Impact of weight loss and lifestyle modifications on liver fibrosis in MASLD and MetALD: A cohort study

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Received March 12, 2025; Accepted May 30, 2025

DOI: 10.3892/br.2025.2036

Abstract. The present study aimed to investigate the impact of weight loss and abstinence and exercise on liver fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatotic liver disease and alcoholic-related liver disease (MetALD). A total of 67 patients with MASLD and 33 patients with MetALD were retrospectively evaluated after six months of follow-up for weight loss, abstinence and exercise. A decrease in liver fibrosis (decrease in dLSM2B) was defined as a reduction in liver stiffness (LS) by FibroScan and macrophage galactose-specific lectin-2 binding protein glycosylation isomer (M2BPGi) over the observation period. The decrease in dLSM2B levels was 35.8 and 39.4% in the MASLD and MetALD groups, respectively. In MASLD, the decreased weight rate (dBW%) was lower for a decrease in dLSM2B than for an increase. However, in MetALD, the dBW% was not significantly different between the groups. In MetALD, patients with complete abstinence and exercise frequency had a higher rate of decrease in dLSM2B. A prediction score of 0, 1 or 2 points was developed to predict the decrease in dLSM2B, with 1 point awarded for a dBW% reduction of ≥3.8 and 1 point for a FIB-4 reduction of ≥0.201. In patients with MASLD, there was a significant difference in the decrease in dLSM2B by 8.3% for a prediction score of 0, 36% for 1, and 72.2% for 2 points, whereas there was no significant difference in the improvement rate for 0-2 points. In conclusion, weight loss during MASLD and abstinence and exercise during MetALD were associated with a decrease in dLSM2B.

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Abbreviations: SLD, steatotic liver disease; ALD, alcoholic-related liver disease; MASLD, metabolic dysfunction-associated SLD; MetALD, metabolic dysfunction-associated SLD and ALD; LS, liver stiffness; CAP, controlled attenuation parameter; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γGTP, γ-glutamyl-transpeptidase; FIB-4, fibrosis-4; TG, triglyceride; M2BPGI, macrophage galactose-specific lectin-2 binding protein glycosylation isomer

Key words: MASLD, MetALD, weight loss, abstinence, exercise

Introduction

In 2023, the term used to replace non-alcoholic fatty liver disease was metabolic dysfunction-associated steatotic liver disease (MASLD) (1). A new category, outside pure MASLD, termed metabolic and alcohol related/associated liver disease (MetALD), was selected to describe those with metabolic dysfunction-associated steatotic liver disease. This included patients who consume greater amounts of alcohol per week (140-350 g/week and 210-420 g/week for women and men, respectively). Within the MetALD group, there is a continuum across which the contribution of MASLD and alcohol-associated (alcohol-related) liver disease (ALD) varies. Part of the renaming of steatotic liver disease (SLD) is intended to define MetALD as a specific disease; however, there are no drugs for the treatment of MetALD as a separate disease (2). Furthermore, metabolic risk factors and alcohol often coexist in the same individual, and a synergistic effect of the interaction markedly increasing the risk of liver disease has been elucidated in recent years (3). Subsequent studies investigated the prevalence of MetALD, which ranges from 1.7-17% in the total cohort (3). A few cohort studies have also assessed the prognosis of this patient population, with preliminary data suggesting that MetALD has an intermediate risk of liver fibrosis, decompensation and mortality among the SLD subtypes (3). MASLD and alcohol consumption are independent risk factors for recurrence after endoscopic treatment of esophageal squamous cell carcinoma (4). The therapeutic significance of diagnosing MetALD separately from MASLD and ALD remains unclear.

In patients with MASLD, 7 to 10% weight loss occurs at the beginning of the lifestyle improvement algorithm (5). The next step in the algorithm is to increase physical activity; at least 150 min/week of moderate-intensity physical activity or 75 min/week of vigorous-intensity physical activity is recommended (5). Alcohol consumption is discouraged, or abstinence is recommended in cases of advanced fibrosis or cirrhosis (5). MetALD is an overlapping disease of MASLD and ALD, and lifestyle changes are required (2,3). However, the relationship among reduced alcohol consumption, additional exercise, and weight loss in patients with MetALD in terms of treatment efficacy remains unclear.

In adults with MASLD, non-invasive scores based on combinations of blood tests or combinations of blood tests with imaging techniques measuring mechanical properties and/or hepatic fat content should be used for the detection of fibrosis since their diagnostic accuracy is higher than standard liver enzyme testing [alanine (ALT) and aspartate aminotransferase (AST)] (5). With the vibration-controlled transient elastography, liver stiffness (LS) measurement and controlled attenuation parameter (CAP) values are determined, which allow for a relatively reliable estimation of the degree of fibrosis and steatosis, respectively (5). Mac-2 binding protein glycosylation isomer (M2BPGi) has favorable diagnostic performance for significant and extensive fibrosis in patients with non-alcoholic fatty liver disease and is an effective, non-invasive and convenient marker (6). In the present study, lifestyle changes (weight loss, additional exercise and abstinence from alcohol) were introduced in patients with MASLD and MetALD, and changes in liver fibrosis were assessed after 6 months using M2BPGi and LS as noninvasive tests (NIT).

