Long-term Effects of Ipragliflozin on Adipose Tissue in Japanese Patients with Obese Type 2 Diabetes

Shin-ichi NISHIO[1)2)*†], Takashi SEKIDO[1)†], Yohsuke OHKUBO[1)2)]
Ako OIWA[1)] and Mitsuhisa KOMATSU[1)]

1) *Division of Diabetes, Endocrinology and Metabolism, Department of Internal Medicine (4), Shinshu University School of Medicine*
2) *Research Center for Next Generation Medicine, Shinshu University School of Medicine*

Objective and Methods : A long-term effect of ipragliflozin on adipose tissue mass reduction in Japanese patients with obese type 2 diabetes (T2D) was investigated. Ipragliflozin was administered (50 mg/day) once daily for 12 months. At 0, 3, 6 and 12 months, visceral and subcutaneous adipose tissue area was determined by two different bioelectrical impedance methods, and blood samples for HbA1c, renal function, lipids and liver function obtained, and body weight and blood pressure recorded. The primary endpoint was decrease in body fat mass. Secondary endpoints included changes in body weight and the laboratory data.

Results : Seventeen of 20 participants (mean body mass index (BMI) 35.1 ± 1.1 kg/m^2) completed this prospective observational study. Visceral fat area (cm^2, mean ± SD) at 0, 3, 6 and 12 months was 166.0 ± 49.7, 149.7 ± 46.1, 149.7 ± 42.4 and 148.5 ± 40.2, respectively : the value at 3 months was significantly lower than baseline (P = 0.027). Subcutaneous fat at the corresponding time points was 359.3 ± 110.5, 316.6 ± 87.1, 326.8 ± 87.2 and 325.9 ± 90.4, respectively : the values at each post treatment period was significantly less than the baseline (P = 0.003, 0.018 and 0.036 for the three points, respectively). Body weight was significantly reduced by 12 months (P = 0.045). Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transpeptidase (γ-GTP) levels decreased significantly. There were no significant correlations between serum hepatobiliary enzyme levels and Δbody weight or Δvisceral fat, but Δγ-GTP was correlated with Δsubcutaneous fat (Spearman's P = 0.004).

Conclusion : During the 1 year interval, ipragliflozin significantly reduced subcutaneous adipose tissue and serum AST, ALT, and γ-GTP levels. *Shinshu Med J 66 : 29—37, 2018*

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Key words : SGLT2 inhibitor, ipragliflozin, subcutaneous fat, γ-glutamyl transpeptidase

I Introduction

Obesity rates are increasing worldwide, with elevated risk of T2D, high blood pressure, dyslipidemia, and cardiovascular disease. In Japan, the mean body mass indexes (BMI) of men and elderly women are increasing[1)], and obesity is becoming a major public health problem. No drugs for treating obesity were available until recently in Japan. The SGLT2 inhibitor, ipragliflozin (Astellas Pharma, Tokyo, Japan and Kotobuki Pharmaceutical, Nagano, Japan), a drug approved for T2D treatment in Japan, was reported to induce weight loss[2)3)]. SGLT2 inhibitors improve glycemia in T2D patients by enhancing urinary glucose excretion via blocking its reabsorption in the renal proximal tubules and reduce body weight due to urinary calorie loss[4)5)]. Therefore, they may have an antiobesity effect. The observed body weight decrease may be attributed to visceral adi-

* Corresponding author : Shin-ichi Nishio
Division of Diabetes, Endocrinology and Metabolism, Department of Internal Medicine (4), Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
E-mail : snishio@shinshu-u.ac.jp
† Shin-ichi Nishio and Takashi Sekido contributed equally to this work

pose tissue lipolysis and enhanced lipid metabolism[6]. Ipragliflozin reduced body fat in rats[7], and clinical reports indicated visceral fat reduction by ipragliflozin in Asian people. Ipragliflozin significantly decreased visceral adipose tissue in 4-week observation in 25 Japanese T2D patients[8]. Visceral fat area was significantly reduced in 6-month observation of 64 diabetic patients[9]. However, obesity is difficult to treat as many subjects regain weight after temporary weight loss[10], so it is important to observe research on obesity for a long term. Body fat reduction by sodium-glucose cotransporter 2 (SGLT2) inhibitors has been observed for up to 1 year in Caucasian patients[11]. Nonetheless, there have been no long-term (12-month) surveys of SGLT2 inhibitors in obese T2D patients in Japan.

