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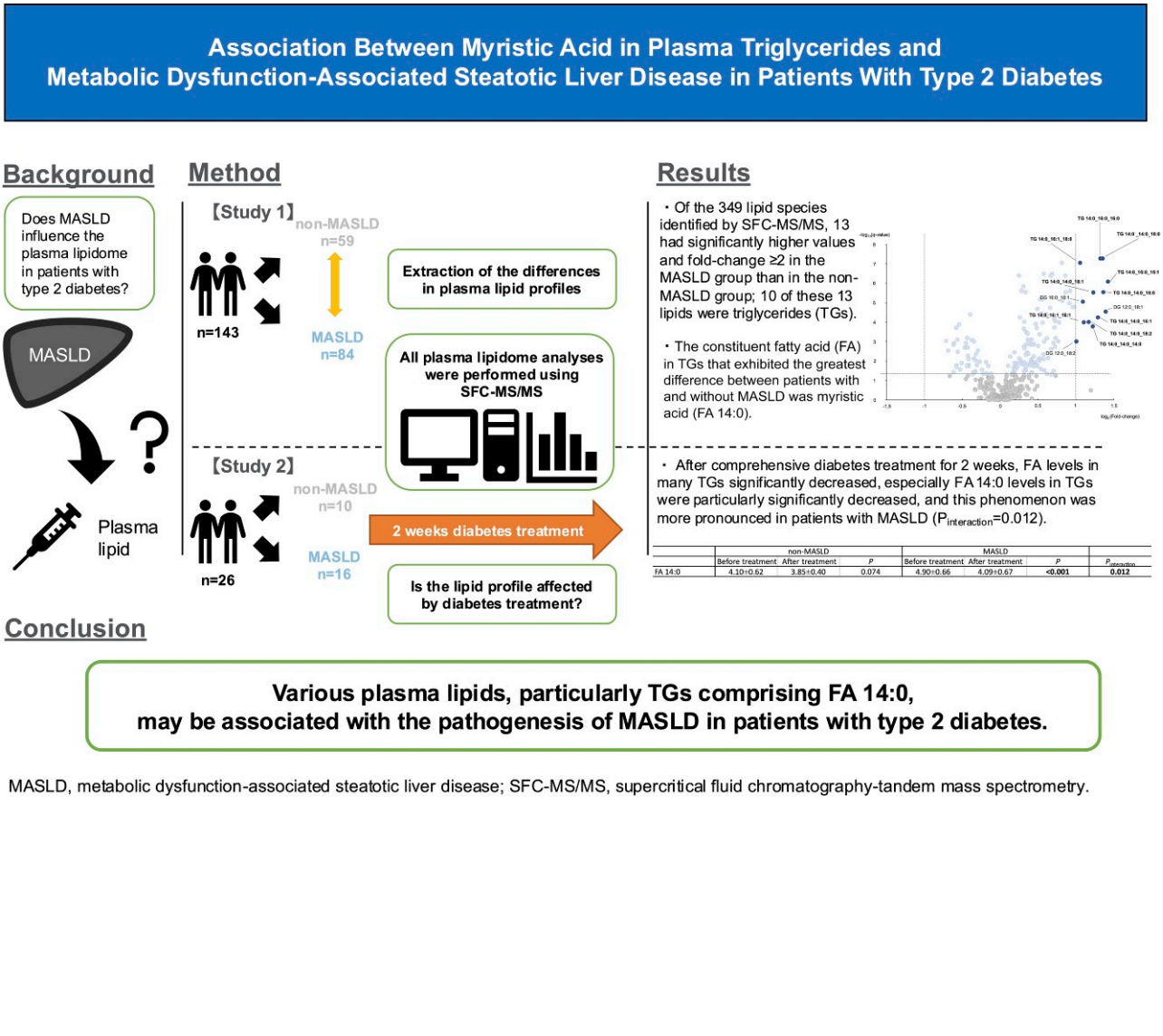

MASLD, metabolic dysfunction-associated steatotic liver disease; SFC-MS/MS, supercritical fluid chromatography-tandem mass spectrometry.

Association Between Myristic Acid in Plasma Triglycerides and Metabolic Dysfunction–Associated Steatotic Liver Disease in Patients With Type 2 Diabetes: A Comprehensive Analysis of Plasma Lipids Using Supercritical Fluid Chromatography–Tandem Mass Spectrometry

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This study aimed to investigate the relationship between the plasma lipidome and metabolic dysfunction–associated steatotic liver disease (MASLD) in type 2 diabetes. Initially, we conducted a plasma lipidome analysis using supercritical fluid chromatography–tandem mass spectrometry in 143 patients with type 2 diabetes with and without MASLD. Of the 349 lipid species identified, 13 had higher levels and a fold-change ≥2 in the MASLD group than in the non-MASLD group; 10 of these 13 lipids were triglycerides (TGs). The constituent fatty acid (FA) in TGs that exhibited the greatest difference between patients with and without MASLD was myristic acid (FA 14:0). The presence of MASLD was an independent explanatory factor for high FA 14:0 levels in TGs, even after adjusting for covariates. Next, we assessed whether the levels of lipids identified in the initial analysis were influenced by comprehensive diabetes treatment in 26 patients. After comprehensive diabetes treatment of 2 weeks, FA levels in many TGs significantly decreased; especially FA 14:0 levels, and this reduction was more pronounced in patients with MASLD. These results suggest that various plasma lipids, particularly TGs comprising FA 14:0, may be associated with the pathogenesis of MASLD in patients with type 2 diabetes.

ARTICLE HIGHLIGHTS

- Changes in blood lipid profiles in type 2 diabetes, particularly when complicated by metabolic dysfunction–associated steatotic liver disease (MASLD), have not been fully elucidated.
- Does MASLD influence the plasma lipidome in patients with type 2 diabetes?
- Patients with MASLD exhibited elevated levels of myristic acid (FA 14:0) in plasma triglycerides, which significantly decreased after comprehensive diabetes treatment.
- Elevated FA 14:0 levels in triglycerides may be associated with MASLD pathogenesis in type 2 diabetes.

Type 2 diabetes is associated with various complications, one of the most important being steatotic liver disease (SLD). Both type 2 diabetes and SLD are associated with

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obesity and insulin resistance (1), and the prevalence of these diseases has increased in recent years (2,3). Accordingly, a new concept termed metabolic dysfunction–associated SLD (MASLD) was proposed and has gained attention (4).