Materials and methods

Patients. The present study included 100 patients with MASLD and MetALD who had visited liver disease outpatient clinic in Nagasaki Harber Medical center between June 2017 and January 2024 for the first time (Table IA). Of the 100 patients, 70 were women and 30 men. The median age of the patients was 63 years (range: 83-18 years). These patients did not include any cases that were anti-HCV antibody positive or HBs antigen positive. Diagnostic criteria for MASLD and MetALD were established as previously described (1). A total of 67 patients with MASLD and 33 patients with MetALD were retrospectively evaluated after six months of lifestyle changes (weight loss, abstinence, and exercise) (Table IB). The medical records of 100 patients were retrospectively reviewed. All laboratory measurements were obtained from medical records. Hypertensive patients (HT) were defined as those who had been taking antihypertensive medication for at least six months prior to their visit to our department. Patients with hyperlipidemia (HL) were defined as those with a fasting low-density lipoprotein (LDL) cholesterol level of 140 mg/dl or higher or a TG level of 150 mg/dl or higher. Patients receiving statin therapy were included in the HL group; however, those receiving fibrate therapy were excluded. The diabetes group (diabetes mellitus; DM) consisted of patients with fasting serum glucose ≥100 mg/dl or HbA1c ≥5.7%, or with a diagnosis of type 2 diabetes or being treated for type 2 diabetes. The DM group did not include patients treated with sodium-glucose cotransporter 2 inhibitors, incretin preparations containing glucagon-like peptide 1 agonists, or metformin.

For lifestyle modification, the patients were instructed to lose weight, abstain from alcohol, and increase exercise (Table IB). All patients with MASLD and MetALD were advised to add at least 30 min of walking daily and were instructed to increase their walking speed as they became accustomed to walking. Exercise was defined as 100% of 30 min of walking; if less, the self-reported walking time was divided by 30 min and expressed as a percentage. The exercise + (Ex+) group was able to add any degree of exercise, while the None group did not add any exercise. Nutritional guidance was recommended to all patients except those who did not request it. Nutritional guidance was provided by a dietitian with the goal of a 10% reduction in weight at the time of intervention to 25 calories per target weight (kg). All patients were instructed to abstain from alcohol; those who stopped drinking were defined as abstinent, and those who drank less were defined as the reduced drinking group. The abstinence period is six months, as is the observation period. Abstinence was recommended at the first visit, total or partial abstinence was confirmed at two weeks later, and alcohol consumption was checked again at the final assessment six months later. The AbEx group comprised of an Ex^+ group and an abstinence group. Patients were weighed at least once daily, snacking and soft drinks were stopped, and had a goal of losing 10% of their body weight in one year. Decreased body weight (dBW%) is calculated as follows: (BW at entry-BW at 0.5 year after)/BW at entry. BW decrease rate groups (dBWG) were divided by quartiles of dBW% as follows: G1, -6.1%>; G2, -6.1 to -3.1; G3, -3.1 to -0.77; G4, -0.77< (Fig. S1A).

Informed consent was obtained from each patient included in the study and they were guaranteed the right to leave the study if desired. The study protocol conformed to the 1975 Declaration of Helsinki guidelines (7) and was approved by the Human Research Ethics Committee of Nagasaki Harbor Medical Center (approval no. H30-031; Nagasaki, China).

Laboratory measurements. At the start of change of lifestyle and 0.5 years later, platelet [(PLT): M, 13.1-26.2; F, 13-36.9 X $10^4/\mu$l], AST (10-40 U/l), ALT (5-40 U/l) and M2BPGi [1> cut off index (C.O.I.)] levels were evaluated. Fibrosis-4 (FIB-4) levels were calculated based on age and AST, ALT and PLT levels (8). Overall, 98 patients were evaluated using FibroScan. LS (kPa) was evaluated using vibration-controlled transient elastography, and liver fat content (dB/m) was evaluated using the controlled attenuation parameter (CAP). 'd' is the difference between baseline and endpoint (Table IC). A decrease in liver fibrosis (a decrease in dLSM2B) was defined as a reduction in LS (dLS) using FibroScan and M2BPGi (dM2B) during the observation period.

Statistical analysis. Data were analyzed using StatFlex (version 6.0; Artech Co., Ltd.) and presented as median and 95% confidence intervals (CI). Laboratory variables were compared using Mann-Whitney U tests (for differences between the two groups) and χ^2 tests. The detection level was analyzed using receiver operating characteristic (ROC) curves. $P<0.05$ was considered to indicate a statistically significant difference. Correlations were evaluated based on Pearson's correlation

Table I. Clinical characteristics.

A, Base line

	MASLD	MetALD	P-value
Sex			
Female	55 (82.1)	15 (45.5)	0.00017
Male	12 (17.9)	18 (54.5)	
Age, years			
N	67	33	0.38905
Me (Q1~Q3)	62.8 (51.6~71.6)	65.1 (55.3~70.9)	
ALDG			
0	62 (92.5)	0 (0.0)	<0.00001
Alcoholic consumption	5 (7.5)	33 (100.0)	
BMIG			
Normal	3 (4.5)	5 (15.2)	0.11092
Obesity	64 (95.5)	28 (84.8)	
BMI			
N	67	33	0.22226
Me (Q1, Q3)	27.2 (25.8, 30.1)	27.3 (24.1, 29.8)	
AST			
N	67	33	0.68677
Me (Q1, Q3)	56.0 (36.0, 84.5)	56.0 (30.0, 78.5)	
ALT			
N	67	33	0.13190
Me (Q1, Q3)	71.0 (43.5, 112.8)	61.0 (38.5, 81.0)	
PLT			
N	67	33	0.03602
Me (Q1, Q3)	22.0 (19.1, 25.38)	18.0 (14.58, 24.30)	
FIB-4			
N	67	33	0.02465
Me (Q1, Q3)	1.658 (1.20, 2.639)	2.279 (1.807, 3.459)	
LS			
N	66	32	0.02615
Me (Q1, Q3)	6.50 (5.00, 8.70)	7.90 (6.35, 12.55)	
CAP			
N	66	32	0.06396
Me (Q1, Q3)	318.5 (290, 341)	288.5 (270, 340)	
M2BPGi			
N	66	33	0.01600
Me (Q1, Q3)	0.880 (0.620, 1.210)	1.110 (0.835, 2.538)	
HT			
HT	24 (35.8)	17 (51.5)	0.13350
none	43 (64.2)	16 (48.5)	
HT			
HL	25 (37.3)	10 (30.3)	0.48950
None	42 (62.7)	23 (69.7)	
DM			
None	50 (74.6)	24 (72.7)	0.83864
DM	17 (25.4)	9 (27.3)	

Table I. Continued.