Therefore, we examined long-term effects of ipragliflozin in obese T2D patients and evaluated the influence of ipragliflozin on adipose tissue and liver function by monitoring changes in serum AST, ALT, and γ-GTP levels.

Ⅱ Materials and Methods

A Ethics

This study conformed to the Declaration of Helsinki, received approval from our university ethics committee (Study no. 3049), and subjects provided written informed consent before participation.

B Inclusion/exclusion criteria

Inclusion criteria were age 20-65 years old, HbA1c >6.2 %, BMI>25 kg/m^2, and estimated glomerular filtration rate (eGFR)>60 ml/min/1.73 m^2. Subjects with unstable diabetic retinopathy, serious hepatic dysfunction, renal failure, heart complications, and pregnancy were excluded. In Japan, BMI≥25 kg/m^2 and≥ 35 kg/m^2 are defined as obesity and severe obesity, respectively. Participants' average BMI (± SD) was 35.1 ± 1.1 kg/m^2, and 13 patients were severely obese. Diet therapy, exercise therapy, and/or treatment with any antidiabetic drugs other than SGLT2 inhibitors were continued. No changes in antidiabetic drug regimens were allowed during the observation period unless deemed necessary to prevent hypo-/hyperglycemia.

C Intervention/monitoring

This study was a prospective observational study. The study population consisted of 20 patients with obese T2D presenting to Shinshu University Hospital outpatient clinic due to obesity between August 2015 and January 2017. Oral ipragliflozin administration (50 mg once daily) was continued for 12 months in 17 cases. Patients received diet and nutritional guidance before and at least once after initiation of ipragliflozin treatment. The primary endpoint was change in adipose tissue. Secondary endpoints included changes in body weight, HbA1c, blood pressure, liver and renal function, and lipid profile.

D Method of fat area measurement

The adipose tissue was estimated on a Dual Scan Ⓡ (HDS 2000Ⓡ; Omron, Kyoto, Japan) using the dual impedance method[12] every 3 months at more than 2 hours after meals. The Dual Scan instrument consists of a bioelectrical impedance component that measures truncal and surface impedance of the body. There was a good agreement of measured values by Dual Scan and intra-abdominal fat area measured by computed tomography (CT) with a correlation coefficient of 0.888 ($n = 98$, $P<.001$)[13].

E Clinical parameter measurement

The following variables were monitored before and at 3, 6, and 12 months after commencement of ipragliflozin treatment: HbA1c, body weight, BMI, estimated visceral fat area, estimated subcutaneous fat area, systolic blood pressure, diastolic blood pressure, serum ALT, AST, γ-GTP, blood urea nitrogen, creatinine, uric acid, glomerular filtration rate (eGFR), and serum levels of low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). The data were collected before or≥2 hours after a meal. There were variations in time after meals, so we did not evaluate blood glucose level and TG value.

F Statistical analysis

Data were analyzed by paired t test. Microsoft Excel 2013 and SPSS ver. 22.0 for Windows (IBM Japan, Tokyo, Japan) were used for statistical analyses. All P-values for comparison before and after administration were subjected to Bonferroni adjustment.

Relationships between changes in adipose tissue and ALT, AST, and γ-GTP were assessed using Spearman's rank correlation coefficients. In all analyses, $P<0.05$ was taken to indicate statistical significance.

Ⅲ Results

Twenty T2D patients were enrolled in this study (**Table 1**). Three subjects dropped out : one failed to be evaluated for urinary tract infections, and the other two discontinued ipragliflozin due to development of eruptions within 1 week after administration. Seventeen subjects completed the full protocol and were included in statistical analyses. Antidiabetic drugs other than SGLT2 inhibitors are shown in **Table 2**. **Table 3** shows changes in test items every 3 months during ipragliflozin treatment.

Mean body weight decreased over the observation period (**Table 3**, **Fig. 1**), with a significant decrease at 12 months (97.8 kg to 93.8 kg ; $P=0.045$). Mean visceral adipose tissue decreased at 3 months (166.0 cm^2 to 149.7 cm^2 ; $P=0.027$), but after 6 months there was no significant difference (**Fig. 2**). Estimated mean subcutaneous adipose tissue decreased significantly from 359.3 cm^2 to 316.6 cm^2 at 3 months ($P=0.003$), 326.8 cm^2 at 6 months ($P=0.018$), and 325.9 cm^2 at 12 months ($P=0.036$) (**Fig. 3**).