The combination of type 2 diabetes and MASLD increases the risk of other clinically significant diseases. Previous studies have demonstrated that patients with type 2 diabetes have elevated risks of cardiovascular disease (CVD) (5), chronic kidney disease (6), and all-cause mortality (7) in the presence of comorbid MASLD, highlighting the strong association between MASLD and type 2 diabetes.

MASLD is mainly caused by triglyceride (TG) accumulation in the liver. Recent studies suggested that qualitative changes in intrahepatic TGs (8) and other lipids, such as phospholipids (9), contribute to MASLD development. While liver biopsies are traditionally required to assess these changes, there is growing interest in blood lipids as noninvasive alternatives (10). Some circulating lipids correlate with intrahepatic fat and histological severity (11) and may reflect disease activity. Serum lipid-based MASLD tests have shown promise in Europeans without type 2 diabetes (12,13) but lack diagnostic accuracy in those with type 2 diabetes (14). Although SLD is often viewed as a single disease, it involves diverse mechanisms including insulin resistance, abnormal lipid metabolism, gut microbiota changes, inflammation, and mitochondrial dysfunction. Metabolomics has identified distinct MASLD subtypes (13), suggesting that MASLD/metabolic dysfunction–associated steatohepatitis (MASH) pathogenesis in type 2 diabetes may differ, with intrahepatic fat often driven by de novo lipogenesis (DNL). Thus, models developed in populations without diabetes may not apply to patients with type 2 diabetes. New models reflecting diabetes-specific metabolic features are needed.

In addition, clarifying how the lipid metabolic profile of MASLD changes during treatment, when the metabolic environment shifts rapidly, will be important for identifying noninvasive biomarkers that sensitively reflect MASLD pathology. Thus, while some studies have assessed blood lipid changes in MASLD, much remains unclear in patients with both type 2 diabetes and MASLD. Therefore, to elucidate MASLD pathogenesis in this population and identify blood lipids as candidate biomarkers for screening and evaluating therapeutic efficacy, this study *1*) analyzed blood lipid profiles in patients with type 2 diabetes with and without MASLD and *2*) assessed changes after short-term comprehensive diabetes treatment using supercritical fluid chromatography–tandem mass spectrometry (SFC-MS/MS)–based semitargeted lipidomics.

RESEARCH DESIGN AND METHODS

Ethics, Consent, and Permissions

The research protocol was approved by the Research Ethics Committee of Osaka University Hospital (Osaka, Japan, approval no. 23201) and strictly adhered to the tenets of the Declaration of Helsinki. All participants were fully informed of the study, and written informed consent was obtained.

Study Design

This study used plasma lipidome data from existing clinical studies (studies 1 [15] and 2 [16]). Study 1, a cross-sectional observational study primarily aimed at assessing the association between plasma metabolites and lipids and diabetes complications, included 240 patients with type 2 diabetes aged 20–65 years and 20 healthy volunteers without diabetes. Study 2, a longitudinal observational study, included 31 patients with type 2 diabetes aged 20–65 years. The primary aim of study 2 was to evaluate changes in the lipid profile of MASLD during a 2-week comprehensive diabetes treatment, when the metabolic environment changes rapidly, and to confirm whether the MASLD-related plasma TG changes observed in study 1 were also detectable at baseline in the cross-sectional analysis. Participants were recruited between June 2014 and October 2016 for study 1 and between 2017 and 2019 for study 2. Herein, cross-sectional analyses were conducted using data from study 1, and longitudinal analyses were conducted using data from study 2.

Participants

The current study comprised three patient populations. The healthy population included healthy volunteers without diabetes enrolled in study 1. Population 1 with diabetes included patients with type 2 diabetes from study 1 who underwent abdominal ultrasound or CT scan and liver morphological assessment within 1 year prior to enrollment. Population 2 with diabetes included patients with type 2 diabetes from study 2 who underwent abdominal ultrasound or CT scan and liver morphological assessment within 1 year prior to enrollment.

Diabetes was diagnosed according to the criteria of the Japan Diabetes Society (17), including fasting plasma glucose (PG) ≥7.0 mmol/L (≥126 mg/dL), 2-h PG ≥11.1 mmol/L (≥200 mg/dL) after a 75-g glucose load; casual PG ≥11.1 mmol/L (≥200 mg/dL); or current use of glucose-lowering medications. In populations 1 and 2 with diabetes, patients were excluded if they were unable to undergo strict glycemic control at enrollment (e.g., frequent severe hypoglycemic episodes, unstable diabetic retinopathy as assessed by an ophthalmologist), had serum creatinine ≥176.80 μmol/L (≥2.0 mg/dL), had severe infections or trauma, were in the preoperative or postoperative period, or were receiving steroid treatment.

Definition of MASLD

MASLD was diagnosed according to the criteria proposed by Rinella et al. (4). Specifically, patients with type 2 diabetes and a steatotic liver detected by abdominal imaging who did not consume excessive alcohol (<30 g/day of pure alcohol for men and <20 g/day for women) were classified as having MASLD. Patients who underwent abdominal imaging but did not have fatty liver and had alcohol

intake below these thresholds were classified as not having MASLD.

Clinical and Biochemical Analysis

At enrollment, each patient underwent a comprehensive medical history assessment, and fasting plasma samples were obtained. HbA_{1c} levels were quantified using high-performance liquid chromatography, while serum TG concentrations were determined using enzymatic assays. Simultaneously, fasting plasma specimens were collected for lipidomic analysis and immediately placed in a 4°C refrigerator. Samples were subsequently centrifuged (3,000*g*) for 10 min and stored at −80°C for 4 h.

Hypertension, defined as systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg, or use of antihypertensive medications, and dyslipidemia, characterized by serum LDL cholesterol ≥3.1 mmol/L (120 mg/dL), serum TGs ≥1.7 mmol/L (150 mg/dL), HDL cholesterol <1.0 mmol/L (40 mg/dL), or use of lipid-lowering medications, were diagnosed based on criteria from the Japan Diabetes Society (17). The estimated glomerular filtration rate (eGFR) (in mL/min/1.73 m^2) was calculated using the equation proposed by the Japanese Society of Nephrology (18).