B, Change of lifestyle

	MASLD	MetALD	P-value
Exercise			
N	67	33	0.77342
Me (Q1, Q3)	0.5 (0.0, 1.0)	0.5 (0.0, 1.0)	
Exercise G			
Ex	47 (70.1)	23 (69.7)	0.96299
None	20 (29.9)	10 (30.3)	
Nutritional Guidance			
Done	38 (56.7)	10 (30.3)	0.01292
Abstinence			
Abstinence	1 (20.0)	11 (33.3)	1.00000
None	4 (80.0)	22 (66.7)	
dBW%			
N	67	33	0.18334
Me (Q1, Q3)	-3.52 (-6.24, -1.20)	-2.32 (-5.98, 0.70)	
dBW% G1			
G1	17 (25.4)	9 (27.3)	0.83864
G2-4	50 (74.6)	24 (72.7)	
dBW% G12/34			
G1, 2	36 (53.7)	14 (42.4)	0.28762
G3, 4	31 (46.3)	19 (57.6)	
dBW% G			
G1	17 (25.4)	8 (24.2)	0.51125
G2	19 (28.4)	6 (18.2)	
G3	17 (25.4)	8 (24.2)	
G4	14 (20.9)	33.3	

C, Change of clinical factors

	MASLD	MetALD	P-value
dAST			
N	67	33	0.82019
Me (Q1, Q3)	-15.0 (-36.8, 0.0)	-13.0 (-37.0, -2.0)	
dALT			
N	67	33	0.57236
Me (Q1, Q3)	-24.0 (-51.8, -4.3)	-17.0 (-43.5, -3.0)	
dPLT			
N	67	33	0.39098
Me (Q1, Q3)	-0.7 (-2.8, 1.0)	-0.3 (-1.7, 1.7)	
dLS			
N	66	32	0.66030
Me (Q1, Q3)	-0.7 (-2.2, 0.7)	-0.8 (-2.5, 0.6)	
dLSG			
Decrease	44 (66.7)	21 (65.6)	0.91850
Increase	22 (33.3)	11 (34.4)	
dCAP			
N	66	32	0.77922
Me (Q1, Q3)	-21.5 (-61.0, 11.0)	-23.0 (-60.0, -2.0)	

Table I. Continued.

C, Change of clinical factors

	MASLD	MetALD	P-value
dM2BPGi			
N	61	30	0.40795
Me (Q1, Q3)	0.0 (-0.2, 0.1)	-0.1 (-0.4, 0.2)	
dM2BG			
Decrease	27 (44.3)	16 (53.3)	0.41519
Increase	34 (55.7)	14 (46.7)	
dFIB-4			
N	67	33	0.34621
Me (Q1, Q3)	-0.1 (-0.4, 0.1)	-0.3 (-0.7, 0.3)	
dFIBG			
Decrease	41 (61.2)	21 (63.6)	0.81297
Increase	26 (38.8)	12 (36.4)	

Number (N), Medium (Me), Q1, and Q3 represent the first and third quartiles. AST, 10-40 U/l; ALT, 5-40 U/l; PLT, M: 13.1-26.2, W: 13-36.9x10^4/μl; LS: kPa; CAP, dB/m; [M2BPGi; <1 cut-off index (C.O.I.)]; exercise (%) and 'd' is difference between baseline and endpoint. dBW% G; G1, -6.1%>; G2, -6.1 to -3.1; G3, -3.1 to -0.77; G4, -0.77<. AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet count; Fib-4, Fibrosis-4; LS, liver stiffness; CAP, controlled attenuation parameter; M2BPGi, macrophage galactose-specific lectin-2 binding protein glycosylation isomer; HT, hypertension; HL, hyperlipidemia, DM, diabetes mellitus; SLD, steatotic liver disease; ALD, alcoholic-related liver disease; MASLD, metabolic dysfunction-associated SLD; MetALD, metabolic dysfunction-associated SLD and ALD; BMI, body mass index.

coefficient (R). A multivariate analysis was performed using logistic regression.

Results

Difference between MASLD and MetALD. Patients with MetALD were more likely to be men and had higher FIB-4, LS, and M2BPGi scores than those with MASLD (Table IA). There were no significant differences in age, body mass index (BMI), HT, HL, or DM. Nutritional guidance interventions were more common in patients with MASLD; however, exercise and dBW% did not differ significantly (Table IB). The rate of abstinence due to MetALD was 33.3%. No differences were found between the MASLD and MetALD groups with respect to changes in clinical factors (Table IC).

Weight loss is associated with a decrease in liver fibrosis in patients with MASLD, but no association can be observed in patients with MetALD. The correlation between dM2BPGi and dLS was R=0.5896 (P<0.00001) in all cases (N=87). When only one of LS and M2BPGi was measured, fibrosis reduction was defined as a decrease in the measured item. The rates of decrease in dLSM2B levels were 35.8 and 39.4% in MASLD and MetALD (no significance difference (Fig. S1B). Among patients with MASLD, a decrease in the dLSM2B group was associated with weight loss (Table II). Patients with MASLD had greater dBW% in the decreased dLSM2B group; however, patients with MetALD showed no significant differences (Fig. 1A). The distribution of the weight loss rate was associated with a decrease in dLSM2B in patients with MASLD, but not in those with MetALD (Figs. 1B and S1C).