Systolic and diastolic blood pressures tended to decrease during the treatment period (not significant) (**Table 3**).

Changes in various clinical parameters with administration of ipragliflozin are shown in **Table 3**. Mean HbA1c level improved, and decreased significantly from 7.7 % at baseline to 7.2 % at 6 months ($P=0.032$) ; there was no significant difference at 12 months. Blood urea nitrogen and creatinine showed no significant changes. Mean uric acid level decreased significantly from 6.4 mg/dL at baseline to 5.1 mg/dL at 6 months ($P=0.030$) ; however, there was no significant difference at 12 months. eGFR remained unchanged during the 12 months of treatment ; it tended to increase during the treatment period, but the differences were not statistically significant. AST, ALT, and γ-GTP levels at the end of treatment were significantly decreased compared to baseline (**Table 3**, **Fig. 4**). Serum LDL-C tended to decrease, while serum HDL-C tended to increase, but the differences were not significant (**Table 3**). There were no correlations between changes in ALT or AST levels and those in visceral adipose tissue (**Fig. 5A**, **B**) or subcutaneous adipose tissue (**Fig. 5D**, **E**). Change in γ-GTP levels was not related to those in visceral adipose tissue (**Fig. 5C**), but correlated with change in subcutaneous adipose tissue volume (Spearman's $\rho=0.664$, $P=0.004$) (**Fig. 5F**).

Table 1 Participant characteristics
The values are expressed as means ± SD.

Age (years)	47.1 ± 2.5
Sex (male/female)	10/10
Diabetes duration (years)	9.8 ± 1.6
Body weight (kg)	97.6 ± 15.2
BMI (kg/m^2)	35.1 ± 1.1
Blood pressure (mmHg)	134 ± 14/85 ± 11
VAT (cm^2)	166.0 ± 49.7
SAT (cm^2)	359.3 ± 110.5
HbA1c (%)	7.7 ± 1.3

BMI, body mass index ; VAT, visceral adipose tissue ; SAT, subcutaneous adipose tissue ; HbA1c, glycated hemoglobin

Table 2 Antidiabetic drugs other than SGLT2 inhibitors used in combination

Drug	Case (n) (%)
Biganide	16 (80%)
Sulfonylurea	8 (40%)
Pioglitazone	4 (20%)
DPP-4 inhibitors	10 (50%)
Glinides	1 (5%)
α-Glucosidase inhibitors	3 (15%)
Insulin	7 (35%)
GLP-1R agonists	3 (15%)
No concomitant drugs	2 (10%)

DPP-4, dipeptidyl peptidase-4 ; GLP-1R, glucagon-like peptide-1 receptor

Table 3 Changes in various values every 3 months with administration of ipragliflozin

The values are expressed as means ± SD. BMI : body mass index ; HbA1c : glycated hemoglobin ; AST : aspartate aminotransferase ; ALT : alanine aminotransferase ; γ-GTP : γ-glutamyl transferase ; BUN : blood urea nitrogen ; Cr : creatinine ; eGFR : estimated glomerular filtration rate ; UA : uric acid ; LDL-C : low-density lipoprotein cholesterol ; HDL-C : high-density lipoprotein cholesterol.

P-values : 0 vs. 1 months, 0 vs. 3 months, 0 vs. 6 months, and 0 vs. 12 months (Bonferroni adgustment).