Additionally, the Fatty Liver Index (19); Hepatic Steatosis Index (20); Nonalcoholic Fatty Liver Disease Liver Fat Score (NAFLD-LFS) (21), a surrogate marker for liver steatosis; and Fibrosis-4 (FIB-4) index (22), a surrogate marker for liver fibrosis, were calculated using the following equations: Fatty Liver Index = e^x / $(1+e^x)$ × 100, where $x = 0.953 \times \log_e(\text{TG}) + 0.139 \times \text{BMI} + 0.718 \times \log_e(\gamma\text{-GTP}) + 0.053 \times \text{waist circumference} - 15.745$; Hepatic Steatosis Index = 8 × (ALT/AST) + BMI + type 2 diabetes (yes = 2, no = 0) + female sex (yes = 2, no = 0); NAFLD-LFS = $-2.89 + 1.18$ × metabolic syndrome (yes = 1, no = 0) + $0.45 \times$ type 2 diabetes (yes = 2, no = 0) + $0.15 \times$ insulin + $0.04 \times \text{AST} - 0.94 \times$ (AST/ALT); and FIB-4 index = (age × AST) / (platelet × $\sqrt{}$ALT).

Overview of Treatment During Hospitalization

Participants in the longitudinal study received comprehensive diabetes risk management in a hospital setting, including intensive glycemic control and interventions for blood pressure, dyslipidemia, and body weight, in accordance with the Japanese Diabetes Treatment Guidelines (17). Blood samples were collected early in the morning after ∼15 h of fasting. Data were obtained on the 2nd day of hospitalization (before treatment) and the 16th day after treatment initiation (after treatment).

Lipidomic Measurement

Plasma samples were prepared for lipid extraction using the Bligh and Dyer method (23), with minor modifications. Lipid analyses in the two original studies were conducted independently using an SFC system (Nexera UC System; Shimadzu, Kyoto, Japan) coupled to a triple-quadrupole MS (LCMS-8060; Shimadzu) in multiple reaction monitoring (MRM) mode, as described previously (24). Data processing was performed using LabSolution software version 5.99 SP2 (Shimadzu).

A reference sample was prepared by mixing equal amounts (10 μL each) of plasma extracts from the participants in each study. Twenty fatty acid (FA) constituents of TGs and 35 FA constituents of other lipid classes were selected by SFC-MS/MS analysis of the hydrolyzed reference sample in study 1 (25). To determine the target lipids in each study, a reference sample was analyzed using an in-house MRM library for lipids composed of selected FA constituents (25). Targeted quantitative analysis of lipids belonging to 16 classes, including cholesterol, free FA (FFA), diacylglycerol (DG), TG, cholesterol ester, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylglycerol, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylinositol, ceramide, hexosylceramide, and sphingomyelin, was performed using the selected MRM method (25). Details of the analytical conditions for lipid analyses and the internal standards are described in Supplementary Tables 1 and 2.

Statistical Analysis

Clinical data are presented as mean ± SD for continuous variables and as counts and percentages for dichotomous variables. Comparative analyses between the MASLD and non-MASLD groups were performed using unpaired *t* tests for continuous variables and Pearson χ^2 tests for categorical variables.

In the initial phase, data from population 1 with diabetes were used to compare the log-transformed quantitative values of each plasma lipid using unpaired *t* tests to identify lipids associated with MASLD. To address multiple testing, the false discovery rate (FDR) method was used to calculate adjusted *P* values (*Q* values), with the FDR set at 0.05. The *Q* values and fold-changes (median of the MASLD group/median of the non-MASLD group) were used to construct volcano plots.

Next, we focused on the lipid classes representative of the lipids that showed marked differences between groups in the prior analysis and applied the following methods. The constituent FA quantities (hereafter referred to as estimated quantities) were calculated by summing the products of each lipid quantity and the number of FAs that constitute the lipid. These estimated quantities were compared between the MASLD and non-MASLD groups using the same statistical methods, and the FA showing the greatest intergroup difference was extracted. Additionally, the estimated quantities and percentages of the extracted constituent FAs were compared among the healthy, non-MASLD, and MASLD groups using one-way ANOVA. The percentage of a constituent FA (hereafter referred to as percentage) was calculated as the estimated quantities of the constituent FAs divided by the total estimated quantities of constituent FAs in the lipid class. For post hoc

comparisons between two groups, a significance level of $P < 0.0167$ was applied using Bonferroni correction. Additionally, the relationship between the constituent FAs of the isolated lipids and the clinical factors associated with SLD and MASLD was evaluated using multiple regression analysis (forced entry method).

In the subsequent phase, in population 2 with diabetes, the plasma levels of each lipid at baseline were compared between patients with and without MASLD using the same methods used for population 1. Next, we examined whether the lipid constituent FAs identified in the initial phase were affected by short-term comprehensive diabetes treatment using unpaired *t* tests for the MASLD and non-MASLD groups. Repeated-measures ANOVA was used to determine whether this change was influenced by the presence of MASLD.

Missing data were not imputed in this study. All statistical analyses were performed using SPSS version 26 (IBM Corporation, Armonk, NY).

Data and Resource Availability

The data sets generated during the current study are available upon request. The resources are available upon request.

RESULTS

Patient Characteristics

A total of 143 of the 240 patients with diabetes in study 1 (i.e., population 1 with diabetes) were included in the analysis, excluding those who did not undergo abdominal imaging or met the exclusion criteria (Supplementary Fig. 1). The characteristics of patients with and without MASLD are shown in Table 1. Compared with the non-MASLD group, the MASLD group was significantly younger; had a shorter duration of diabetes, lower serum HDL cholesterol levels, and higher fasting blood glucose, immunoreactive insulin (IRI), C-peptide immunoreactivity (CPR), HOMA for insulin resistance (HOMA-IR), BMI, TGs, serum hepatic enzyme levels, Fatty Liver Index, Hepatic Steatosis Index, and NAFLD Liver Fat Score; and had higher proportions of patients with dyslipidemia and those using biguanides. There was no significant difference in the use of lipid-lowering agents between the two groups.

Plasma Lipid Profile in Patients With and Without MASLD

Using semitargeted lipidomic analysis based on SFC-MS/MS technology, we identified 349 lipids with diverse FA compositions in the plasma collected from patients with and without MASLD (Supplementary Table 3). Figure 1 shows a comparison of plasma lipid levels between the non-MASLD and MASLD groups illustrated as a volcano plot. After correcting for multiple testing using the FDR method, the plasma levels of 120 lipids were significantly higher and those of 41 lipids significantly lower in the MASLD group than in the non-MASLD group (Supplementary Table 3). Although no lipids had significantly lower values and fold-change values <0.5 in the MASLD group than in the non-MASLD group, 13 lipids had significantly higher values and fold-change values ≥2 in the MASLD group than in the non-MASLD group. Ten of these were TGs (TG 14:0_14:0_14:0, TG 14:0_14:0_16:0, TG 14:0_14:0_16:1, TG 14:0_14:0_18:0, TG 14:0_14:0_18:1, TG 14:0_14:0_18:2, TG 14:0_16:0_16:0, TG 14:0_16:0_16:1, TG 14:0_16:1_16:1, TG 14:0_16:1_18:0), and the other three were DGs (DG 12:0_18:1, DG 12:0_18:2, DG 16:0_16:1). Notably, these TGs consistently contained myristic acid (FA 14:0) as a constituent FA.

