Association between liver fibrosis and appendicular skeletal muscle mass during antiviral therapy in chronic hepatitis B

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Association between liver fibrosis and appendicular skeletal muscle mass during antiviral therapy in chronic hepatitis B

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Dynamic association between the change in liver fibrosis and appendicular skeletal muscle mass during antiviral therapy in patients with chronic hepatitis B

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Sarcopenia is associated with significant liver fibrosis in patients with chronic hepatitis B (CHB). We investigated the dynamic association between hepatic fibrosis and changes in appendicular skeletal muscle mass during antiviral therapy (AVT). Patients with CHB who underwent paired liver stiffness measurements between 2015 and 2018, using transient elastography to assess fibrotic burden and bioelectrical impedance analysis to assess appendicular skeletal muscle mass (ASMM), were recruited retrospectively. The mean time interval between two bioelectrical impedance analyses was 19.0 months. Significant liver fibrosis was defined as liver stiffness ≥ 8 kPa. The mean age of the study population (252 men and 163 women) was 55.9 years. Among all participants, 223 (53.7%) received AVT (AVT group), whereas 192 (46.3%) did not receive AVT (no AVT group). During AVT, ASMM decreased significantly in the AVT group (from mean 21.16 to 21.00 kg, P=0.01) but showed no significant change in the no AVT

group (from mean 20.77 to 20.64 kg, *P*=0.134). In the subgroup with significant liver fibrosis (66 and 42 participants with and without AVT, respectively), ASMM decreased significantly in the AVT group during AVT (from mean 20.73 to 20.54 kg, *P*=0.037) but showed no significant change in the no AVT group (from mean 21.39 to 21.07 kg, *P*=0.097). ASMM was significantly decreased during AVT. Thus, efforts should be made to maintain ASMM in patients with CHB receiving AVT.

Key words : appendicular skeletal muscle mass, chronic hepatitis B, antiviral therapy.

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I. INTRODUCTION

Chronic hepatitis B virus (HBV) infection continues to be a major public health issue worldwide despite the availability of an effective vaccine and potent antiviral therapy (1). More than 350 million people have HBV infections worldwide, and nearly 1 million deaths occur each year because of HBV-related complications, such as liver cirrhosis and hepatocellular carcinoma (2). HBV infection is associated with a wide spectrum of clinical manifestations, ranging from acute or fulminant hepatitis to various forms of chronic infection, including asymptomatic carrier state, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) (3).

Antiviral therapy (AVT) to suppress viral replication is the mainstay of HBV treatment. Effective AVT can stabilize hepatic necroinflammation due to HBV replication, which ultimately result in the reduced risk of developing HCC or cirrhosis-related complications in patients with CHB (4, 5). This favorable response is mainly due to the regression of liver fibrosis by appropriate AVT, which has been supported by recent studies. In a study by Chon YE, *et al.* (6), over the 5-year AVT treatment, liver fibrosis, as determined by LS value, progressively improved. The proportion of patients with LS-defined liver

cirrhosis was markedly decreased from 66.7% at baseline to 17.5% at year 5, and the proportion of patients with LS-defined mild or no fibrosis was significantly increased from 3.3% at baseline to 52.5% at year 5, resulting in the overall decrease in LS value in most patients (90.0% [n=108 of 120]) (6).

Moreover, a recent study reported that sarcopenia is independently associated with the degree of liver fibrosis in patients with CHB, especially in those with metabolically unhealthy status such as obesity, insulin resistance, metabolic syndrome, and liver steatosis (7). However, due to the cross-sectional nature of the study design, the longitudinal dynamic association between the progression or regression of liver fibrosis and changes in skeletal muscle mass, which would provide their causal relationship, could not be assessed (7).

Accordingly, based on the hypothesis that long-term AVT regresses liver fibrosis and sarcopenia is independently associated with significant liver fibrosis in patients with CHB, we investigated the dynamic association between the change in liver fibrosis and ASM during AVT in patients with CHB.

II. MATERIALS AND METHODS

1. Patients

A retrospective review of database from Yonsei Liver Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, was performed. Between 2015 and 2018, patients with CHB who started or already under AVT using entecavir (ETV) or tenofovir (TDF) and received transient elastography (TE) to assess fibrotic burden in liver and bioelectrical impedance (BIA) analysis to assess appendicular skeletal muscle mass (ASM) were considered eligible. Exclusion criteria were as follows: 1) not available paired TE and BIA assessment; 2) TE or BIA measurement failure; 3) insufficient clinical and laboratory information; 4) co-infection with hepatitis C virus or HIV; 5) right-sided heart failure; 6) pregnancy; or 7) ascites (**Figure 1**).

The study protocol was in accordance with the ethics guidelines of the 1975 Declaration of Helsinki and the study procedure was approved by the Institutional Review Board of Severance Hospital. Written informed consent

was waived because of the retrospective nature of the study.

2. Assessment of appendicular skeletal muscle mass using BIA

As described previously (8), ASM was measured using BIA (InBody®, InBody770, Seoul, Republic of Korea). In order to obtain the changes in ASM, two or more BIA were carried out in the same patients during the study period, with the mean interval between the first and last BIA assessment being 19.0 (interquartile range 11.8-25.4) months.

The InBody770 are produced from the same manufacturer. Each device utilizes hand-to-foot BIA that sends varying frequencies of alternating current through the body. These impedance values are then used to predict several analyses including Body Composition Analysis, Muscle-Fat Analysis, Obesity Analysis, Segmental Lean Analysis, ECW Ratio Analysis and Body Composition History. Before testing on each device the following protocols were employed: age, sex, and height were entered into the software for each participant (9). Before contact with the electrodes, participants cleansed their hands and feet with antibacterial tissue from the manufacturer (9). Standing in an upright position, the feet were then centered on the electrodes and the hand electrodes were grasped with arms being held wide enough so that there was no contact between the arms and torso (9). This position was held for the duration of the test (9). Once the assessment was completed, participants were prompted to return the hand electrodes and step off the device (9).