	n	Before (M_0)	n	Month 3	*P*-value (M_0 vs M_3)	n	Month 6	*P*-value (M_0 vs M_6)	n	Month 12	*P*-value (M_0 vs M_{12})
BW (kg)	17	97.6 ± 15.2	17	94.1 ± 14.1	0.006	17	93.4 ± 14.1	0.003	17	93.8 ± 13.4	0.045
VAT (cm^2)	17	166.0 ± 49.7	16	149.7 ± 46.1	0.027	14	149.7 ± 42.4	0.121	17	148.5 ± 40.2	0.159
SAT (cm^2)	17	359.3 ± 110.5	16	316.6 ± 87.1	0.003	14	326.8 ± 87.2	0.018	17	325.9 ± 90.4	0.036
Systolic blood pressure (mmHg)	17	134 ± 14	16	132 ± 12	0.672	16	131 ± 17	>0.999	17	132 ± 16	>0.999
Diastolic blood pressure (mmHg)	17	85 ± 11	16	82 ± 14	>0.999	16	80 ± 14	0.867	17	81 ± 9	0.498
HbA1c (%)	17	7.7 ± 1.3	17	7.1 ± 1.1	0.099	17	7.2 ± 1.2	0.03	17	7.2 ± 1.3	0.387
AST (IU/l)	17	36 ± 20	15	29 ± 14	0.021	15	23 ± 8	0.003	17	23 ± 8	0.015
ALT (IU/l)	17	53 ± 33	15	38 ± 23	0.024	15	28 ± 11	0.006	17	29 ± 16	0.015
γGTP (IU/l)	17	61 ± 46	15	46 ± 30	0.047	15	40 ± 25	0.021	17	39 ± 26	0.043
BUN (mg/dl)	17	15.1 ± 3.5	16	16 ± 4.0	0.516	16	17.4 ± 4.1	0.054	17	17.3 ± 5.6	0.231
Cr (mg/dl)	17	0.78 ± 0.13	16	0.79 ± 0.14	>0.999	16	0.77 ± 0.13	>0.999	17	0.80 ± 0.14	0.834
eGFR (ml/min/1.73 m^2)	17	77 ± 18	16	76 ± 18	>0.999	16	77 ± 20	>0.999	17	77 ± 19	>0.999
UA (mg/dl)	17	6.4 ± .1.4	15	5.7 ± 1.4	0.396	13	5.1 ± 1.1	0.03	16	5.5 ± 1.4	0.165
HDL-C (mg/dl)	17	43 ± 8.7	15	47 ± 10	0.708	15	49 ± 13	0.018	13	50 ± 13	0.456
LDL-C (mg/dl)	17	111 ± 23	15	107 ± 25	0.662	14	105 ± 24	>0.999	13	107 ± 26	>0.999

BMI : body mass index ; HbA1c : glycated hemoglobin ; AST : aspartate aminotransferase ; ALT : alanine aminotransferase ; γ-GTP : γ-glutamyl transferase ; BUN : blood urea nitrogen ; Cr : creatinine ; eGFR : estimated glomerular filtration rate ; UA : uric acid ; LDL-C : low-density lipoprotein cholesterol ; HDL-C : high-density lipoprotein cholesterol