Subsequent analyses focused on the constituent FAs of TGs. The 89 TGs identified in this study were composed of one to three combinations of 15 FAs listed in Supplementary Table 3. The estimated quantities of these 15 constituent FAs in each TG were calculated and compared between the MASLD and non-MASLD groups. As shown in Fig. 2*A*, FA 14:0 had the highest relative ratio of the estimated quantities of FAs constituting the TGs. Next, the estimated quantities of FA 14:0 in TGs and the percentage of FA 14:0 of the total constituent FAs were compared among the healthy, non-MASLD, and MASLD groups (Fig. 2*B* and *C*). The estimated quantities and percentage of FA 14:0 in TGs were significantly elevated in the MASLD group compared with the healthy population and non-MASLD group ($P < 0.001$). In addition, we compared enzymatic activities of elongation of very-long-chain FA 6 (ELOVL6) and stearoyl-CoA desaturase-1 (SCD1), markers of hepatic de novo lipogenesis, between the non-MASLD and MASLD groups and found that ELOVL6 activity was markedly higher in the MASLD group ($P = 0.007$), with a similar trend observed for SCD1 activity ($P = 0.053$) (Supplementary Fig. 2*A* and *B*).

Table 2 presents the results of the linear regression analysis with estimated quantities of FA 14:0 in TGs as the objective variable, and the presence of MASLD and principal factors associated with SLD (e.g., age, sex, BMI, HbA_{1c}, hypertension, dyslipidemia, and C-reactive protein) as explanatory variables. The presence of MASLD was significantly associated with estimated quantities of FA 14:0 in TGs ($\beta = 0.419$, $P < 0.001$). This association remained robust even after adjusting for covariates ($\beta = 0.310$, $P < 0.001$). A significant association was also observed between estimated quantities of FA 14:0 in TGs and HOMA-IR ($\beta = 0.232$, $P = 0.031$) in a selected group of 86 patients who were not using insulin.

The estimated quantities of FA 14:0 in TGs also exhibited a significant association with serum hepatic enzymes, such as AST and ALT, even after adjusting for covariates. However, the estimated quantities of FA 14:0 in TGs in the MASLD group was not significantly associated with the FIB-4 index (Supplementary Table 4).

Change in the Estimated Quantities of FA 14:0 in TGs After Diabetes Treatment

Population 2 with diabetes ($n = 26$) was used to investigate whether the estimated quantities of constituent FAs

Table 1—Clinical characteristics of the study groups in study 1 (population 1 with diabetes)

Characteristic	Non-MASLD group	MASLD group	*P*
Participants, *n*	59	84	
Age (years)	64.0 ± 10.0	56.8 ± 13.1	**0.001**
Male sex	37 (62.7)	42 (50.0)	0.132
BMI (kg/m^2)	25.8 ± 6.1	29.6 ± 5.9*	**<0.001**
eGFR (mL/min/1.73 m^2)	65.9 ± 23.8	75.3 ± 25.7	**0.027**
Diabetes duration (years)	16.7 ± 10.0	10.0 ± 8.5*	**<0.001**
HbA_{1c} (%)	8.7 ± 1.6	9.2 ± 1.9	0.083
HbA_{1c} (mmol/mol)	71.5 ± 17.8	76.9 ± 20.9	0.083
FPG (mmol/L)	7.4 ± 2.7‡	8.7 ± 2.6§	**0.015**
IRI (μIU/mL)	5.3 ± 4.4‖	10.1 ± 5.4¶	**<0.001**
CPR (ng/mL)	1.8 ± 1.4‖	2.8 ± 1.2¶	**0.002**
HOMA-IR	1.7 ± 1.1‖	3.9 ± 2.7¶	**<0.001**
Smoking history	31 (52.5)	37 (44.6)*	0.349
Hypertension	38 (64.4)	53 (63.1)	0.872
SBP (mmHg)	122.5 ± 16.2	125.8 ± 15.2*	0.221
DBP (mmHg)	69.2 ± 11.4	76.2 ± 11.9*	**0.001**
Dyslipidemia	33 (55.9)	62 (73.8)	**0.026**
Total cholesterol (mmol/L)	5.0 ± 1.2	5.2 ± 1.4	0.327
HDL-C (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	**0.008**
LDL-C (mmol/L)	2.9 ± 1.0	3.1 ± 1.0	0.184
TGs (mmol/L)	14.0 ± 7.8	23.7 ± 18.0	**<0.001**
AST (units/L)	20.4 ± 8.2	37.4 ± 23.1	**<0.001**
ALT (units/L)	19.1 ± 13.5	47.6 ± 37.4	**<0.001**
γ-GTP (units/L)	32.3 ± 39.9	56.2 ± 39.9§	**0.001**
Platelets (×10^9/μL)	227.8 ± 76.6	237.0 ± 60.8	0.431
Fatty Liver Index	52.0 ± 29.6#	69.6 ± 25.1**	**0.010**
Hepatic Steatosis Index	36.2 ± 6.6	42.6 ± 6.9*	**<0.001**
NAFLD-LFS	−0.2 ± 1.3††	1.2 ± 1.7‡‡	**0.021**
FIB-4 index	1.5 ± 0.7	1.5 ± 0.9	0.647
CRP (mg/L)	2.2 ± 3.7†	2.9 ± 4.4§	0.296
Diabetic macroangiopathy	19 (30.5)	17 (20.2)	0.160
Diabetes medication use			
Insulin	26 (44.1)	25 (29.8)	0.079
GLP-1RAs	5 (8.5)	13 (15.5)	0.214
Sulfonylureas	14 (23.7)	26 (31.0)	0.343
Biguanides	10 (16.9)	31 (36.9)	**0.009**
Thiazolidines	7 (11.9)	9 (10.7)	0.830
DPP-4 inhibitors	19 (32.2)	36 (42.9)	0.192
Glinides	4 (6.8)	2 (2.4)	0.230
α-GIs	9 (17.0)†	5 (6.0)	0.060
SGLT2 inhibitors	0 (0.0)	4 (4.8)	0.143
Dyslipidemia medication use			
Statin	25 (42.4)	38 (45.2)	0.734
Fibrate	1 (1.7)	3 (3.6)	0.643
EPA	0 (0.0)	3 (3.6)	1.000
EPA/DHA	0 (0.0)	1 (1.2)	1.000
NPC1L1 inhibitor	2 (3.4)	3 (3.6)	1.000