3. Assessment of liver fibrosis using TE

As described previously (10), the degree of liver fibrosis assessed using TE was expressed as liver stiffness (LS) value. In order to obtain the changes in LS value, two or more TE were carried out in the same patients during the study period. In our institute, BIA has been performed at the same time with TE. Accordingly, the mean interval between the first and last TE assessment was same as that of BIA 19.0 (interquartile range 11.8-25.4) months.

In term of technical point of view, experienced technicians at our hospital,

blinded to the clinical information of patients, performed the TE examinations. TE was performed on the right lobe of the liver through the intercostal space with the participant lying in the dorsal decubitus position with the right arm in maximal abduction. All TE examinations were performed at least 10 times, between the 5th and 7th intercostal spaces, at the mid-to-anterior axillary line (11). The TE results for the degree of liver fibrosis were expressed as kilopascals (kPa) for LS. The median value of successful measurements was selected as the representative LS value for a given participant. As an indicator of variability, the ratio of the interquartile range (IQR) to the median LS value was calculated. TE assessment failure was defined as the absence of valid shots (i.e., valid shots=0). A reliable LS value was defined by the following criteria: (i) at least 10 valid shots and (ii) an IQR 30% of the median LS value. Moreover, we collected data on the degree of liver steatosis which can be expressed as the controlled attenuation parameter (CAP) values. The CAP measures the ultrasonic attenuation by hepatic steatosis at 3.5 MHz using signals acquired by TE, and is simultaneously calculated with the LS value by using the same signals (12).

4. Definition

TE-defined significant liver fibrosis and fatty liver were defined as LS measurement >8 kPa (10) and controlled attenuation parameter >250 dB/m, respectively (13). Based on the criteria for the Asian Pacific region, subjects were considered obese when their body mass index was ≥25 kg/m^2 (14). Liver cirrhosis was diagnosed with abdominal ultrasonography. The sarcopenia index was calculated as follows: sarcopenia index = total appendicular skeletal muscle mass (kg)/body mass index (kg/m^2); this was the official definition provided by a recent consensus meeting known as the “Foundation for the National Institutes of Health Sarcopenia Project” (15). The Foundation for the National Institutes of Health Sarcopenia Project used 9 sources of community dwelling elderly cohorts to derive the recommendations for cutoff points of low lean mass in men and women. In this meeting, sarcopenia was defined using

cutoff points of SI<0.789 in men and <0.521 in women, which was also adopted for our study.

5. Statistical analysis

The characteristics of the study subjects were analyzed according to sarcopenia status or antiviral therapy status using Student's *t*-tests for continuous variables and χ^2 tests for categorical variables. Paired *t* -tests were used to compare the assessment of ASM between the first and last BIA. Multivariable logistic binary regression analysis was applied to determine the independent association between appendicular skeletal muscle mass changes and other variables. In multivariable logistic binary regression analysis, we used the variables that univariate *P* values of whom were lower than 0.1. *P*<0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 23.0 for Windows (IBM Corp., Armonk, NY, USA).

III. RESULTS

1. Baseline characteristics of the entire study population

Between 2015 and 2018, 2,298 patients with CHB who received TE and BIA assessment were considered eligible. After excluding 1,883 patients according to our exclusion criteria, 415 patients (252 men and 163 women) were finally selected and divided into two groups with or without AVT for the statistical analysis (**Figure 1**).

The baseline clinical characteristics of the study population are shown in **Table 1**. The mean age of the entire study population was 55.9 years. Male gender predominated (n=252, 60.7%). The mean BMI was 25.8 kg/m^2. The proportion of patients with diabetes, hypertension, liver cirrhosis, and obesity was 20.5, 21.7, 30.1, and 54.7%, respectively. The mean LS and CAP values were 7.8 kPa and 276.9 dB/m, respectively. Significant liver fibrosis and fatty liver were identified in 108 (26.0%) and 294 (70.8%) patients, respectively. The mean ASM was 20.9 kg.