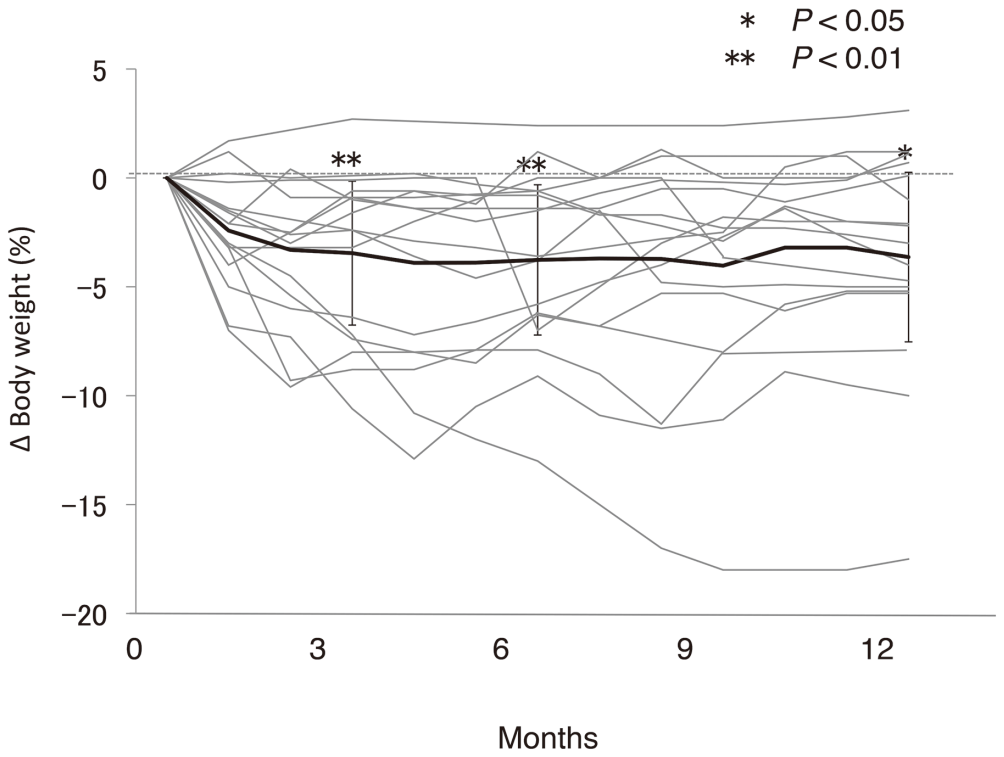

Fig. 1 Changes in body weight

The data show the mean values of body weight at 0, 3, 6, and 12 months (thin gray lines indicate individual data). *P*-values : 0 vs. 1 month, 0 vs. 3 months, 0 vs. 6 months, and 0 vs. 12 months (Bonferroni adgustment ($n = 17$).

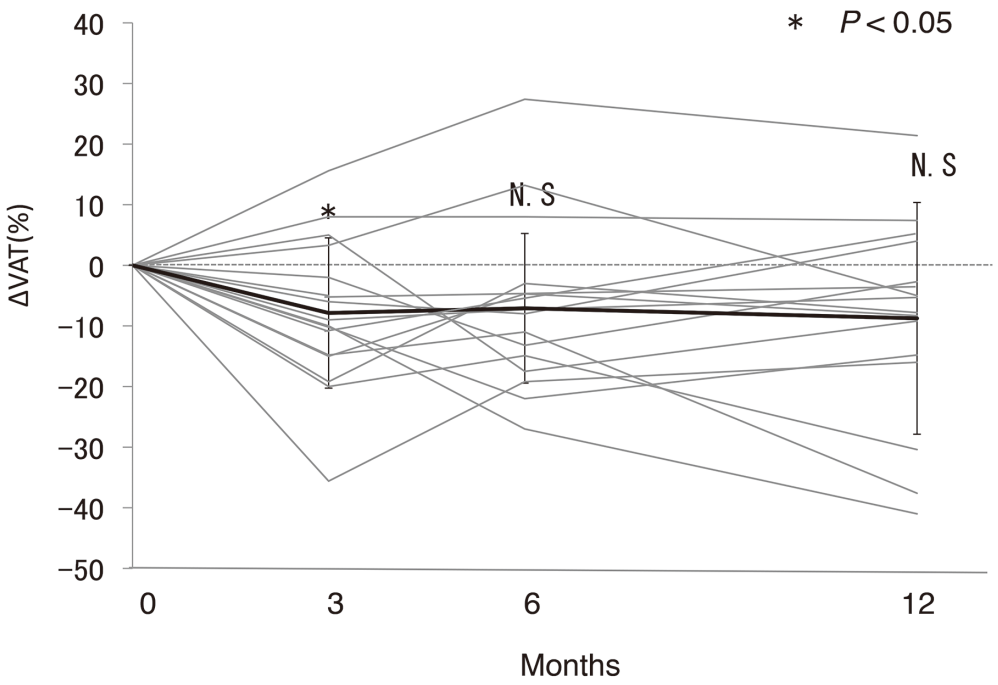

Fig. 2 Changes in visceral adipose tissue

The data show the mean values of visceral adipose tissue at 0, 3, 6, and 12 months (thin gray lines indicate individual data). *P*-values : 0 vs. 3 months, 0 vs. 6 months, and 0 vs. 12 months (Bonferroni adgustment) ($n = 17$). N.S : Not significant.