Data are mean ± standard deviation or *n* (%). Continuous and categorical variables were compared between the non-MASLD and MASLD groups using the unpaired *t* test and Pearson χ^2 test, respectively. Bold font indicates statistically significant differences ($P < 0.05$). α-GI, α-glucosidase inhibitor; CRP, C-reactive protein; DBP, diastolic blood pressure; DHA, docosahexaenoic acid; DPP-4, dipeptidyl peptidase 4; EPA, eicosapentaenoic acid; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide 1 receptor agonist; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; NPC1L1, Niemann-Pick C1-like 1; SBP, systolic blood pressure; SGLT2, sodium–glucose cotransporter 2. **n* = 83. †*n* = 57. ‡*n* = 58. §*n* = 82. ‖*n* = 30. ¶*n* = 56. #*n* =26. ***n* = 84. ††*n* =10. ‡‡*n* =32.

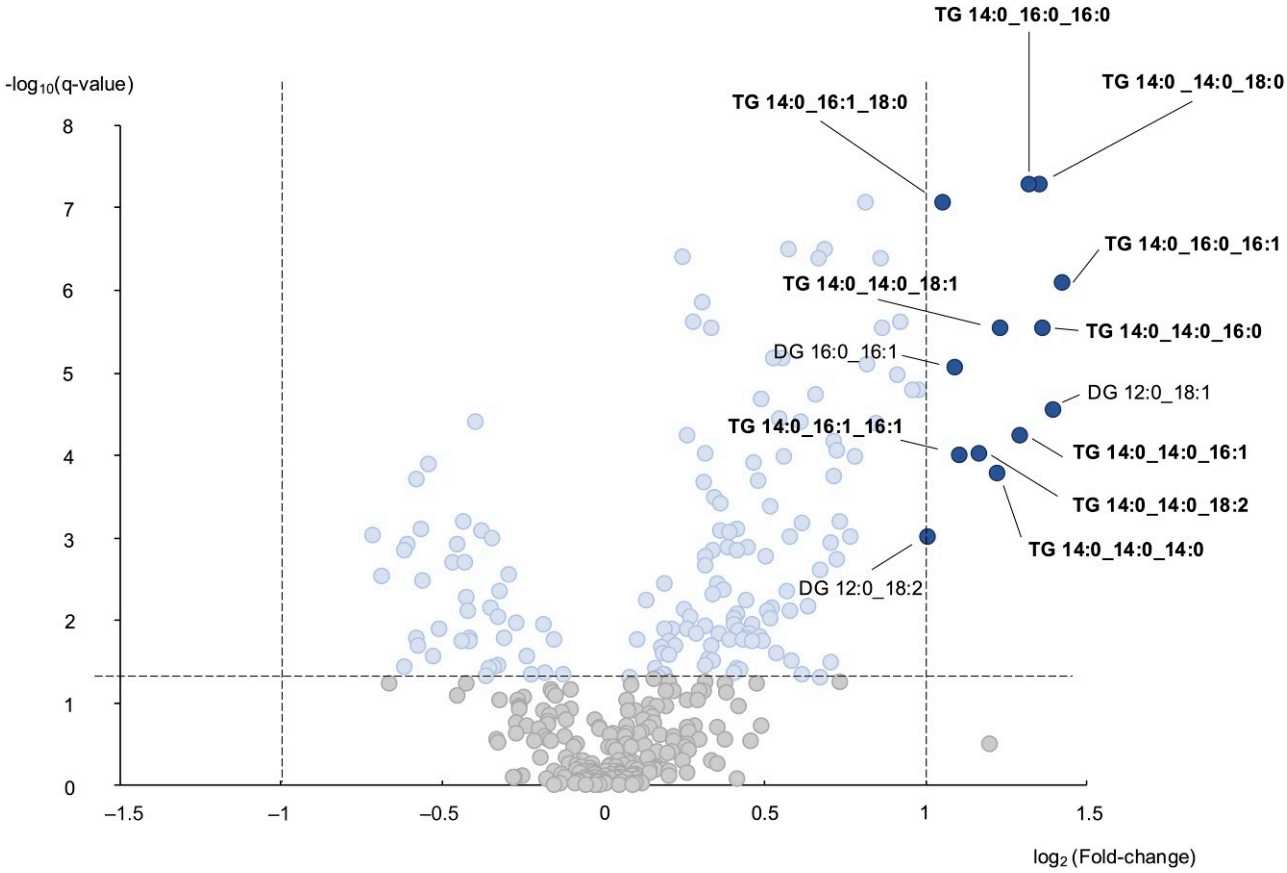


Figure 1—Comparison of plasma lipid levels between patients with and without MASLD in study 1. Volcano plot showing the results of unpaired *t* tests comparing plasma lipid levels in patients with type 2 diabetes with and without MASLD (MASLD and non-MASLD groups, respectively). The *x*-axis represents the fold-change values (ratio of the median values in the MASLD group to those in the non-MASLD group), whereas the *y*-axis represents the *Q* values (*P* values adjusted using the FDR method). Dark blue points represent lipids with a significant difference ($Q \leq 0.05$) and fold-change ≥2.0 or ≤0.5. Light blue points represent the lipids with a significant difference ($Q \leq 0.05$) and fold-change >0.5 and <2.0. Gray points represent other lipids.