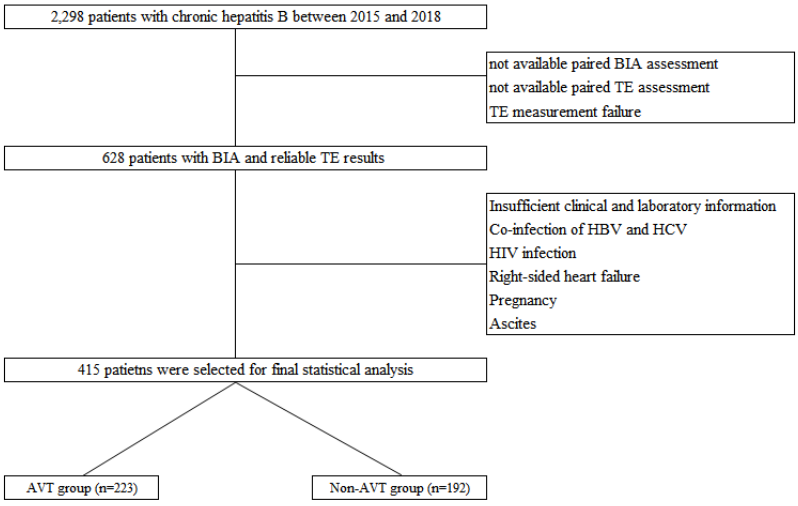


Figure 1. Flow of selecting the study populations

Table 1. Baseline characteristics of the study population

Variables	All (n=415)	AVT group (n=223, 53.7%)	Non-AVT group (n=192, 46.3%)	*P* value
Demographic variables				
Age, years	55.9 ± 10.9	55.2 ± 10.9	56.7 ± 10.9	0.168
Male gender	252.0 (60.7)	137.0 (61.4)	115.0 (59.9)	0.749
Body mass index, kg/m^2	25.8 ± 3.6	25.6 ± 3.6	26.0 ± 3.6	0.278
Diabetes	85.0 (20.5)	46.0 (20.6)	39.0 (20.3)	0.937
Hypertension	90.0 (21.7)	40.0 (17.9)	50.0 (26.0)	0.046
Liver cirrhosis	125.0 (30.1)	87.0 (39.0)	38.0 (19.8)	<0.001
Obesity	227.0 (54.7)	112.0 (50.2)	115.0 (59.9)	0.048
Laboratory variables				
Fasting glucose, mg/dL	106.9 ± 27.2	106.2 ± 22.6	107.8 ± 31.8	0.547
Aspartate aminotransferase, IU/L	31.9 ± 34.9	32.4 ± 28.6	31.5 ± 41.2	0.793
Alanine aminotransferase, IU/L	34.7 ± 32.6	36.1 ± 38.2	33.1 ± 24.6	0.357
Total bilirubin, mg/dL	0.9 ± 0.7	0.9 ± 0.9	0.9 ± 0.4	0.259
Serum albumin, g/dL	4.4 ± 0.4	4.3 ± 0.4	4.4 ± 0.3	0.079
Platelet count, 10^9/L	193 ± 68	179 ± 68	206 ± 65	0.001
HBeAg positivity	77.0 (18.6)	72.0 (32.3)	5.0 (2.6)	<0.001
HBV DNA, logIU/mL	3.3 ± 1.9	4.2 ± 2.4	2.9 ± 1.4	0.544
Transient elastography				
Liver stiffness, kPa	7.8 ± 6.1	8.4 ± 6.9	7.1 ± 5.0	0.030
Significant liver fibrosis (>8 kPa)	108.0 (26.0)	66.0 (29.6)	42.0 (21.9)	0.068
Controlled attenuation parameter, dB/m	276.9 ± 46.3	273.5 ± 46.7	280.8 ± 45.5	0.113
Fatty liver (> 250 dB/m)	294.0 (70.8)	147.0 (65.9)	147.0 (76.6)	0.012
Muscle indices				
Appendicular skeletal muscle, kg	20.9 ± 4.8	21.2 ± 4.9	20.8 ± 4.5	0.398
Sarcopenia index	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.3	0.661

Variables are expressed as n (%) or mean ± SD.

AVT, antiviral therapy; HBeAg, hepatitis B e antigen; kPa, kilopascal.

2. Comparison of the baseline characteristics between the subgroups with and without AVT

When the study population was divided into two sub-groups with and without AVT and compared (**Table 1**), AVT group had significantly higher platelet count (mean 205.8 vs. 179.2 10^9/L) and LS value (mean 8.4 vs. 7.1 kPa) (all $P<0.05$). The proportion of liver cirrhosis and HBeAg positivity was significantly higher than in Non-AVT group (all $P<0.05$). However, the proportion of hypertension, obesity and fatty liver was significantly lower than in Non-AVT group (all $P<0.05$).

3. Change in ASM in the entire study population and the subgroups with and without AVT

Based on the results of TE and BIA in the entire study population, ASM significantly decreased from the baseline (mean 20.98 → 20.83 kg, $P=0.005$) (**Figure 2A**). ASM significantly decreased in AVT group (n=223) (mean 21.16 → 21.00 kg, $P=0.01$), not in Non-AVT group (n=192) (mean 20.77 → 20.64 kg, $P=0.134$) (**Figure 2B**). When 108 patients with significant liver fibrosis were selected (n=66 in AVT group and n=42 in Non-AVT group), ASM significantly decreased only in AVT group (mean 20.72 → 20.53 kg, $P=0.037$), not in Non-AVT group (mean 21.39 → 21.07 kg, $P=0.097$) (**Figure 2C**).

Figure 2A

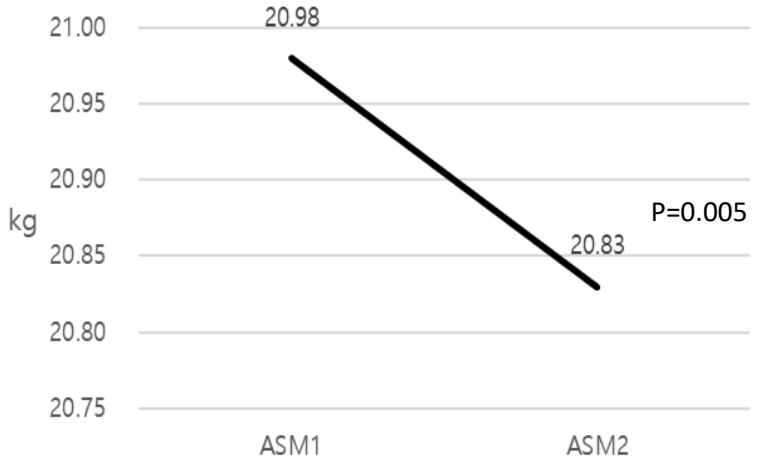
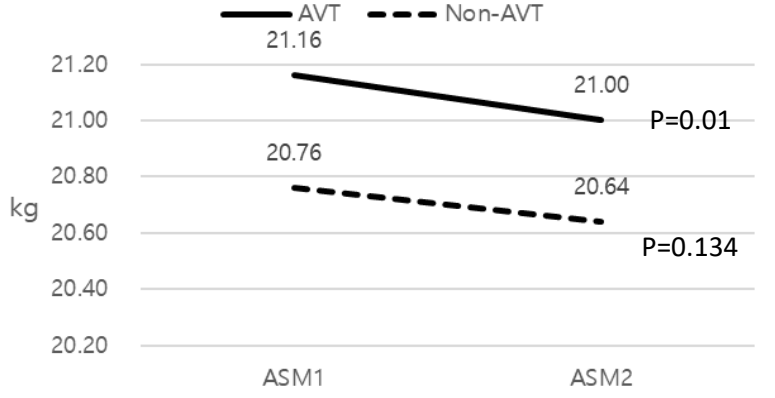