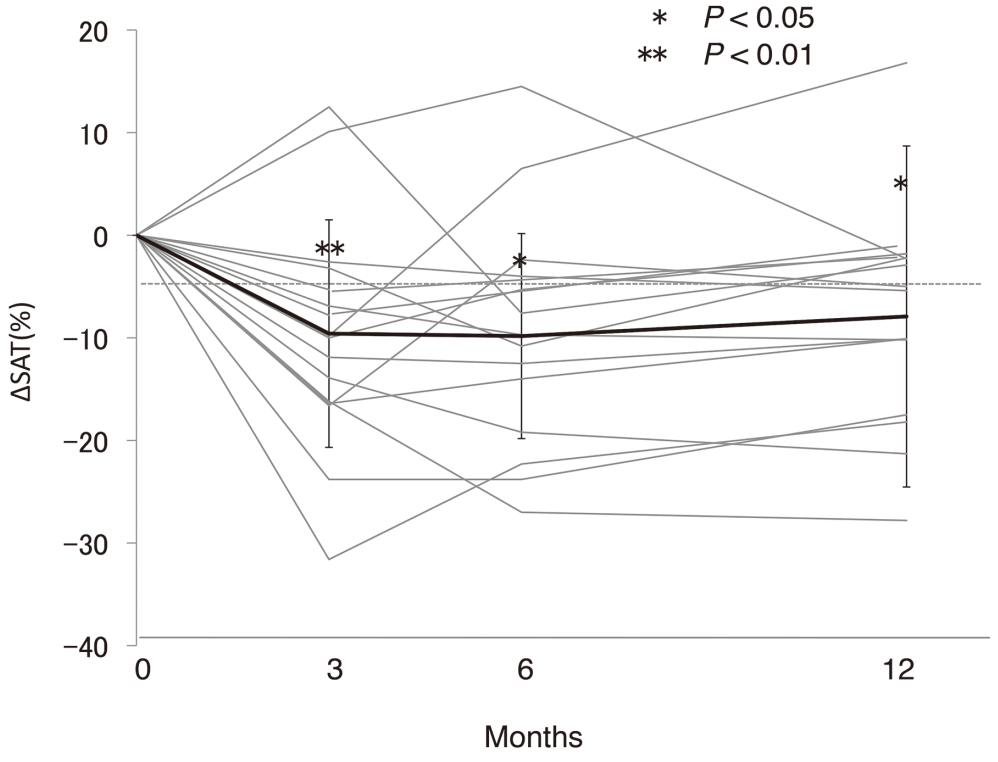

Fig. 3 Changes in subcutaneous adipose tissue

The data show the mean values of subcutaneous adipose tissue at 0, 3, 6, and 12 months (thin gray lines indicate individual data). *P*-values : 0 vs. 3 months, 0 vs. 6 months, and 0 vs. 12 months (Bonferroni adgustment) ($n = 17$).

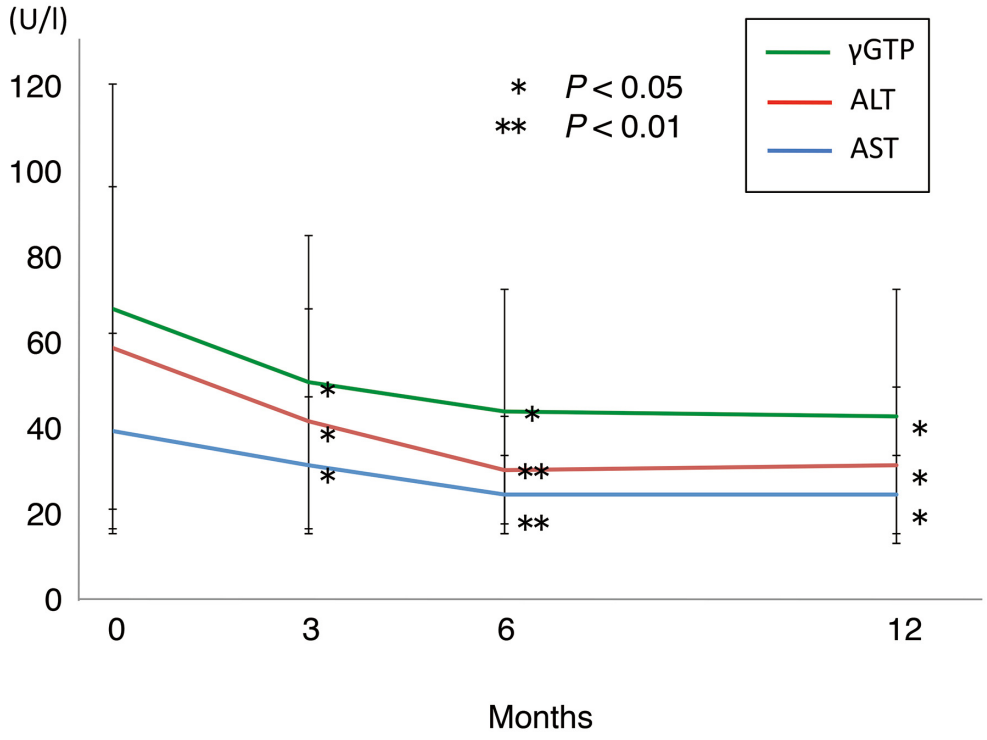

Fig. 4 Change in ALT, AST, and γ-GTP
P-values : 0 vs. 3 months ($n=15$), 0 vs. 6 months ($n=15$), and 0 vs. 12 months ($n=17$) (Bonferroni adgustment).