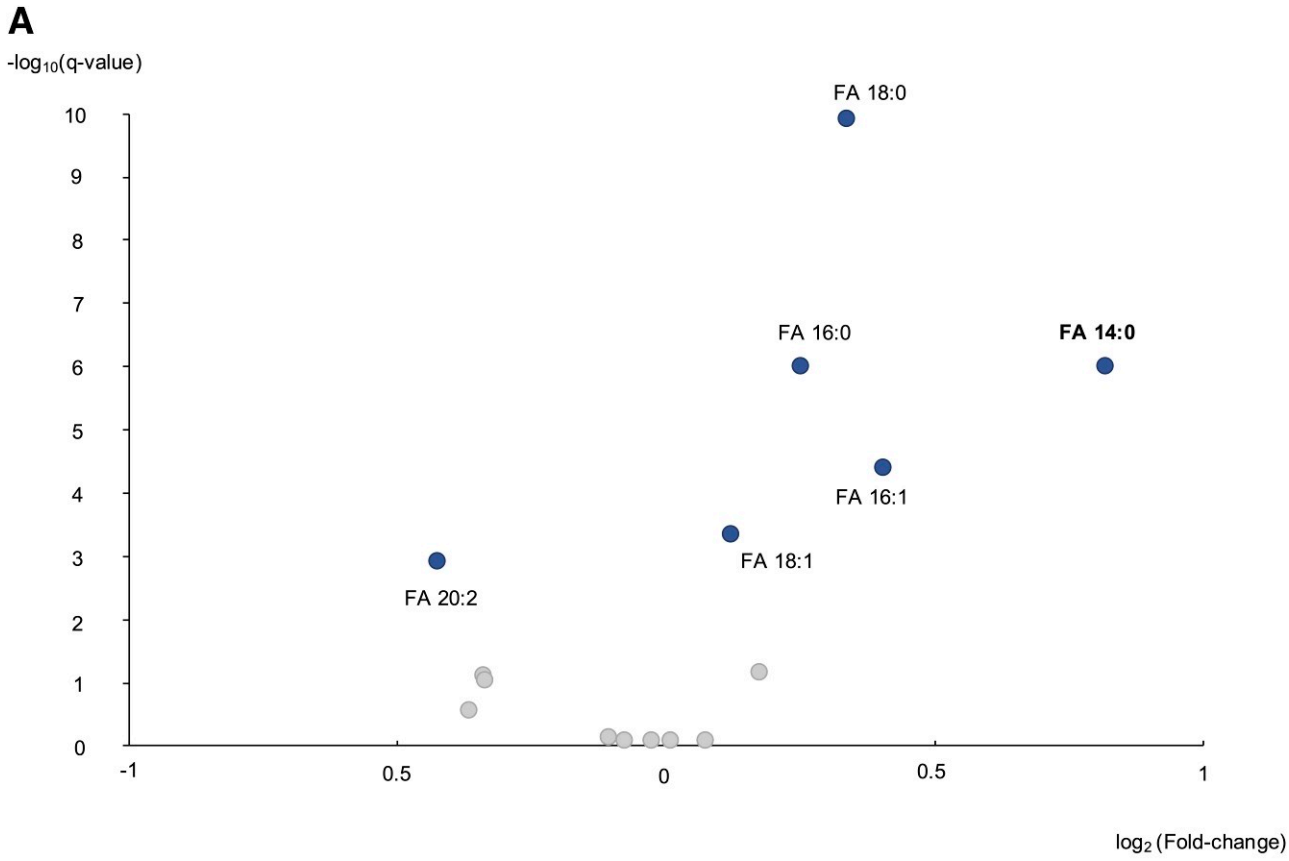
in TGs were altered by comprehensive diabetes treatment. The MASLD group (n = 16) was characterized by significantly higher levels of hepatic enzymes and Fatty Liver Index and tended to have higher IRI, CPR, HOMA-IR, and Hepatic Steatosis Index than the non-MASLD group (n = 10) (Supplementary Table 5). Lipidome analysis of the plasma using SFC-MS/MS identified 292 lipids with different FA compositions in this population. A comparison of plasma lipid levels in the non-MASLD and MASLD groups showed that TGs containing FA 14:0 tended to be higher in the MASLD group (Supplementary Fig. 3), and the presence of MASLD was significantly associated with the total estimated quantities of FA 14:0 in TGs, even after adjusting for covariates in linear regression (β = 0.615, P = 0.005) (Supplementary Table 6).

After 2 weeks of comprehensive diabetes treatment, many clinical parameters, including BMI, glucose parameters, HOMA-IR, lipid parameters, hepatic enzyme levels, and Fatty Liver Index, significantly improved, and the Hepatic Steatosis Index showed a decreasing trend, although improvement in MASLD was not confirmed by formal testing, such as pathology or imaging studies. This trend was particularly pronounced in the group with MASLD at baseline (Supplementary Table 7).

Table 3 summarizes the changes in constituent FAs in TGs before and after comprehensive diabetes treatment in the non-MASLD and MASLD groups. In the non-MASLD group, while the estimated quantities of constituent FAs in TGs exhibited a decreasing trend, most reductions were not statistically significant. In the MASLD group, the estimated quantities of constituent FAs in many TGs declined significantly after treatment. Specifically, FAs synthesized via DNL showed a pronounced decrease in the MASLD group compared with the non-MASLD group, as shown by repeated-measures ANOVA. Among the constituent FAs in TGs, FA 14:0 exhibited the most substantial reduction.

DISCUSSION

Given that concurrent type 2 diabetes and SLD increase the risk of clinically significant disease, such as CVD (5), chronic kidney disease (6), and all-cause mortality (7), the characterization of SLD associated with type 2 diabetes is clinically important. To our knowledge, this study is the