Figure 2B



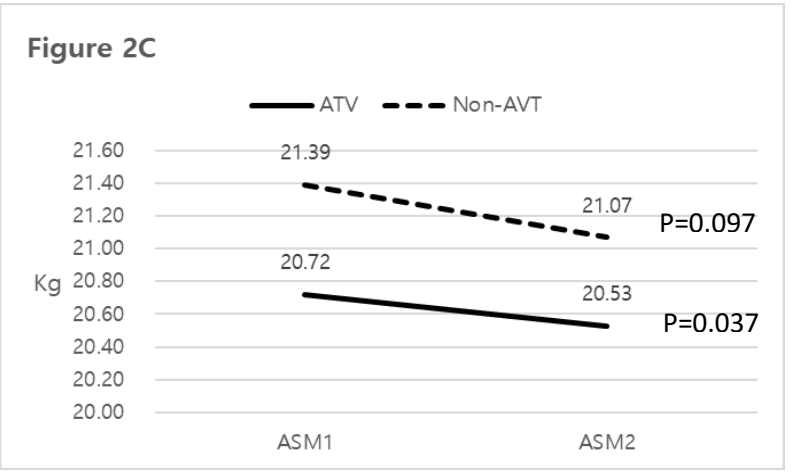


Figure 2. Changes in appendicular skeletal muscle mass

Table 2. Comparison between patients with and without sarcopenia

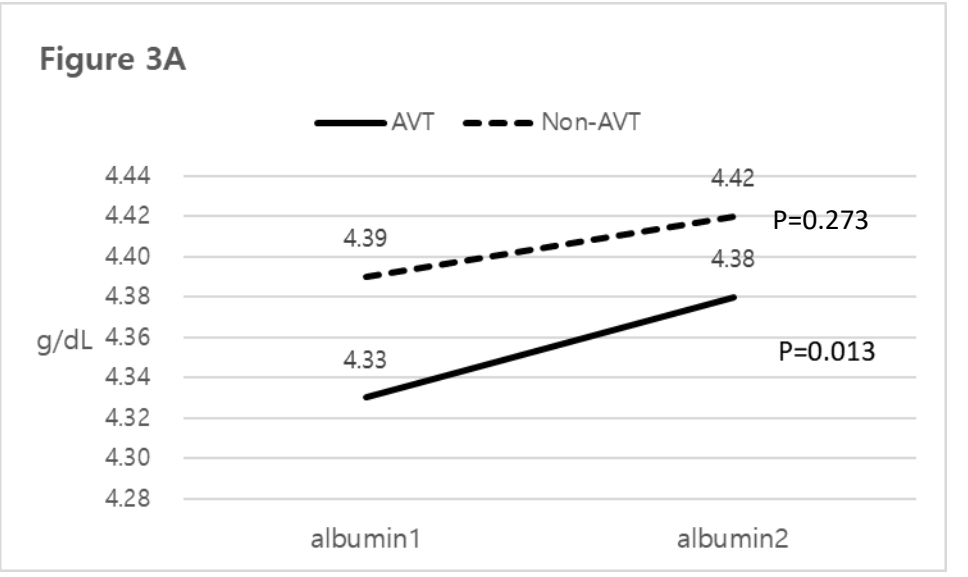
Variables	All			AVT			Non-AVT		
	Without sarcopenia (n=376, 90.6%)	With sarcopenia (n=39, 9.4%)	*P* value	Without sarcopenia (n=206, 92.4%)	With sarcopenia (n=17, 7.6%)	*P* value	Without sarcopenia (n=170, 88.5%)	With sarcopenia (n=22, 11.5%)	*P* value
Demographic variables									
Age, years	55.6 ± 10.8	57.8 ± 11.9	0.232	55.3 ± 11.0	53.5 ± 10.1	0.522	56.1 ± 10.6	61.2 ± 12.3	0.038
Male gender	219.0 (58.2)	33.0 (84.6)	0.001	124.0 (60.2)	13.0 (76.5)	0.185	95.0 (55.9)	20.0 (90.9)	0.002
Body mass index, kg/m^2	25.4 ± 3.3	29.4 ± 3.8	<0.001	25.2 ± 3.4	30.2 ± 3.5	<0.001	25.6 ± 3.3	28.7 ± 4.0	<0.001
Diabetes	73.0 (19.4)	12.0 (30.8)	0.094	41.0 (19.9)	5.0 (29.4)	0.352	32.0 (18.8)	7.0 (31.8)	0.154
Hypertension	72.0 (19.1)	18.0 (46.2)	<0.001	34.0 (16.5)	6.0 (35.3)	0.052	38.0 (22.4)	12.0 (54.5)	0.001
Liver cirrhosis	111.0 (29.5)	14.0 (35.9)	0.409	79.0 (38.3)	8.0 (47.1)	0.479	32.0 (18.8)	6.0 (27.3)	0.349
Obesity	194.0 (51.6)	33.0 (84.6)	<0.001	96.0 (46.6)	16.0 (94.1)	<0.001	98.0 (57.6)	17.0 (77.3)	0.077
Laboratory variables									
Fasting glucose, mg/dL	105.8 ± 26.3	117.6 ± 33.1	0.036	105.3 ± 21.7	117.2 ± 30.0	0.127	106.5 ± 31.0	118.0 ± 36.1	0.109
Aspartate aminotransferase, IU/L	32.2 ± 36.2	29.8 ± 20.1	0.684	32.8 ± 29.6	27.8 ± 10.9	0.489	31.5 ± 42.9	31.4 ± 25.2	0.988
Alanine aminotransferase, IU/L	35.2 ± 33.7	30.1 ± 18.9	0.355	36.6 ± 39.2	30.0 ± 22.4	0.494	33.5 ± 25.4	30.2 ± 16.4	0.556
Total bilirubin, mg/dL	0.9 ± 0.8	0.9 ± 0.4	0.969	0.9 ± 1.0	0.9 ± 0.4	0.787	0.9 ± 0.4	0.9 ± 0.4	0.463
Serum albumin, g/dL	4.3 ± 0.4	4.4 ± 0.3	0.938	4.3 ± 0.4	4.3 ± 0.3	0.897	4.4 ± 0.3	4.4 ± 0.4	0.878
Platelet count, 10^9/L	190 ± 66	213 ± 82	0.092	177 ± 67	199 ± 80	0.290	204 ± 62	222 ± 84	0.275
HBeAg positivity	74.0 (30.5)	3.0 (11.1)	0.035	69.0 (44.2)	3.0 (21.4)	0.098	5.0 (5.7)	0.0 (0.0)	0.375
HBV DNA, logIU/mL	3.4 ± 1.9	2.6 ± 1.9	0.150	4.3 ± 2.4	3.3 ± 2.7	0.403	3.0 ± 1.4	1.9 ± 0.6	0.070
Transient elastography									
Liver stiffness, kPa	7.6 ± 5.9	10.2 ± 7.5	0.011	8.2 ± 6.7	10.9 ± 8.7	0.134	6.8 ± 4.6	9.7 ± 6.7	0.010
Significant liver fibrosis (>8 kPa)	92.0 (25.4)	16.0 (43.2)	0.020	58.0 (29.3)	8.0 (50.0)	0.085	34.0 (20.7)	8.0 (38.1)	0.074
Controlled attenuation parameter, dB/m	274.8 ± 46.3	297.2 ± 41.0	0.005	272.2 ± 47.2	288.8 ± 38.8	0.173	277.9 ± 45.2	303.6 ± 42.4	0.015
Fatty liver (> 250 dB/m)	259.0 (71.3)	35.0 (94.6)	0.002	133.0 (66.8)	14.0 (87.5)	0.087	126.0 (76.8)	21.0 (100.0)	0.013
Muscle indices									
Appendicular skeletal muscle, kg	21.0 ± 4.9	20.4 ± 3.6	0.300	21.2 ± 5.0	20.8 ± 4.2	0.780	20.9 ± 4.7	20.0 ± 3.1	0.276
Sarcopenia index	0.8 ± 0.2	0.7 ± 0.1	<0.001	0.8 ± 0.2	0.7 ± 0.1	<0.001	0.8 ± 0.3	0.7 ± 0.1	0.037

