

[ORIGINAL ARTICLE]

The Long-term Efficacy of Sodium Glucose Co-transporter 2 Inhibitor in Patients with Non-alcoholic Fatty Liver Disease

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Abstract:

Objective Sodium glucose co-transporter 2 inhibitor (SGLT-2i), recommended for patients with type 2 diabetes, has been reported to improve the liver function test results in non-alcoholic fatty liver disease (NAFLD). However, the long-term effects of SGLT-2i on the liver function and body weight in NAFLD patients have not been fully elucidated. In this study, we investigated the long-term effects of SGLT-2i in NAFLD patients.

Methods Twenty-two diabetic patients with NAFLD were enrolled in this study. We assessed the body weight, liver enzyme levels, metabolism, and glucose levels at 12 months (22 cases) and 24 months (15 cases) after the initiation of SGLT-2i. The changes in controlled attenuation parameter (CAP) and liver stiffness in 20 of the 22 patients were evaluated using transient elastography (TE) and acoustic radiation force impulse (ARFI) elastography before the initiation of treatment and 1 year later.

Results Body weight and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were significantly decreased at 12 and 24 months after SGLT-2i treatment. The decrease in the levels of ALT at 12 and 24 months was significantly correlated with the level of ALT at the initiation of SGLT-2i ($r=0.813$, $p=0.001$ and $r=0.867$, $p=0.0001$, respectively). SGLT-2i also reduced the CAP and velocity of shear wave (Vs) values at 12 months (CAP 315.1 ± 43.4 db/mL \rightarrow 293.1 ± 27.2 db/mL, $p=0.027$; Vs 1.87 ± 0.8 m/s \rightarrow 1.48 ± 0.6 m/s, $p=0.011$).

Conclusion SGLT-2i treatment improved the liver function test results and reduced the body weight in NAFLD patients over a period of 12-24 months. This improvement was greater in patients with higher ALT values at baseline than in those with lower values.

Key words: SGLT-2i, NAFLD, fibroscan

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, worldwide (1, 2). It includes a wide spectrum of pathological changes, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), burnout cirrhosis, and hepatocellular carcinoma (HCC) (3). NAFLD is associated with metabolic factors, such as obesity, type 2

diabetes, and dyslipidemia (2). With the increasing number of people with metabolic syndrome, the prevalence of NAFLD is also increasing in Japan (2, 4).

The “two hit hypotheses” have been considered for a long time in the development of NASH (5). Recently, the “multi-parallel hit” hypothesis was advocated. This hypothesis states that various factors, such as endoplasmic reticulum stress and cytokine-mediated stress, can lead to steatosis as well as inflammation (6).

Table 1. Characteristics of 22 Patients with Non-alcoholic Fatty Liver Disease Treated with SGLT-2i.

Age (years)	59.3±10.5
Male:Female	10:12
SGLT-2i (Ipragliflozin: Dapagliflozin: Tofogliflozin: Empagliflozin)	18:2:1:1
Body weight (kg)	67.0±43.4
BMI (kg/m ²)	29.7±4.2
Platelet count	22.9±11.0
AST (IU/L)	67.0±43.4
ALT (IU/L)	88.0±53.5
γGTP (IU/L)	84.5±58.6
FPG (mg/dL)	132.0±32.2
HbA1c (%)	6.5±0.6
TG (mg/dL)	142.6±64.9
TC (mg/dL)	200.5±29.0
LDL-C (mg/dL)	120.2±17.8
HDL-C (mg/dL)	55.2±11.6
Ferritin (ng/mL)	363.6±374.7

Data are shown as the mean±SD.

BMI: body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: γ-glutamyl transferase, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, T-cho: Total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, SGLT-2i: sodium glucose cotransporter 2 inhibitor, SD: standard deviation

Lifestyle improvement, such as dietary restrictions and exercise, is the only therapy for NAFLD. However, it is difficult to achieve and maintain such life style changes, so pharmacotherapy is necessary for NAFLD, but no drugs have yet been approved for NAFLD. According to some guidelines, such as those established by the American Association of the Study of Liver Disease (AASLD), the Japan Society of Gastroenterology (JSG)-Japan Society of Hepatology (JSH), and the European Association for the Study of the Liver, pioglitazone, vitamin E, statins, and ω3 fatty acid are recommended as therapeutic agents for NASH patients, although their associated long-term efficacy still needs to be assessed (7-9).

Sodium glucose co-transporter 2 inhibitors (SGLT-2is), which were developed for the management of type 2 diabetes, inhibit the reabsorption of glucose in the kidney and decrease blood glucose levels. Several recent clinical studies have shown that SGLT-2is can improve the liver function in patients with NAFLD as well as type 2 diabetes (10-13). However, the follow-up period of these studies was relatively short. The long-term effects of SGLT-2i on the liver functions and body weight in NAFLD patients have not been fully elucidated.

In this study, we examined the long-term effects of SGLT-2i on the liver function and the correlated factors in NAFLD patients.

Materials and Methods

Patients and study design

This was a retrospective observational study. Twenty-two NAFLD patients with type 2 diabetes were enrolled in this study. We treated 22 patients for 12 months and 15 patients for 24 months with SGLT-2i. Table 1 shows the clinical characteristics of the 22 patients. NAFLD was diagnosed based on a liver biopsy in 12 patients and ultrasonography findings in 10 patients. A serial biopsy was performed in one case (Fig. 1). We excluded patients consuming more than 20 g alcohol/day (for women) or 30 g alcohol/day. We assessed the body weight, body mass index (BMI), laboratory data [aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γGTP), fasting glucose, ferritin, hemoglobin A1c (HbA1c), total cholesterol (T-cho), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)] at 1, 3, 6, 12, and 24 months. All participants provided their written informed consent.