In patients with MetALD, complete abstinence from alcohol and the addition of exercise were associated with a decrease in liver fibrosis. In patients with MetALD, alcohol abstinence and additional exercise, but not weight loss, were associated with a decrease in dLSM2B (Table II and Fig. 1C). Patients with MetALD were more likely to show a decrease in the dLSM2B group for complete abstinence from alcohol (with exercise) than for those with partial abstinence (with exercise) or others (Fig. 1D). There was no significant difference in the decrease in dLSM2B between achieving exercise goals (with abstinence), partial exercise goals (with abstinence), and other goals in patients with MetALD (Fig. 1E). The percentage of patients with MetALD with reduced dLSM2B levels was 23% in the abstinence alone or exercise alone group, 30% in other (the non-abstinence and non-exercise) groups, and 70% in the AbEx group, with no significant difference between the three groups; however, a trend toward a difference was observed (Fig. S1D). Patients with MetALD treated with AbEx did not differ from non-AbEx patients with dBW%G1 or others in terms of the rate of dLSM2B reduction (Fig. 1F). Although the difference was not significant, the rate of reduction in dLSM2B was 80% with AbEx and G1 weight loss, 60% with AbEx and no G1 weight loss, and 33% with G1 weight loss alone (Fig. S1E). In MetALD cases, there was no significant difference in dLSM2B between the three groups of complete Ab, partial Ab, and no Ab (Fig. S1F), and similarly no significant difference between the three groups of complete Ex, partial Ex, and no Ex (Fig. S1G).

Table II. The relation with dLSM2B and clinical factors.

	MASLD			MetALD		
	Decrease	Increase	P-value	Decrease	Increase	P-value
dLSM2B						
dBW%						
n	24	43	0.00152	13	20	0.58050
Me (Q1~Q3)	-5.63 (-7.92~-2.98)	-2.50 (-4.37~-0.40)		-1.84 (-8.28~1.04)	-2.63 (-5.28~0.77)	
dBW%G1						
G1	10 (41.7)	7 (16.3)	0.02204	5 (38.5)	3 (15.0)	0.21338
G2-4	14 (58.3)	36 (83.7)		8 (61.5)	17 (85.0)	
Ex						
n	24	43	0.94625	13	20	0.31540
Me (Q1, Q3)	0.5 (0.0, 0.9)	0.5 (0.0, 1.0)		0.8 (0.2, 1.0)	0.3 (0.0, 1.0)	
Ex G						
Ex+	17 (70.8)	30 (69.8)	0.92716	10 (76.9)	13 (65.0)	0.70059
None	7 (29.2)	13 (30.2)		3 (23.1)	7 (35.0)	
Nutritional guidance						
Done	16 (66.7)	22 (51.2)	0.21942	5 (38.5)	5 (25.0)	0.46107
None	8 (33.3)	21 (48.8)		8 (61.5)	15 (75.0)	
Abstinence						
abstinence	0 (0.0)	1 (2.3)	1.00000	7 (53.8)	4 (20.0)	0.06455
None	24 (100.0)	42 (97.7)		6 (46.2)	16 (80.0)	
abEx						
none	24 (100.0)	43 (100.0)	Insufficient number	6 (46.2)	17 (85.0)	0.02593
abEx	0 (0.0)	0 (0.0)		7 (53.8)	3 (15.0)	

The dLSM2B decreased group had no increase in LS or M2BPI, while the dLSM2B increased group was the group other than the decreased group. dBWG were divided by quartiles of dBW% as follows: G1, -6.1%>; G2, -6.1 to -3.1; G3, -3.1 to -0.77; G4, -0.77<. Exercise (Ex) was defined as 100% of 30 min of walking; if less, the self-reported walking time was divided by 30 min and expressed as a percentage. The Ex^+ group was able to add any degree of exercise, while the None group did not add any exercise. Nutritional guidance was provided by a dietitian with the goal of a 10% reduction in weight at the time of intervention to 25 calories per target weight. The abstinence group was defined as the group that completely stopped drinking alcohol based on self-reporting. The AbEx group comprised of an Ex^+ group and an abstinence group. SLD, steatotic liver disease; ALD, alcoholic-related liver disease; MASLD, metabolic dysfunction-associated SLD; MetALD, metabolic dysfunction-associated SLD and ALD.

Decrease in dLSM2B by lifestyle modification for patients with MASLD is predicted by a decrease in FIB-4 and weight loss, but not for patients with MetALD. Predictive factors that could improve liver fibrosis in patients with MASLD were searched. In patients with MASLD, no baseline factors differed significantly between the decreased and increased dLSM2B groups (Table SI). However, among the factors that changed over the observation period, there were significant differences in the AST, ALT, CAP and FIB-4 levels between the two groups (Table SII). Using ROC analysis, the cutoff values for the dLSM2B reduced group were calculated for five factors (these four factors plus dBW%). No significant differences were observed in the area under the curve (AUC) of the five factors (Fig. S2A). Since AST and ALT were included in FIB-4, and dBW and dCAP were significantly correlated (Table SIII), dFIB-4 and dBW% were selected as predictors. dBW% (-3.8% over) and dFIB-4 (-0.201 over) were used as predictors of a decrease in the dLSM2B group. The odds ratios (ORs) of the dBW% (-3.8% or more) and dFIB-4 (-0.201 or more) groups contributing to a decrease in dLSM2B were assessed using logistic analysis. The results indicated that these two predictors contributed independently (Fig. S2B). A prediction score of 0, 1 or 2 points was developed to predict the decrease in dLSM2B, with 1 point awarded for a dBW% reduction of ≥3.8 and 1 point for a FIB-4 reduction of ≥0.201. In patients with MASLD, there was a significant difference in the decrease in dLSM2B by 8.3% for a prediction score of 0, 36% for 1, and 72.2% for 2 (Fig. 2A), whereas there was no significant difference in the improvement rate for 0-2 points (Fig. 2B). In patients with MASLD, a prediction score contributed to a decrease in dLSM2B in univariate logistic analysis (OR, 5.224; 95% CI lower-upper: 2.231-12.232; P=0.00014),