Variables are expressed as n (%) or mean ± SD.

AVT, antiviral therapy; HBeAg, hepatitis B e antigen; kPa, kilopascal.

4. Changes in laboratory parameters

In AVT group, serum albumin (mean 4.33 → 4.38 g/dB, *P*=0.013) and platelet count (mean 178 → 184 10^9/L, *P*=0.028) significantly increased, whereas they were similarly maintained in Non-AVT group (mean 4.39 → 4.42, *P*=0.273 for serum albumin; mean 200 → 201 10^9/L, *P*=0.550 for platelet count) (Figures 3A and 3B).



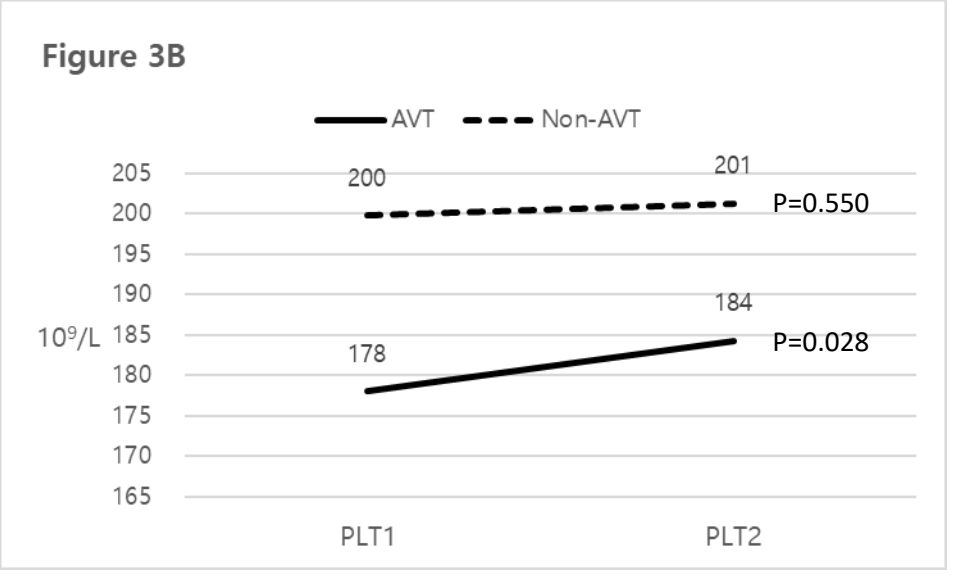


Figure 3. Changes in two variables with and without AVT

5. Comparison between sarcopenic and nonsarcopenic patients in the entire study population

Among the entire study population, 39 (9.4%) had sarcopenia (**Table 2**). When compared, sarcopenic patients had significantly higher BMI (mean 29.4 vs. 25.4 kg/m^2) and fasting glucose (117.6 vs. 105.8 mg/dL) (all P<0.05), whereas they had significantly lower sarcopenia index than non-sarcopenic patients (all P<0.05). In addition, sarcopenic patients had significantly higher LS (mean 10.2 vs. 7.6 kPa) and CAP values (mean 297.2 vs. 274.8 dB/m) (all P<0.05). The proportion of male sex, hypertension, obesity, significant fibrosis, and fatty liver was significantly higher than in non-sarcopenic patients (all P<0.05).