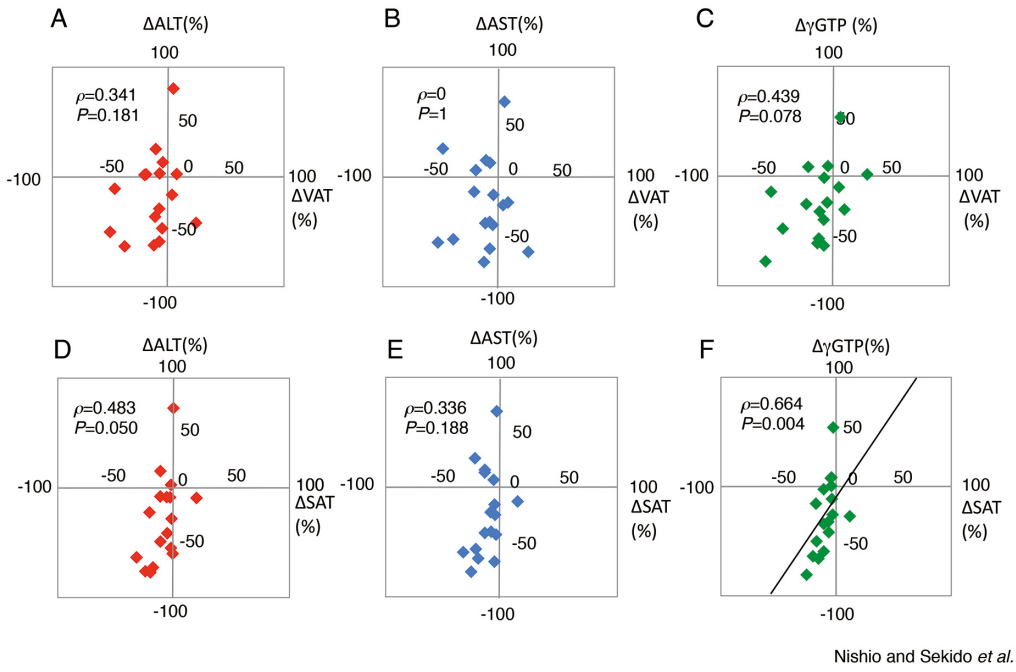

Fig. 5 Correlations between changes in serum hepatobiliary enzyme levels and visceral adipose tissue and subcutaneous adipose tissue after 12 months of ipragliflozin treatment
The relationships between changes in adipose tissue and hepatobiliary enzymes were assessed using Spearman's rank correlation coefficients. In all analyses, $P<0.05$ was taken to indicate statistical significance.
A : Correlation between changes in serum ALT levels and visceral adipose tissue ($n=17$). B : Correlation between changes in serum AST levels and visceral adipose tissue ($n=17$). C : Correlation between changes in serum γ-GTP levels and visceral adipose tissue ($n=17$). D : Correlation between changes in serum ALT levels and subcutaneous adipose tissue ($n=17$). E : Correlation between changes in serum AST levels and subcutaneous adipose tissue ($n=17$). F : Correlation between changes in serum γ-GTP levels and subcutaneous adipose tissue ($n=17$). The change in subcutaneous adipose tissue was significantly correlated with that in serum γ-GTP level.

Ⅳ Discussion

Long-term studies of the effects of SGLT 2 inhibitor on body weight and body fat loss have been reported in Caucasians[11)14)], but there have been no such studies in Japan. We clearly demonstrated long-term body fat reduction by SGLT2 inhibitor (ipragliflozin) treatment in Japanese T2D patients. Ipragliflozin reduced body weight in Japanese patients with obese T2D (average BMI≥30 kg/m^2), with no rebound as long as regular dietary guidance continued and lasted for >1 year. Ipragliflozin reduced both visceral and subcutaneous fat up to 3 months, but decreased subcutaneous fat mainly after 6 months. Ipragliflozin lowered ALT, AST, and γ-GTP levels after 12 months, which was not correlated with body weight loss or visceral fat reduction, while decreases in γ-GTP were correlated with subcutaneous fat reduction.

