hyperlipidemia. All patients had achieved an SVR at 24 weeks after the end of treatment.

First, we selected factors related to metabolic disease and atherosclerosis, and these factors at the start of treatment were compared with those a year later (Table 2 and Figure). sdLDL, %sdLDL, LDL, and HDL were exacerbated after a year of treatment, but the HDL/LDL, TG, HbA1c, HOMA-IR, and body weight did not change markedly during the observation period. The max-IMT (median: 1.45; range: 0.7-4.8), not mean-IMT (0.755; 0.5-1.76), after a year was larger than that at the start of treatment (max-IMT: 1.4; 0.5-3.9, mean-IMT: 0.75; 0.5-1.76) (Figure a and b).

Second, we evaluated the relationship between changes in the max-IMT and clinical factors (Table 3 and Figure). Differences in the max-IMT (dmax-IMT) were calculated as follows: dmax-IMT=max-IMT after a year - max-IMT at the start of treatment. Changes in the factor value (dfactor) were calculated as follows: dfactor=factor value after a year - factor value at the start of treatment (factor pre). The dmax-IMT in men was larger than that in women (Table 3 and Figure c). The max-IMT (2.15; 1.1-4.1)

| Parameter              | Before DAA          | One year later       | p value  |
|------------------------|---------------------|----------------------|----------|
| sdLDL (mg/dL)          | 19.8(10.6)          | 30.2(15.6)           | <0.001   |
| %sdLDL                 | 18(7.2)             | 24.5(9.9)            | <0.001   |
| LDL (mg/dL)            | 107.5(34.8)         | 119.8(36.2)          | <0.001   |
| HDL (mg/dL)            | 60.9(19.4)          | 66.3(22.4)           | 0.002    |
| HDL/LDL                | 0.618(0.255)        | 0.609(0.38)          | NS       |
| TG (mg/dL)             | 107.8(72.9)         | 114.9(83.4)          | NS       |
| HbA1c (%)              | 5.7(0.7)            | 5.8(0.7)             | NS       |
| HOMA-IR                | 2.76(1.72)          | 3.22(2.8)            | NS       |
| Body weight (kg)       | 54(11)              | 54.5(11.2)           | NS       |

Values represent the mean (SD). Laboratory results were compared using t-tests.
in men after a year was higher than that at the start of treatment (1.75; 0.7-3.9), but the max-IMT in women did not change markedly during the observation period (pre: 1.3; 0.5-3.7; post: 1.215; 0.7-4.8) (Figure c). The HCV genotype, FIB-4, hypertension, hyperlipidemia, diabetes, obesity, and dialysis did not significantly affect the dmax-IMT. In addition, the dsdLDL in SOF/LDV [mean (standard deviation; SD): 10.86 (9.22)] was not significantly different from that in SOF/RBV [9.27 (4.78)] and DCV/ASV [1.87 (0.92)]. The dsdLDL [mean (SD): 7.32 (5.53)] in patients with hyperlipidemia who used statins did not differ markedly from that in patients without hyperlipidemia [10.39 (8.92)]. A negative correlation was observed between the dHbA1c and dmax-IMT, but the HbA1c values at the start of treatment and a year later did not differ markedly. A positive correlation was observed between the %sdLDL at the start and a year later and the dmax-IMT, but the sdLDL at the start and a year later was only weakly correlated with the dmax-IMT.
The LDL, HDL, HDL/LDL, TG, BMI, and HOMA-IR values were not correlated with the dmax-IMT.

Finally, we explored the effect of contributing factors on the dmax-IMT by a multilinear regression analysis (Table 5A) and multivariate logistic regression analyses (Table 5B). A positive correlation was observed between the %sdLDL and the dmax-IMT at the start of treatment and the dmax-IMT, but the dHbA1c did not have any statistical relationship. Because the median %sdLDL was 16%, we divided the patients into those with %sdLDL<16% and ≥16%. The outcomes of patients with %sdLDL<16% at the start of treatment and male gender were evaluated by a logistic regression analysis (Table 5B). In uni- and multivariate analyses, both of these factors significantly contributed to the dmax-IMT.

In patients with %sdLDL≥16%, the dmax-IMT did not differ markedly between sexes [women: (median) 0; (range) -0.1-1.5; men: 0.4; -0.2-1.9]; however, the dmax-IMT in women with a %sdLDL<16% was higher than in women with a %sdLDL<16%. The dmax-IMT in men (0.1; -0.1-0.6) was higher than that in women (-0.1; -0.4-0.1) with a %sdLDL<16%. The dmax-IMT in women with a %sdLDL≥16% was higher than that in women with a %sdLDL<16%; however, the dmax-IMT in men remained unaltered (Figure d). Similarly, the dsdLDL [mean (SD): 15.1 (10.2)] in men with %sdLDL>16% was larger than in other groups [8.28 (7.39)] (p=0.0171).

**Table 3. Association between the Dmax-IMT and Each Clinical Factor.**

| Factors                  | Mean (SD)       | p value |
|--------------------------|-----------------|---------|
| Women/Men                | 0.057 (0.412)/0.465 (0.623) | 0.0089  |
| Genotype 1B/2A+2B        | 0.182 (0.5)/0.455 (0.723)   | NS      |
| FIB-4 (≥3.5/<3.5)        | 0.116 (0.53)/0.314 (0.556)  | NS      |
| Hypertension +/-         | 0.219 (0.538)/0.236 (0.563) | NS      |
| Hyperlipidemia +/-       | 0.189 (0.527)/0.492 (0.636) | NS      |
| Diabetes +/-             | 0.227 (0.547)/0.225 (0.591)  | NS      |
| Obesity +/-              | 0.216 (0.545)/0.264 (0.563)  | NS      |
| Dialysis +/-             | 0.23 (0.555)/0.22 (0.22)     | NS      |

dmax-IMT was calculated as follows: max-IMT at the start of treatment - max-IMT after a year. Laboratory results were compared using t-tests.