6. Comparison between sarcopenic and nonsarcopenic patients in the subgroups with and without AVT

In AVT group, 17 (7.6%) patients had sarcopenia, whereas 22 (11.5%) patients had sarcopenia in Non-AVT group. When compared in AVT group, sarcopenic patients had significantly higher BMI (mean 30.2 vs. 25.2 kg/m^2), whereas they had significantly lower sarcopenia index than non-sarcopenic patients (all P<0.05). The proportion of obesity was significantly higher than in non-sarcopenic patients (all P<0.05).

When compared in Non-AVT group, sarcopenic patients had significantly higher BMI (mean 28.7 vs. 25.6 kg/m2) and age (mean 61.2 vs. 56.1 years), whereas they had significantly lower sarcopenia index than non-sarcopenic patients (all P<0.05). In addition, sarcopenic patients had significantly higher LS (mean 9.7 vs. 6.8 kPa) and CAP values (mean 303.6 vs. 277.9 dB/m) (all P<0.05). The proportion of male sex, hypertension and fatty liver was significantly higher than in non-sarcopenic patients (all P<0.05).

7. Change in ASM in AVT group according to sarcopenic status

Due to the significant reduction of ASM in AVT group, the change in ASM according to sarcopenic status was assessed (**Figure 4**). ASM significantly decreased in the nonsarcopenic patients (mean 21.19 → 21.02 10^9/L, P=0.010),

not in the sarcopenic patients (mean 20.84 → 20.77 10^9/L, *P*=0.794).

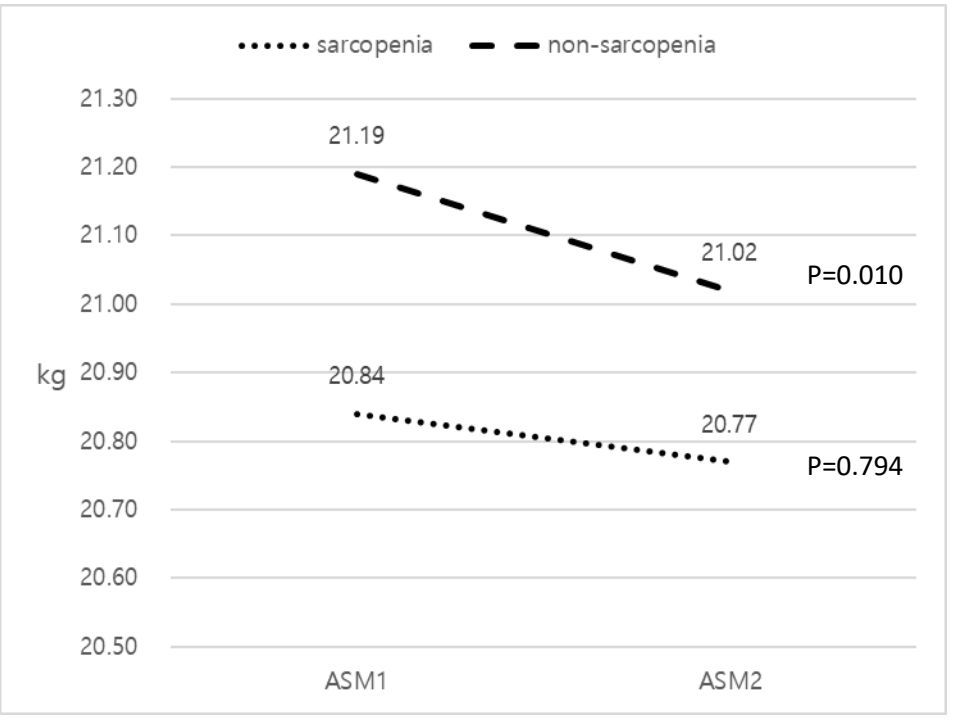


Figure 4. Changes in appendicular skeletal muscle mass with and without sarcopenia in AVT subgroup

8. Independent predictors of the reduction in ASM (≥ 5% from the baseline)

Univariate and subsequent multivariate analyses to identify the independent predictors of the reduction in ASM are shown in **Table 3**. In univariate analysis, BMI, diabetes, total bilirubin, serum albumin, LS, and significant liver fibrosis significantly predicted the risk of ASM reduction (P<0.05). After adjustment using LS value, higher BMI (OR=1.133, 95% CI, 1.011-1.270), diabetes (OR=2.550, 95% CI, 1.000-6.499), and higher LS value (OR=1.053, 95% CI, 1.001-1.107) were independently associated with an increased risk of ASM reduction (all P<0.05). However, the changes in LS value and CAP were not significantly associated with the risk of ASM reduction (all P>0.05). When age and gender, well-known influencing factors for ASM, were additionally adjusted, similar findings were observed (**Table 3**).