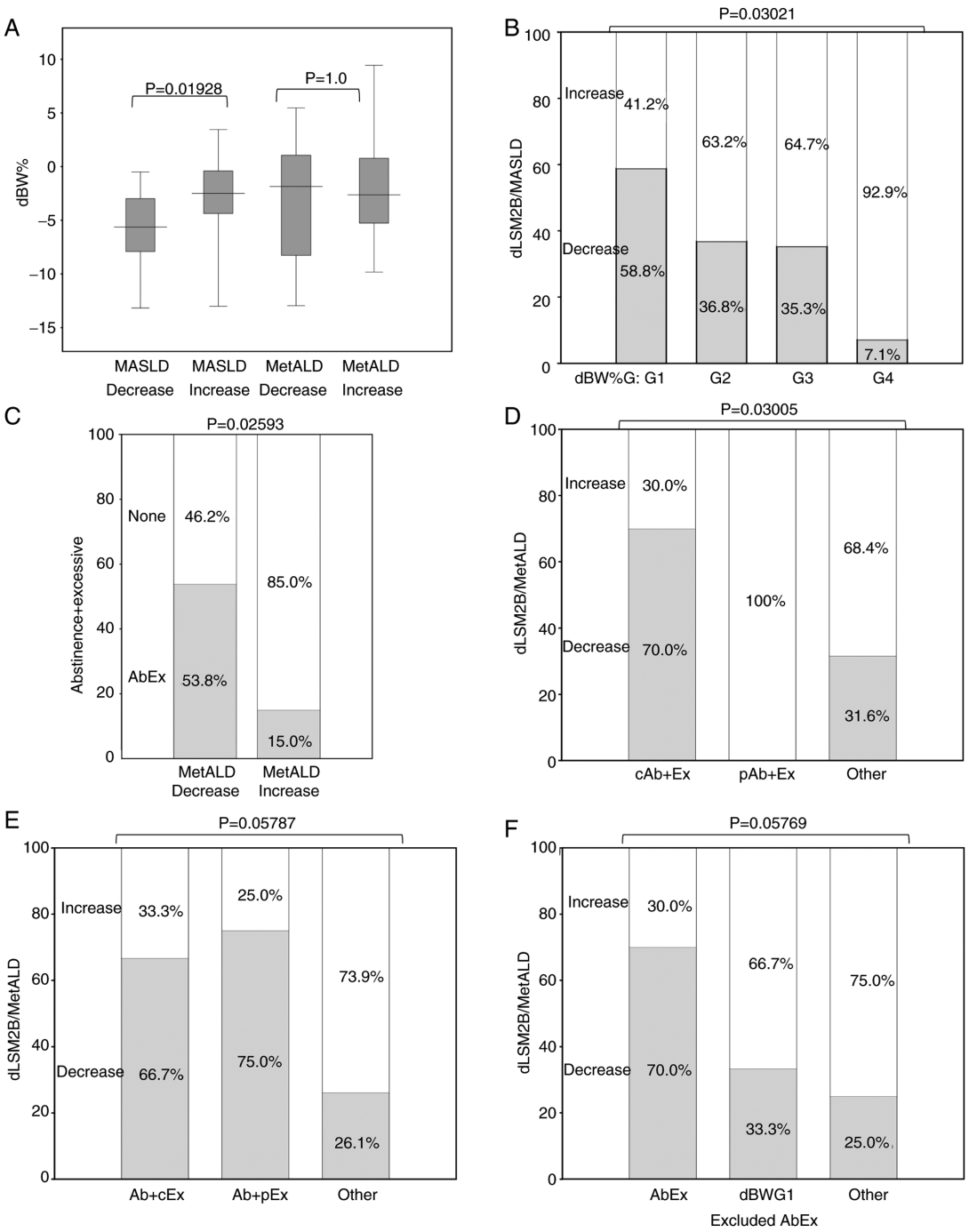

Figure 1. Relationship between with dLSM2B decrease and change of lifestyle. The dLSM2B decreased group is the group with no increase in LS (dLS) and no increase in M2BPI (dM2B), and the dLSM2B increased group is the group other than the decreased group. Change of LS and M2B were difference form entry to 0.5 year after. Exercise (Ex) was defined as 100% of 30 min of walking; if less, self-reported walking time was divided by 30 min and expressed as a percentage. The Ex^+ group is the group that was able to add any degree of exercise, and the None group is the group that did not add any exercise at all. The abstinence group was the group that completely stopped drinking alcohol by self-report. The AbEx group is an Ex^+ and abstinence group. Decreased body weight (dBW%) is calculated as follows: (BW at entry-BW at 0.5 year after)/BW at entry. BW decrease rate groups (dBWG) were divided by quartiles of dBW% as follows: G1: -6.1%>; G2, -6.1 to -3.1; G3, -3.1 to -0.77; G4, -0.77<. (A) Differences in the relationship between weight loss and liver fibrosis improvement in MASLD and MetALD. dBW% was compered between dLSM2B decrease and increase groups in MASLD and MetALD. Y axis is dBW%. (B) Association between weight loss and liver fibrosis improvement in MASLD. In MASLD, dBWG and dLSM2B decrease group. G1, 17 patients; G2, 19 patients; G3, 17 patients; G4, 14 patients. Y axis is dLSM2B decrease group percentile. (C) Association between abstinence + exercise and improvement of liver fibrosis in MetALD. Rate of AbEx in groups related to dLSM2B decrease group. Y axis is AbEx percentile. (D) Relationship between complete abstinence and liver fibrosis improvement in MetALD. In MetALD, the relation between degree of abstinence and dLSM2B decrease group. cAb is complete abstinence and pAb is partial abstinence included decrease drink. Ex is the group that was able to add any degree of exercise. cAb + Ex group, 10 patients; pAb + Ex group, 4 patients; other group, 19 patients. Y axis is dLSM2B decrease group