**Table 5. Uni- and Multivariate Analyses of Changes in the dmax-IMT.**

**A.**

|         | Uni-variate | Multi-variate |
|---------|-------------|---------------|
|         | β           | p value       | B           | p value       |
| %sdLDLpre | 0.391       | 0.0066        | 0.334       | 0.0189        |
| dHbA1c (%) | -0.328      | 0.0229        | -0.254      | 0.071         |

**B.**

|         | Uni-variate | Multi-variate |
|---------|-------------|---------------|
|         | Odds ratio  | 95% CI        | Odds ratio  | 95% CI        | p value |
| %sdLDL<16% | 0.081       | 0.0009-0.698  | 0.074       | 0.008-0.698   | 0.02   |
| Gender M  | 6.818       | 1.542-30.157  | 7.528       | 1.485-38.165  | 0.01   |

Multivariate analyses were performed with a multiple linear regression analysis (A) and logistic regression tests (B).

**Discussion**

In patients achieving an SVR after DAA treatment, the LDL, HDL, sdLDL, %sdLDL, and max-IMT increased a
year after starting treatment. However, the HOMA-IR, body weight, and TG level remained unaltered. An elevated max-IMT was associated with a %sdLDL≥16% at the start of treatment and male gender. After a year of such treatment, the atherosclerosis status should be evaluated in patients achieving an SVR.

The clearance of HCV by interferon-based therapy or treatment with any DAA is accompanied by an elevation in the serum LDL level (10-15, 20), indicating a risk of coronary (11) and metabolic diseases (20); however, patients with SVR exhibit decreased extrahepatic mortality due to cardiovascular diseases after interferon-based therapy (8, 9). Interferon-based and DAA treatments differ with respect to the period of treatment, adverse effects, and SVR rate. Because the duration of interferon-based treatment is long and because such therapy causes severe adverse effects, the serum total cholesterol decreases in the treatment period (11). However, after DAA treatment, the serum LDL decreases in the early treatment period (12); thus, the elevation in the LDL level is greater after DAA treatment than after interferon-based therapy. In addition, a high serum LDL level before treatment may be a significant prognostic indicator for the treatment outcome in patients with chronic HCV infection, particularly in those with genotype 1 and 2 infections (21). In contrast, no association between SVR and the pre-treatment lipid profile has been reported for DAA therapy (1-3). Nevertheless, it has been reported that HCV is associated with atherosclerosis (22-24). Effective HCV clearance may prevent atherosclerosis; however, the elevation in the LDL level must be evaluated in the future.

In addition to an increase in the LDL level after a year of starting treatment, the sdLDL and %sdLDL were also elevated in the present study. The association between HCV clearance and sdLDL has not been evaluated previously. Patients with non-alcoholic fatty liver disease had increased levels of sdLDL and %sdLDL, and ex vivo studies showed that these patients exhibited increased sensitivity of hepatic TG levels and cholesterol synthesis to insulin (25). Central obesity with hypertriglyceridemia is associated with high hepatic lipase activity that leads to the formation of proatherogenic sdLDL (26). In addition, HCV inhibits hepatic TG lipase production in hepatocytes, thereby elevating the TG-rich LDL level (27). sdLDL concentrations predict the risk for coronary heart disease (28) and exacerbation of the IMT (29). The change in the IMT in diabetes patients has been predicted by the comparison of the sdLDL level at baseline to that after two years (26). Consistent with previous reports, HCV-induced sdLDL production by hepatic TG lipase before DAA treatment and increased %sdLDL at the start of treatment were associated with an increased IMT after a year. However, while it has been reported that changes in the sdLDL are related to obesity, TG, and insulin resistance (25, 26, 29), the body weight, TG, and insulin resistance remained unaltered after a year of treatment in the present study despite an elevated sdLDL level. The association of the elevated sdLDL level and HCV clearance must be evaluated, and the IMT in patients with %sdLDL≥16% at the start of DAA treatment must be evaluated a year after starting DAA treatment.

Men are more prone to an exacerbated dmax-IMT than women. It has been reported that carotid plaque formation is associated with men, but sex does not affect the association between the HCV core protein and carotid atherosclerosis (30). Men with sdLDL levels in the high quartile were found to have diabetes, hypertension, and metabolic syndrome (28). In patients treated with interferon-based therapy, a rebound increase in the LDL and total cholesterol levels was not associated with sex (11); however, the IMT in men treated with DAA must be evaluated after one year of DAA treatment. The max-IMT in men at the start of treatment was higher than that in women (Figure c). According to the clinical features shown in Table 1, the ALT value in men was higher than that in women only at the start of treatment (mean value in men, 63.35 and in women, 35.75; p=0.025). There was no marked difference between men and women regarding the demographic and clinical features except for the max-IMT and the serum ALT level at the start of treatment. Sex-related differences in the IMT after DAA treatment should also be examined in the future.

This study had a relatively short observation period and included a small patient sample size. Thus, the long-term changes in sdLDL and IMT must be observed in another study. Because the sdLDL and IMT values were exacerbated after a year of DAA treatment, atherosclerosis, including cardio- and cerebrovascular diseases, must also be evaluated in patients achieving an SVR at least one year after starting DAA treatment.

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

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