Table 3. Independent predictors of ASM reduction (>5%)

Variables	Univariate	Multivariate using liver stiffness			Multivariate using liver stiffness		
	P value	*P* value	HR	95% CI	*P* value	HR	95% CI
Demographic variables							
Age, years	0.146	-	-	-	0.712	1.008	0.965-1.053
Male gender	0.830	-	-	-	0.980	1.012	0.407-2.515
Body mass index, kg/m^2	0.018	0.031	1.125	1.011-1.251	0.032	1.133	1.011-1.270
Diabetes	<0.001	0.038	2.598	1.054-6.403	0.050	2.550	1.000-6.499
Hypertension	0.075	0.789	0.874	0.325-2.346	0.725	0.833	0.302-2.302
Liver cirrhosis	0.586	-	-	-	-	-	-
Obesity	0.358	-	-	-	-	-	-
AVT	0.506	-	-	-	-	-	-
Laboratory variables							
Aspartate aminotransferase, IU/L	0.069	0.256	1.004	0.997-1.012	0.253	1.004	0.997-1.012
Alanine aminotransferase, IU/L	0.163	-	-	-	-	-	-
Platelet count, 10^9/L	0.412	-	-	-	-	-	-
HBeAg positivity	0.690	-	-	-	-	-	-
HBV DNA, IU/mL	0.912	-	-	-	-	-	-
Transient elastography							
Liver stiffness, kPa	<0.001	0.032	1.055	1.005-1.108	0.046	1.053	1.001-1.107
Significant liver fibrosis (>8 kPa)	0.006	-	-	-	-	-	-
Change in liver stiffness, kPa	0.839	-	-	-	-	-	-
Change in liver stiffness, kPa (15%이 상감소)	0.096	-	-	-	-	-	-
Change in liver stiffness, kPa (30%이 상감소)	0.937						
Controlled attenuation parameter, dB/m	0.881	-	-	-	-	-	-
Controlled attenuation parameter > 250 dB/m	0.530	-	-	-	-	-	-

NAFLD, nonalcoholic fatty liver disease; HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval; AVT, antiviral therapy; HBeAg, hepatitis B e antigen; kPa, kilopasca

6. Independent predictors of the reduction in ASM (≥ 5% from the baseline) in AVT group

Univariate and subsequent multivariate analyses to identify the independent predictors of ASM reduction in AVT group are shown in **Table 4**. In univariate analysis, diabetes, AST, LS, and significant liver fibrosis were significantly associated with the increased risk of ASM reduction (P<0.05). After adjustment using LS value, higher BMI (OR=1.211, 95% CI 1.031-1.422) and diabetes (OR=3.378, 95% CI 1.066-10.702) were independently associated with an increased risk of ASM reduction (all P<0.05), whereas the statistical significance of LS value was attenuated (P=0.281). When gender, well-known influencing factor for ASM, were additionally adjusted, only higher BMI was independently associated with the increased risk of ASM reduction (OR=1.226, 95% CI 1.037-1.449, P=0.017), whereas older age (P=0.089), diabetes (P=0.071), and higher AST level (P=0.089) tended to be associated with the increased risk of ASM reduction (**Table 4**).

Table 4. Independent predictors of ASM reduction (>5%) in AVT

Variables	Univariate	Multivariate using liver stiffness			Multivariate using liver stiffness		
	P value	*P* value	HR	95% CI	*P* value	HR	95% CI
Demographic variables							
Age, years	0.068	0.122	1.051	0.987-1.118	0.089	1.060	0.991-1.134
Male gender	0.872	-	-	-	0.451	1.662	0.443-6.228
Body mass index, kg/m^2	0.063	0.020	1.211	1.031-1.422	0.017	1.226	1.037-1.449
Diabetes	0.001	0.039	3.378	1.066-10.702	0.071	2.994	0.912-9.828
Hypertension	0.113	-	-	-	-	-	-
Liver cirrhosis	0.437	-	-	-	-	-	-
Obesity	0.486	-	-	-	-	-	-
Laboratory variables							
Aspartate aminotransferase, IU/L	0.015	0.103	1.014	0.997-1.031	0.089	1.016	0.998-1.034
Alanine aminotransferase, IU/L	0.139	-	-	-	-	-	-
Platelet count, $10^9/L$	0.721	-	-	-	-	-	-
HBeAg positivity	0.680	-	-	-	-	-	-
HBV DNA, IU/mL	0.982	-	-	-	-	-	-
Transient elastography							
Liver stiffness, kPa	0.002	0.281	1.037	0.971-1.109	0.341	1.033	0.966-1.105
Significant liver fibrosis (>8 kPa)	0.028	-	-	-	-	-	-
Change in liver stiffness, kPa	0.432	-	-	-	-	-	-
Change in liver stiffness, kPa (15%이 상감소)	0.215	-	-	-	-	-	-
Controlled attenuation parameter, dB/m	0.822	-	-	-	-	-	-
Controlled attenuation parameter > 250 dB/m	0.259	-	-	-			

NAFLD, nonalcoholic fatty liver disease; HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval; AVT, antiviral therapy; HBeAg, hepatitis B e antigen; kPa, kilopascal.

IV. DISCUSSION

According to current literature, fibrotic burden frequently decreases during AVT in patients with CHB (6). In addition, it has been confirmed that the high probability of having low ASM is associated with high fibrotic burden in liver in patients with CHB (7). Accordingly, we hypothesized that fibrotic burden would decrease and ASM would increase during AVT. However, our current study failed to show the longitudinal association between the changes in fibrotic burden and ASM during AVT. Unexpectedly, we found that ASM was significantly decreased in our entire cohort, especially in patients receiving AVT, and that older age, higher BMI and diabetes, which have been already known as influencing factors on ASM (16), were associated with the increased risk of ASM reduction during AVT.

Our study has several clinical implications and strengths. First, this is the first study to show the changes in ASM measured by BIA in association with fibrotic burden change during AVT in patients with CHB. Although we failed to prove the primary end-point, the results of our study might be informative for designing the following prospective studies to reveal the confirmatory association between long-term AVT and the change in ASM in patients with CHB. However, because our study found that the reduction in ASM was identified in the subgroup with AVT, it might be suggested that medical efforts to increase or maintain ASM, such as exercise, high-protein diets, and administration of BCAA, might be required during AVT (17).