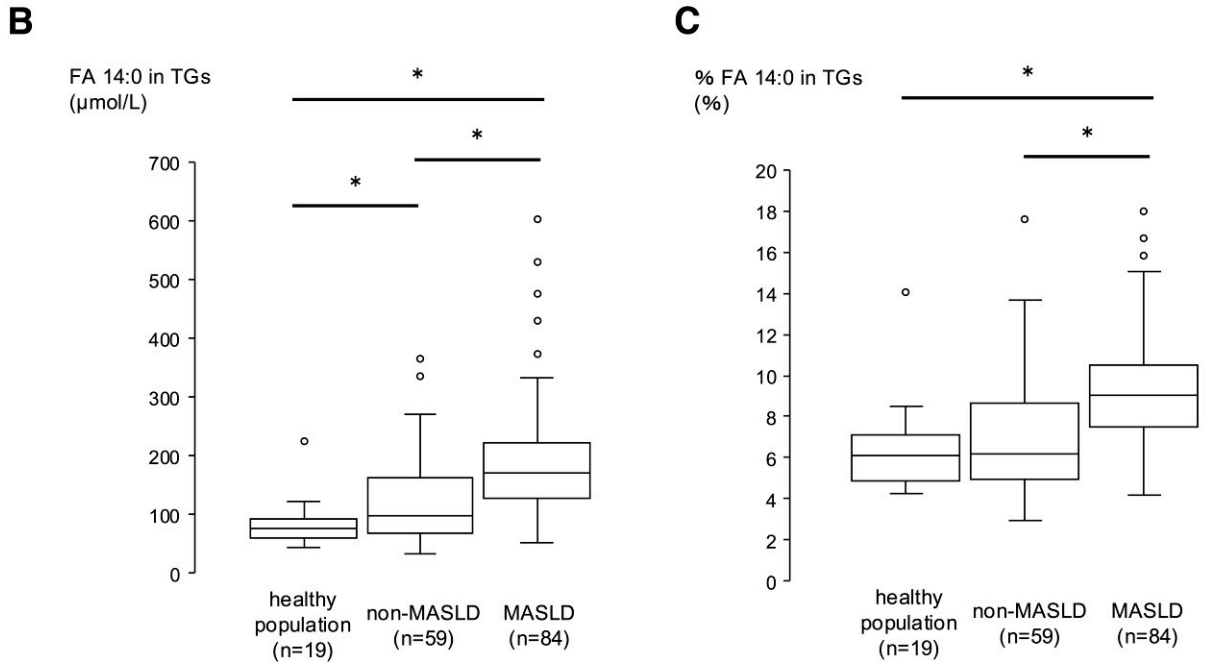


Figure 2—Characteristics of FA constituents of plasma TGs in the MASLD and non-MASLD groups in study 1. *A*: Volcano plot showing the results of the unpaired *t* tests comparing the values of each FA as a constituent of TGs in the non-MASLD and MASLD groups. The *x*-axis represents the fold-change values (ratio of the median values in the MASLD group to those in the non-MASLD group), whereas the *y*-axis represents the *Q* values (*P* values adjusted using the FDR method). Blue points represent FAs with a significant difference ($Q \leq 0.05$). Gray points represent other FAs. *B*: Box plot showing the estimated quantities of FA 14:0 as a constituent of TGs. *C*: Box plot showing the percentage of FA 14:0 as a TG constituent. The percentage of FA 14:0 was calculated as the ratio of FA 14:0 to the total FA content of TGs. *For comparisons between two groups in the post hoc test following one-way ANOVA, a significance level of $P < 0.0167$ was applied with Bonferroni correction.

Table 2—Associations between the estimated quantities of FA 14:0 in TGs and clinical parameters in study 1

	Simple linear regression		Multiple linear regression	
Variable	β	*P*	β	*P*
Age	−0.190	**0.023**	−0.148	0.103
Sex	0.014	0.872	0.042	0.580
BMI	0.235	**0.005**	0.030	0.730
HbA_{1c}	0.090	0.284	−0.002	0.983
Hypertension	0.190	**0.023**	0.166	0.050
Dyslipidemia	0.337	**<0.001**	0.249	**0.002**
CRP※	0.191	**0.023**	0.093	0.246
MASLD	0.419	**<0.001**	0.310	**<0.001**

Multiple regression (forced entry method) was used to evaluate the association between the estimated quantities of FA 14:0 in TGs and clinical parameters. The explanatory variables were the classical risk factors considered to be involved in the exacerbation of fatty liver disease. Bold font indicates statistically significant differences ($P < 0.05$). CRP, C-reactive protein. ※The estimated quantities of FA 14:0 in TGs and CRP were included in the analysis after log-transformation.

first detailed investigation of the plasma lipidome in patients with type 2 diabetes with and without MASLD. We conducted a comprehensive analysis of plasma lipids in two independent populations of patients with type 2 diabetes and revealed that numerous plasma lipids, particularly TGs containing FA 14:0, were higher in patients with MASLD than in those without MASLD, suggesting that these lipids may serve as potential biomarkers. In addition, the estimated quantities of FA 14:0 in plasma TGs were significantly associated with serum levels of hepatic enzymes, such as AST and ALT, even after adjusting for major risk factors for SLD. Furthermore, the estimated quantities of

Table 3—Alterations in the estimated quantities of constituent FAs in TGs before and after comprehensive diabetes treatment in the non-MASLD and MASLD groups in study 2

	non-MASLD			MASLD			
	Before treatment	After treatment	*P*	Before treatment	After treatment	*P*	$P_{interaction}$
FA 14:0	4.10 ± 0.62	3.85 ± 0.40	0.074	4.90 ± 0.66	4.09 ± 0.67	**<0.001**	**0.012**
FA 16:0	6.84 ± 0.55	6.73 ± 0.29	0.324	7.46 ± 0.52	6.93 ± 0.37	**<0.001**	**0.002**
FA 16:1	5.85 ± 0.55	5.74 ± 0.32	0.327	6.50 ± 0.60	5.95 ± 0.46	**<0.001**	**0.006**
FA 18:0	5.24 ± 0.51	5.11 ± 0.27	0.222	5.86 ± 0.46	5.32 ± 0.33	**<0.001**	**0.002**
FA 18:1	7.00 ± 0.43	6.94 ± 0.29	0.456	7.41 ± 0.47	7.02 ± 0.36	**<0.001**	**0.005**
FA 18:2	6.56 ± 0.49	6.51 ± 0.30	0.592	6.96 ± 0.54	6.57 ± 0.40	**<0.001**	**0.010**
FA 20:0	0.27 ± 0.43	0.15 ± 0.39	0.368	0.59 ± 0.55	0.24 ± 0.42	**<0.001**	0.148
FA 20:1	1.89 ± 0.35	1.86 ± 0.36	0.727	2.06 ± 0.49	1.81 ± 0.47	**0.013**	0.095
FA 20:2	1.74 ± 0.39	1.57 ± 0.30	**0.040**	1.89 ± 0.51	1.56 ± 0.39	**<0.001**	0.111
FA 20:3	4.16 ± 0.59	4.12 ± 0.34	0.746	4.46 ± 0.64	4.11 ± 0.46	**<0.001**	0.035
FA 20:4	3.75 ± 0.55	3.61 ± 0.32	0.260	4.02 ± 0.68	3.71 ± 0.46	**0.015**	0.309
FA 20:5	2.76 ± 0.61	2.60 ± 0.41	0.250	3.01 ± 0.75	2.76 ± 0.50	0.070	0.628
FA 22:1	−3.37 ± 0.86	−3.08 ± 0.88	0.214	−2.88 ± 1.28	−3.30 ± 1.23	0.586	0.283
FA 22:5	2.72 ± 0.59	2.54 ± 0.38	0.155	2.96 ± 0.72	2.75 ± 0.45	0.107	0.935
FA 22:6	2.94 ± 0.58	2.77 ± 0.38	0.171	3.18 ± 0.73	2.96 ± 0.46	0.084	0.808

The estimated quantities of constituent FAs in TGs were included in the analysis after log-transformation. The difference in the estimated quantities of constituent FAs in TGs before and after comprehensive diabetes treatment in the non-MASLD and MASLD groups was examined using a paired *t* test. A two-way ANOVA with repeated measures was used to examine whether there was an interaction between the presence or absence of MASLD and the change in the estimated quantities of constituent FAs in TGs before and after treatment (i.e., whether there was a difference in the treatment effect depending on the presence or absence of MASLD). The table shows the logarithmically transformed before and after treatment values, as well as *P* values calculated using paired *t* tests and $P_{interaction}$ calculated using two-way ANOVA with repeated measures. Bold font indicates statistically significant differences ($P < 0.05$ or $P_{interaction} < 0.05$).