percentile. (E) Relationship between achievement of exercise goal and improvement of liver fibrosis in MetALD. In MetALD, the relation between degree of exercise and dLSM2B decrease group. cEx is 30 min of more of walking and pEx is less than 30 min of walking. Ab is stop of drinking. Ab + cEx group, 6 patients; Ab + pEx, 4 patients; other, 23 patients. (F) Comparison of liver fibrosis improvement between alcohol abstinence exercise group and weight loss group in MetALD. In MetALD, the relation between degree of BW and dLSM2B decrease group. AbEx is an Ex^+ group and an abstinence group. dBWG1 excluded AbEx group is dBWG1 and non-AbEx group. AbEx group, 10 patients; dBWG1 excluded AbEx, 3 patients; other, 20 patients. MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease and alcoholic-related liver disease.

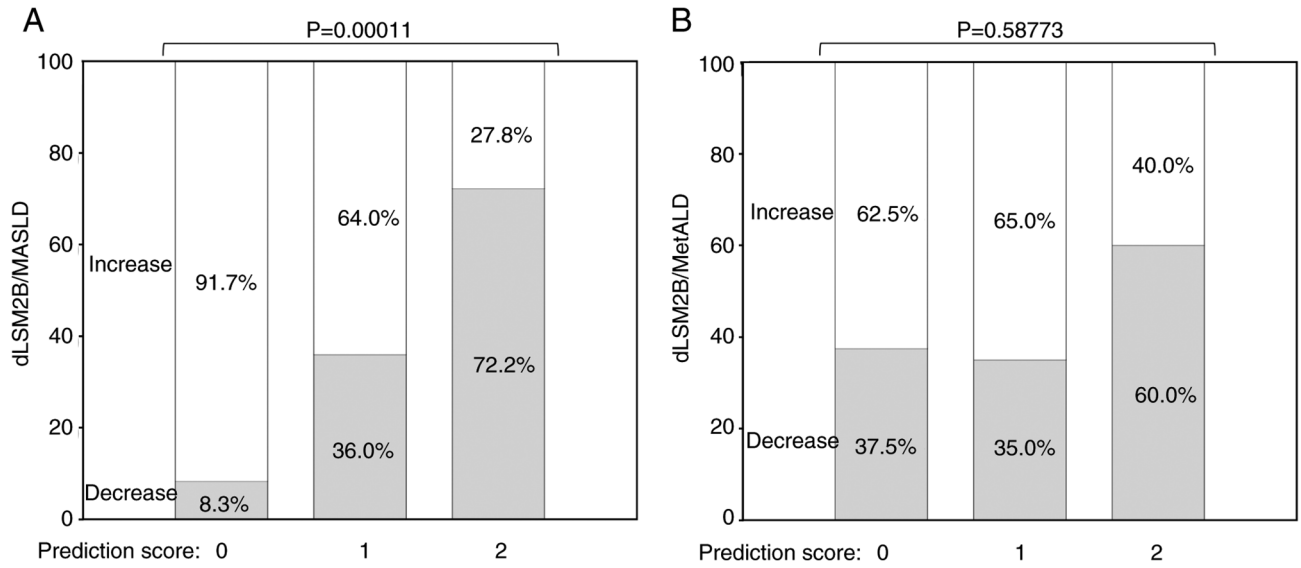

Figure 2. Evaluating effectiveness prediction scores for dLSM2B decrease group. One point was given for a decrease of 0.201 or more in FIB-4 and one point for a decrease of 3.8% or more in BW, and the total score was used as the predictor. (A) Association between prediction score and improvement of liver fibrosis in MASLD. In MASLD, percentage of dLSM2B decrease groups by prediction score 0-2. Score 0; 24 patients, Score1; 25 patients, Score 2; 18 patients. P=0.00205 (ANOVA). (B) Association between prediction score and improvement of liver fibrosis in MetALD. In MetALD. Score 0, 8 patients; Score 1, 20 patients; Score 2, 5 patients. P=0.00054 (ANOVA). Y axis is dLSM2B decrease percentile. MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease and alcoholic-related liver disease.

but not in the MetALD group (OR, 1.482; 95% CI lower-upper: 0.472-4.650; P=0.50048). In patients with MASLD, multiple logistic analysis of the effects of a prediction score and dBW% (-3.8% or more) on dLSM2B decrease showed that only a prediction score was significant [Fig. S2C; variance inflation factors (VIF); 2.667], as was the comparison of a prediction score and dFIB-4 (-0.201 or more) (Fig. S2D; VIF; 2.652).