Second, we found a significant ASM reduction in the entire cohort (mean 0.15 kg during the mean follow-up period of 19.0 months). When compared to the already known the ASM reduction speed as the subjects are getting older (-0.25 kg/year in the Japanese men in their 50s and -0.31 kg/year in the Japanese women in their 50s), the ASM reduction in our entire cohort seems relatively lower (18). The changes in ASM are generally associated with multi-factors within complex interactions (19). Indeed, in our study, older age, higher BMI, and diabetes, not the AVT status, were independently associated with the increased risk of the reduction in ASM in the entire cohort. This might mean that medical intervention, such as

exercise to reduce BMI and strict sugar control to manage diabetes, to maintain the amount of ASM is required for patients with CHB and metabolically unhealthy status.

Third, in contrast to our hypothesis, the longitudinal association between the changes in fibrotic burden and ASM was not identified in the entire cohort. Although the exact reason for this unexpected phenomenon is still unclear, this can be explained in several ways. First, single factor of AVT status might be insufficient in proving the influence of AVT on ASM, because other powerful factors such as age and gender might have attenuated the influence of AVT. Second, changes in ASM itself were extremely small compared to the baseline amount of ASM. Thus, the small changes in ASM might not be sufficient to show the association with the change in fibrotic burden during AVT. Third, the relatively small sample size of our study population might have resulted in the false negative results. However, when considering that the significant improvement in serum albumin level and platelet count after AVT, it might be questionable that the influence of AVT did not work during the study period.

Fourth, ASM was significantly decreased in the subgroup with AVT, not in the subgroup without AVT. Although no difference in ASM was identified between AVT and Non-AVT groups, the proportion of patients with liver cirrhosis was higher, platelet count was lower, and liver stiffness value was higher in AVT group, all of which might be associated with the inadequate protein metabolism to compensate the losing ASM during AVT. Unlike our study, in a study by Iwasa, *et al*. (20), no significant change in the area of the psoas major muscle was seen in the patients with hepatitis B virus given entecavir. And, they found that an improvement in low muscle mass may thus be expected from AVT for viral liver disease, especially in patients with cachexia and a positive correlation was seen for the amount of change in the psoas muscle and the amount of change in serum albumin (20). Similarly, in another recent study by Sugimoto, *et al*. (21), skeletal muscle mass significantly increased, associated with an elevation of serum albumin levels and/or body weight or reduction in visceral fat area, but only in patients who presented with low skeletal muscle before direct antiviral agent

therapy in hepatitis C virus infection. To resolve this controversial issue, prospective study with large sample size are strongly required.

Fifth, ASM significantly decreased in non-sarcopenic patients, not in sarcopenic patients. This might indicate that the probability of ASM reduction might be low in the subgroup with already low ASM, whereas there is a large room for AVT to reduce ASM in the subgroup with larger ASM. This finding might provide two-way management strategy. First, medical interventions should be required for sarcopenic CHB patients to increase ASM. Second, prophylactic interventions not to lose ASM is strongly required to maintain ASM for non-sarcopenic CHB patients. To resolve issue, prospective interventional studies are warranted.

Despite several strengths of our study, we are also aware of several issues that remained unresolved. First, because of the retrospective, single center study, selection bias may exist. Only those who received paired TE and BIA were included in the study and our institute also conducted TE in hepatitis B patients with regular progress, but BIA may not have implemented relatively thin patients. This might be the reason why our study has shown a high rate of fatty liver and obesity. Second, although the overall sample size of our study is quite similar or larger than those of previous studies (20), it is still relatively insufficient. This is because BIA assessment for patients with chronic liver diseases started in 2015 in our institute. Third, the time interval between paired TE and BIA assessment is relatively narrow (mean 19.0 months for TE and BIA). Thus, the result of study might be subject to the false negativity. As the degree of liver fibrosis persists even after several years, this might be the one of the reasons why AVT status did not influence on ASM change.

V. CONCLUSION

ASM significantly decreased in the entire population with or without AVT. However, this phenomenon was apparent in the subgroup with AVT. Thus, medical interventions to maintain ASM should be considered in patients with CHB under prolonged AVT

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ABSTRACT(IN KOREAN)

만성B형간염에서 항바이러스제 치료로 인한 간섬유화 변화와 근육량 변화와의 관계

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김경현

만성 B형 간염에서 근감소증은 간섬유화와 관련이 있다고 알려져 있습니다. 우리는 항바이러스제 치료하는 동안 간섬유화 변화와 근윤량 변화와의 인과관계에 대해 알아보았습니다.

2015년과 2018년 사이에 2회이상의 체지방검사를 받은 만성B형간염 환자를 대상으로 간섬유화스캔을 이용하여 섬유화 정도를 측정하였고 체지방검사를 이용하여 근육량을 측정하였습니다. 첫번째 체지방검사와 마지막 체지방검사와의 평균 간격은 19.0개월이며 의미있는 간섬유화는 간탄성도가 8kPa이상으로 정의하였습니다

연구 집단(남성 252명, 여성 163명)의 평균 연령은 55.9세였습니다. 223명(53.7%)의 참가자가 항바이러스제 치료를 받았고 192명 (46.3%)의 참가자는 항바이러스제 치료를 받지 않았습니다. 항바이러스제 치료동안, 항바이러스제 치료 집단은 근육량이 21.16kg에서 21.00kg으로 유의하게 감소하였으며 (P=0.01), 항바이러스제 치료를 받지 않은 집단은 20.77kg에서 20.64kg으로 유의한 차이가 없었습니다 (P=0.134). 의미있는 간섬유화 환자 중에서 근육량 변화를 살펴보면, 항바이러스제 치료집단에서 근육량이 20.73kg에서 20.54kg으로 유의하게 감소하였으며 (P=0.037), 반면에 항바이러스제 치료하지 않은 딥단은 21.39kg에서 21.07kg으로 유의미한 차이는 없었습니다

(*P*=0.097).

항바이러스제 치료를 하는동안 근육량의 유의한 감소가 있으므로 근육량을 유지하기위한 노력이 필요합니다.

핵심되는 말 : 근육량, 만성B형간염, 항바이러스제 치료