Oral SGLT2 inhibitor administration reduces body weight. Weight loss was reported with oral dapagliflozin administration[15)], and with short-term (10 days) ipragliflozin treatment[2)]. Japanese subjects given oral ipragliflozin showed body weight reduction of 3.3 % in 16 weeks[8)]. In our study, 12-month ipragliflozin administration resulted in weight loss of 3.6 %. The mean BMI in Yamamoto et al.'s cohort[8)] was 28.9 kg/m^2, while that in our study was 35.1 kg/m^2. Moreover, 65 % of subjects in our study were severely obese. Nevertheless, there was no difference in the weight reduction effect, suggesting that ipragliflozin is also effective in severely obese patients.

SGLT2 inhibitors were reported to reduce visceral fat and weight. Here, visceral fat was reduced by 7.8 % in 3 months, which was similar to the previous report of 8.2 % reduction by 16 weeks of 50 mg ipragliflozin[8)]. A visceral fat loss trend was recognized after 6 months but was not significant. Visceral fat reduction by 8.1 % with 300 mg of canagliflozin for 52 weeks was reported[11)]. The lack of significant difference in our study was probably due to the small sample size. Subcutaneous fat decreased at all time points. Body weight decrease may be attributed to visceral fat tissue lipolysis due to SGLT2 inhibitor induced enhancement in lipid metabolism[6)]. Long-term empagliflozin treatment significantly reduced weight of subcutaneous but not visceral fat in rats[16)]. The authors concluded that the decrease in body weight of rats treated with SGLT2 inhibitor was due to a decrease in subcutaneous rather than visceral fat. Our results were consistent with this previous study. They also showed SGLT2 inhibitor significantly reduced the size of visceral adipocytes and increased the number of smaller size adipocytes, which was associated with the attenuation of oxidative stress. Detailed analyses of body fat content contributing to weight loss in humans are necessary.

Canagliflozin improved liver dysfunction in patients with T2D, assessed by monitoring serum AST, ALT, and γ-GTP levels[16)]. Ogawa and colleagues reported that ipragliflozin improved liver function in clinical and basic research[17)]. They showed that mouse liver weight and retroperitoneal fat mass were negatively correlated in mice. Our results indicated that ALT, AST, and γ-GTP improvement was not correlated with decreases in visceral fat at any time point. Ogawa et al. reported that liver fat decreased and posterior peritoneal adipose tissue in visceral fat increased in mice treated with ipragliflozin. It is impossible to distinguish between liver fat and other visceral fat by dual scan, which represents a limitation of our study.

Mochizuki et al. showed the accumulation of visceral fat is positively associated with γ-GTP independently of subcutaneous fat area in Japanese[18)]. Contrary to our expectations, changes in serum levels of γ-GTP associated with ipragliflozin treatment were correlated with the rate of subcutaneous fat decrease after 12 months.

Further analysis of the relationship between subcutaneous fat and γ-GTP levels is necessary.

This study had several limitations. First, the sample size was small. We think that the mean HbA1c level at 12 months did not differ from baseline because the sample size was small. Second, patients using drugs that affect lipid metabolism (insulin, pioglitazone, and GLP1 analogs) were included. Third, this was a single-arm study. However, the number of participants met the minimum requirement for a

prospective observational study, and concurrent use of antidiabetic drugs is inevitable in clinical practice.

V Conclusion

Where proper dietary and nutritional guidance are provided, administration of the SGLT 2 inhibitor, ipragliflozin, induced weight loss and subcutaneous fat reduction over 12 months. Furthermore, ipragliflozin also improved liver function in obese patients, which was correlated with decrease of subcutaneous fat.

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S.N. designed and performed the research, and wrote the manuscript. T.S performed the research, and wrote the manuscript. Y.O. contributed to data analysis. A.O. contributed to discussion. M.K. reviewed and edited the manuscript. The authors thank Miss Yoshie Takahashi (Shinshu University Hospital, Department of Nursing) for her continued support, and Dr. Toru Aizawa for invaluable comments.

Disclosure Statement

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