Influence of alcohol consumption on lifestyle modification in MetALD patients. The effects of alcohol consumption in patients with MetALD were examined. The amount of alcohol consumed (ALD score) was defined as grade 1 for 30-45 g of alcohol for men and 20-35 g for women, and grade 2 for 45-60 g for men and 35-50 g for women. Differences in sex and LS were observed for MetALD grade 1 (MetALD1) and MetALD2, but not significant for other pretreatment factors (Table SIV). Particular sex differences were observed in MASLD, MetALD1 and MetALD2 (Fig. S3A). In a comparison among the three groups (MASLD, MetALD1, and MetALD2), differences in LS were found between MASLD and MetALD2, whereas MASLD and MetALD1 were similar (Fig. S3B). Considering lifestyle modification, weight loss was less frequent in the MetALD2 group, and there were no significant differences in abstinence from alcohol, physical activity, or frequency of nutritional guidance (Table III). The distribution of dBW% (dBW% G1-4) showed differences among MASLD, MetALD1 and MetALD2, which were characterized by more G1 in MetALD1 and G4 in MetALD2 (Fig. S3C). The dBW% was also not significantly different between the MASLD and MetALD1 groups; only the MetALD2 group showed a lower rate than the MASLD and MetALD1 groups (Fig. S3D). There were no significant differences in AST, ALT, PLT, LS, CAP, M2BPGi and FIB-4 levels between the two groups over the treatment period (Table SV).

Discussion

In the present study, 67 patients with MASLD and 33 patients with MetALD were instructed to improve their lifestyle, and changes in liver fibrosis were assessed after six months. Prior to lifestyle modifications, the evaluation revealed more men with advanced liver fibrosis and MetALD. As a result of lifestyle modifications, weight loss was associated with improved liver fibrosis in patients with MASLD, but not in those with MetALD. By contrast, complete abstinence from alcohol and exercise was associated with improved liver fibrosis in patients with MetALD. The predictive score, consisting of a decrease in FIB-4 index and body weight, was associated with improved liver fibrosis in patients with MASLD, but not in those with MetALD. Patients with MetALD (MetALD1) who drank less alcohol had a similar degree of weight loss to those with MASLD, and their liver fibrosis before lifestyle modification was milder than that of patients (MetALD2) patients who drank more. These results indicate a difference in the effects of weight loss between MASLD and MetALD. Complete abstinence from alcohol and exercise are considered effective in improving the lifestyle of patients with MetALD. Thus, MetALD1 may be similar to MASLD and MetALD2 in ALD.

In the present study, patients with MetALD had more worsening liver fibrosis (FIB-4, M2BPGi and LS) and a male-dominant sex difference than those with MALSD, but age and BMI did not differ between the groups. Although one study did not find a sex difference (9), most studies indicate that MetALD is more common in males than in females as compared with MASLD (10-12). Even after adjusting for sex differences, MetALD has a worse prognosis for liver and cardiovascular diseases than ALD (12-14). The prevalence of MetALD in these studies ranged from 1.7-17.0% in a resident-based cohort (3). When the proportion of patients with

Table III. Lifestyle change in MetALDG1/2.

MetALD Grade 1/2	Grade1	2	P-value
dBW%			
Me (Q1, Q3)	-4.086 (-6.98, -1.596)	1.423 (-1.331, 3.910)	0.00243
dBW%G			
1	7 (33.3)	1 (8.3)	0.02123
2	5 (23.8)	1 (8.3)	
3	6 (28.6)	2 (16.7)	
4	3 (14.3)	8 (66.7)	
dBW%G4			
4	3 (14.3)	7 (58.3)	0.01636
1-3	18 (85.7)	5 (41.7)	
Abstinence/no			
Abstinence	7 (33.3)	4 (33.3)	1.00000
None	14 (66.7)	8 (66.7)	
abEx			
None	14 (66.7)	9 (75.0)	0.70981
abEx	7 (33.3)	3 (25.0)	
Ex G			
Ex	17 (81.0)	6 (50.0)	0.11422
None	4 (19.0)	6 (50.0)	
Nutritional guidance			
Done	7 (33.3)	3 (25.0)	0.70981
None	14 (66.7)	9 (75.0)	

The amount of alcohol consumed (ALD score) was defined as grade 1 for 30-45 g of alcohol for men and 20-35 g for women, and grade 2 for 45-60 g for men and 35-50 g for women. Number (N), Medium (Me), Q1, and Q3 represent the first and third quartiles.

MetALD was 1.7% in the overall cohort, it was 2.5% in the SLD group, and when it was 17% in the overall cohort, it was 24% in the SLD group (3). In the present study, 33 patients with MetALD represented 33% of patients with SLD. When the target SLD is narrowed down to cases with advanced fibrosis, MASLD and MetALD are reported to represent 2.4 and 1.5% of all cases, respectively (9), and it is estimated that the number of MASLD and MetALD cases will converge as fibrosis worsens. The large number of MetALD cases in the present study was presumably because this was a hospital-based study with more cases of advanced liver damage than studies in the general population.

In the present study, differences were found between the MASLD and MetALD groups in the relationship between weight loss and decreased fibrosis. In MASLD, 7-10% weight loss is required to improve MASH and liver fibrosis (5,15,16). The FIB-4 is insufficient as a primary screening tool for liver fibrosis in the general population (17). However, in MASLD, a decrease or normalization of ALT levels is an indicator of improvement in the MASH score, whereas changes in FIB-4 (14,15), is an indicator of liver fibrosis (18). FIB-4 is a first-line test in MASLD practice (5,15) and a cost-effective screening test for high-risk MASLD (19). Decreased FIB-4 and weight were independent ameliorating factors for liver fibrosis in patients with MASLD (Fig. S2B). The combination of these two parameters is a predictor of improvement of liver fibrosis is a new finding. However, weight loss was not associated with improved liver fibrosis in patients with MetALD, and the predictors created by the MASLD results were not valid for MetALD. Because MetALD is a condition that includes MASLD and ALD, MASLD and ALD should be treated separately (2,3). However, because MetALD is a new condition, no studies have examined the effect of weight loss; therefore, it is necessary to develop a lifestyle intervention for MetALD in the future.