FA 14:0 in plasma TGs significantly decreased after comprehensive diabetes treatment, and this trend was more pronounced in patients with MASLD. Interestingly, these findings are consistent with a previous report showing that the quantities of FA 14:0 in the liver are increased in patients with SLD and MASH (26). Although further validation with a larger sample size is required, our findings suggest that FA 14:0 may be involved in the pathogenesis of SLD and that the measurement of FA 14:0 in plasma TGs may be useful in the assessment and management of SLD in patients with type 2 diabetes.

In patients with diabetes, characteristic changes in the blood lipid profile, such as elevated chylomicrons, VLDL, and remnants, are observed. These changes result from increased chylomicron synthesis in the intestinal tract, increased influx of FFAs to the liver and subsequent VLDL synthesis, reduced apoprotein B and E receptor activity in the liver, and catabolic disturbances due to decreased lipoprotein lipase and hepatic TG lipase activity. These lipid abnormalities are also known to play a pivotal role in the development of vascular disorders in diabetes, particularly macroangiopathy (27).

Although the mechanism underlying the observed increase in TGs containing FA 14:0 in the blood of patients with diabetes with MASLD cannot be determined from this study, the following pathways may represent possible origins of FA 14:0 in plasma TGs. First, in general, most FAs that constitute TGs synthesized in the liver originate from FFAs released into the plasma from adipose tissue (28). In this study, when examining the constituent FAs of plasma TGs, the levels of FA 14:0, palmitic acid (FA 16:0), palmitoleic acid (FA 16:1), stearic acid (FA 18:0), oleic acid (FA 18:1), and linoleic acid (FA 18:2) were higher in patients with MASLD than in those without MASLD. On the other hand, although the plasma levels of FFAs, including FFA 16:0, FFA 16:1, FFA 18:1, and FFA 18:2, were higher in patients with MASLD than in those without MASLD, the plasma levels of FFA 14:0 did not differ between the two groups. These findings suggest that hepatic influx of FFA 14:0 may have only a minor impact on FA 14:0 levels in TGs.

DNL in hepatocytes is another source of FAs in TGs. In the typical DNL process, FA 16:0 is initially synthesized from acetyl-CoA by FA synthase (29), followed by elongation of the FA chain by ELOVL6 (30) and desaturation by SCD1 (31). In this process, FA synthase synthesizes not only FA 16:0 but also FA 14:0 (32). Hepatic mRNA levels of ELOVL6 and SCD1 are reportedly elevated in MASH (33), and hepatic DNL and TG secretion are increased in MASLD likely due to insulin resistance–driven activation of SREBP-1c (34–36). Consistent with these findings, our study showed that predicted ELOVL6 and SCD1 activities were higher in the MASLD group (Supplementary Fig. 2), which also exhibited hyperinsulinemia and insulin resistance (Table 1). Since insulin upregulates genes in the lipogenic pathway via SREBP-1c (37), the elevated FA 14:0 in MASLD may reflect altered TG composition resulting from enhanced DNL.

Our study showed that comprehensive diabetes treatment with weight loss significantly reduced plasma levels of FA 14:0 in TGs, which may reflect reduced hepatic production of FA 14:0 following improved insulin resistance. Finally, the effect of dietary FA sources, namely, possible excessive intake of FA 14:0, should also be considered. FA 14:0 is abundant in animal milk (38). Although dairy products are generally considered protective against MASLD (39), some, such as cheese, may increase MASLD risk (40), and FA 14:0 intake may be associated with advanced liver fibrosis (41). Our study did not collect dietary information; therefore, we cannot draw conclusions about the relationship between FA 14:0 intake from dairy and MASLD.

Thus, elevated plasma TGs containing FA 14:0 may reflect the accumulation of the aforementioned atherogenic lipids, particularly remnants, commonly seen in diabetes and insulin resistance. This elevation may indicate a metabolic state in which diabetes and SLD coexist, contributing to increased CVD risk. Conversely, a study using an MASLD mouse model reported that suppressing TG synthesis in hepatocytes led to increased liver inflammation and fibrosis (42), suggesting that in hepatocytes, incorporating saturated FAs into TGs and their subsequent release into the circulation might reflect a protective mechanism against liver damage. Further studies, especially basic medical experiments, are needed to explore these possibilities.

One of the most significant strengths of this study is the individual identification and evaluation of lipids with different FA compositions using semitargeted lipidomic technology based on SFC-MS/MS, as recently developed by our colleagues (43). Although previous studies reported elevated plasma levels of various TGs measured by MS, as well as conventional serum TG levels quantified enzymatically and expressed as the total of various TGs, in patients with SLD (44–46), most only assessed total carbon numbers and double bonds in TG fatty acids due to the limited chromatographic resolution of earlier lipidomic technologies. In contrast, to more precisely evaluate the FA composition of each TG, we used SFC-MS/MS using a supercritical fluid as the mobile phase, which is considered optimal for chromatographic separation (47).

This study also has several limitations. First, study 1 was a cross-sectional analysis, and study 2 was not an intervention study targeting MASLD or lipids. In addition, in study 2, it is not clear whether MASLD actually improved after diabetes treatment since we did not perform liver pathology or imaging studies before and after diabetes treatment. Thus, although this study observed that some indices associated with MASLD improved with changes in TG composition, it remains unclear whether a direct causal relationship exists. Second, the lipoprotein fraction was not measured; therefore, the specific source of plasma TGs remains unknown. Third, although blood samples were obtained after an overnight fast, prior physical activity and

dietary intake were not controlled, which may have influenced the results. In patients with type 2 diabetes, the survival time of chylomicrons is prolonged due to insulin resistance, and these effects cannot be disregarded. Fourth, either abdominal echocardiography or CT was used to diagnose SLD. Although specialists confirmed the diagnosis of SLD, the possibility that imaging modality differences affected the results cannot be ruled out.

In conclusion, numerous plasma lipids, particularly TGs comprising FA 14:0, were more elevated in patients with type 2 diabetes and MASLD than in those without MASLD. These findings suggest that these lipids may be involved in the pathogenesis of MASLD and diseases often comorbid with MASLD in patients with type 2 diabetes.

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