Weight loss was not clearly associated with liver fibrosis in MetALD, but complete abstinence from alcohol and the addition of exercise were associated with liver fibrosis in MetALD. Furthermore, complete abstinence from alcohol was more effective than partial abstinence, and there was no difference in effectiveness between performing daily exercise as directed and performing it less than directed but as little as possible. Education regarding lifestyle modifications for patients with ALD is likely to be optimized by improving physical activity (20). Patients with alcohol use disorder (AUD) who were able to add exercise were less associated with the development of alcoholic liver disease (ALD) than those who did not exercise (21). Patients with MASLD and ALD understand the importance of exercise, but lack of confidence in exercising and fear of falling are associated with difficulties in exercising, which can be modified with education and are goals of exercise acceptance (22). Based on these reports, exercise education is very important for patients with MetALD, and if exercise is enabled, improvement in liver

fibrosis can be expected. Complete abstinence from alcohol is recommended in cases of cirrhosis, whereas alcohol reduction is recommended in SLD other than advanced fibrosis (13), although some studies have indicated that abstinence from alcohol is also required for MetALD (2,15,23). In the present study, complete alcohol abstinence was necessary to improve liver fibrosis, and exercise may have been effective. Even in patients with MASLD and low alcohol intake, there is a relationship between alcohol consumption and risk of liver fibrosis (24). Alcohol consumption and mortality risk both increased, and the amount of alcohol consumed that minimized health losses was zero (25). When metabolic dysfunction and alcohol consumption coexist, pathogenic pathways leading to liver injury are likely to be additive and synergistic (3,26). These results indicate that patients with MetALD but without cirrhosis should also be educated about complete abstinence from alcohol. Alcohol consumption is the most important factor affecting the severity of alcohol-related SLDs (MetALD + ALD) (27). Although the success rate of drinking in patients with MetALD has not been reported, 21% of patients who attended Alcoholics Anonymous (AA) with alcohol-related problems successfully abstained from alcohol for one year if they wanted to abstain, and 10% at one year if they did not want to (28). The effectiveness of AA meetings, cognitive-behavioral therapy, and exercise in improving abstinence rates is expected to be effective (29). All the patients in the present study were referred by their general practitioners, and at the time of their first visit to our department, they had already received an explanation of the effectiveness and necessity of abstinence from alcohol. Therefore, it is assumed that numerous came to our clinic to abstain from alcohol. Additionally, the benefits of abstinence from alcohol were explained to patients with MetALD, and have sought their understanding before promoting physical exercise, which it is considered that has led to the current abstinence rate (33%) in our hospital. Therefore, alcohol abstinence may eliminate aggravating factors and improve liver fibrosis in some patients, independent of weight loss.

Our exercise instructions for patients with MASLD and MetALD followed Western guidelines (4,14), with instructions for 150 min of moderate exercise per week or 75 min of vigorous exercise per week. Specifically, they were encouraged to exercise daily (30), told them to work hard for an average of 30 min per day (31), and checked the amount of time they could achieve. It has been reported that among people undergoing health checkups, those aged 65 or older who have no exercise habits are associated with liver fibrosis (32). Although the effect of exercise was not related to changes in liver fibrosis in patients with MASLD, the median value was 50%, and it is likely that the amount of exercise was low. In the future, patients should be taught to exercise at a minimal level (30 min of walking daily). Conversely, excessive alcohol consumption is associated with increased dietary intake and is related to obesity (33) and metabolic factor appearance (27), and it is also known that decreasing alcohol consumption results in improvement of obesity (34). Weight loss had no clear effect on liver fibrosis in patients with MetALD but should be reexamined in more cases in the future. A comparison between MetALD1 and MetALD2 showed that MetALD1 was closer to the MASLD (LS and dBW%). In the future, classification of patients with MetALD in terms of alcohol consumption may be necessary to predict the effect of lifestyle modifications on liver fibrosis.

The limitation of the present study is that it was a small, single-hospital, and retrospective study. In addition, alcohol consumption and physical activity were patient-reported and not quantifiable. Given the limited observation period of six months in MetALD, it is possible that other factors may contribute to long-term outcomes. Further follow-up and ongoing research are therefore needed. However, the present study found that weight loss in MASLD, alcohol abstinence, and additional exercise in MetALD were associated with an improvement in liver fibrosis. When teaching lifestyle modifications in SLD, it is important to first teach weight loss for MASLD and complete abstinence and additional exercises for MetALD. A combination of FIB-4 index reduction and weight loss may be effective in predicting decreased liver fibrosis in patients with MASLD. The effectiveness of weight loss in MetALD needs to be further investigated in more cases, and the content of exercise instruction also needs to be examined in the MASLD. Screening for liver disease has been reported to increase abstinence rates (35), and the active involvement of hepatologists in MetALD (probably all alcohol-related SLD) may increase abstinence rates. While a multidisciplinary approach is necessary for patients with SLD (5,15), education by hepatologists regarding abstinence, weight loss, and exercise is also considered necessary.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study are not publicly available due to containing information that could compromise the privacy of research participants, but may be requested from the corresponding author.

Authors' contributions

TIc wrote the manuscript, analyzed the data and designed the study. TIc, SM, MYa, SY, MK, YN, HY, OM, TIk, TO, NK, MYo and HM collected the data. TIc and SM confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The protocol for this research project was approved (approval no. H30-031) by the Ethics Committee of of Nagasaki Harbor Medical Center (Nagasaki, Japan). Informed consent was obtained from each patient included in the study and they were guaranteed the right to leave the study if desired.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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