We measured the liver stiffness and Controlled Attenuation Parameter (CAP) in 20 patients before treatment and at 12 months using transient elastography (TE) (Fibroscan[®]; Echosens, Paris, France) and acoustic radiation force impulse (ARFI) elastography (ACUSON S2000[™]; Siemens AG, Erlangen, Germany).

The study protocol was approved by Nagasaki University Hospital (approval No. 30-9-3).

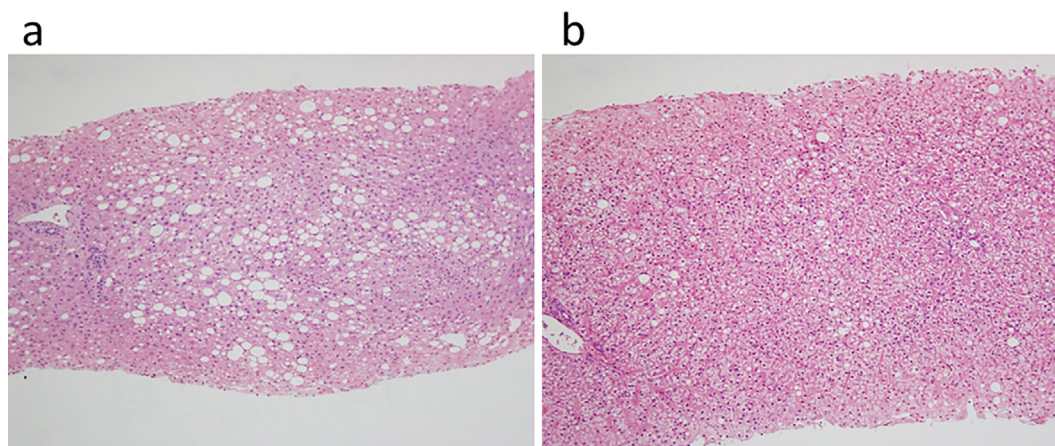


Figure 1. a: Histological findings before the administration of sodium glucose co-transporter 2 inhibitor (SGLT-2i). b: The histological findings after treatment with SGLT-2i for 12 months showed marked improvement, especially in steatosis.

Table 2. Change in Biochemical Parameters of NAFLD Patients Treated with SGLT-2i for 12 Months (n=22).

	Pretreatment	12 months	p value
Body weight(kg)	76.2±12.9	72.9±12.8	0.001
AST (IU/L)	67.0±43.4	36.6±16.0	0.001
ALT (IU/L)	88.0±53.5	48.1±31.5	0.001
γGTP (IU/L)	84.5±58.6	51.5±34.9	0.001
FPG (mg/dL)	132.0±32.2	117.4±33.3	0.007
HbA1c (%)	6.5±0.6	6.2±0.5	0.001
T-cho (mg/dL)	200.5±29.0	198.2±40.0	0.715
TG (mg/dL)	142.6±64.9	134.8±60.7	0.321
LDL-C (mg/dL)	120.2±17.8	117.4±25.4	0.593
HDL-C (mg/dL)	55.2±11.6	60.2±13.1	0.023
Ferritin (ng/mL)	363.6±374.7	178.2±117.4	0.012

Data are shown as the mean±SD, and Wilcoxon's signed-rank test was used.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: γ-glutamyl transferase, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, T-cho: Total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, SGLT-2i: sodium glucose cotransporter 2 inhibitor, SD: standard deviation

Statistical analyses

The SPSS version 20.0 software program (SPSS, Chicago, USA) was used for statistical analyses. Wilcoxon's signed-rank test was used to compare the values obtained before treatment with those obtained at 12 and 24 months after treatment. Correlations were determined using a Pearson's linear regression analysis. All p values were two-sided, and a p value less than 0.05 was considered statistically significant.

Table 3. Change and Variable in Patients Treated with SGLT-2i for 24 Months (n=15 Cases).

	Pretreatment	24 months	
Body weight (kg)	78.4±12.6	74.3±12.0	0.001
AST (IU/L)	60.0±42.7	36.6±16.9	0.010
ALT (IU/L)	77.7±53.5	45.4±23.6	0.012
γGTP (IU/L)	80.9±54.9	55.7±67.2	0.057
FPG (mg/dL)	136.8±33.3	127.5±22.3	0.117
HbA1c (%)	6.6±0.7	6.4±0.5	0.055
T-cho (mg/dL)	200.5±29.0	199.3±39.9	0.315
TG (mg/dL)	158.9±63.3	161.2±74.3	0.568
LDL-C (mg/dL)	116.6±11.4	109.0±17.5	0.118
HDL-C (mg/dL)	54.4±10.5	54.4±9.9	1.000
Ferritin (ng/mL)	271.8±223.8	202.8±155.9	0.306

Data are shown as the mean±SD, and Wilcoxon's signed-rank test was used.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: γ-glutamyl transferase, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, T-cho: Total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, SGLT-2i: sodium glucose cotransporter 2 inhibitor, SD: standard deviation

Results

Change in body weight (Table 2, 3)

The body weight was significantly reduced at 12 and 24 months compared with the pre-treatment levels (pre-treatment 76.2±12.9 kg, 6 months 74.0±12.6 kg, 12 months 72.9±12.8 kg, 24 months 74.3±12.0 kg, p=0.001).

Liver function tests (Table 2, 3)

SGLT-2i reduced the AST, ALT, and γGTP levels at 12 and 24 months compared to the pre-treatment levels: AST (pre-treatment 67.0±43.4 IU/L, 12 months 36.6±16.0 IU/L, 24 months 36.6±16.9 IU/L), ALT (pre-treatment 88.0±53.5

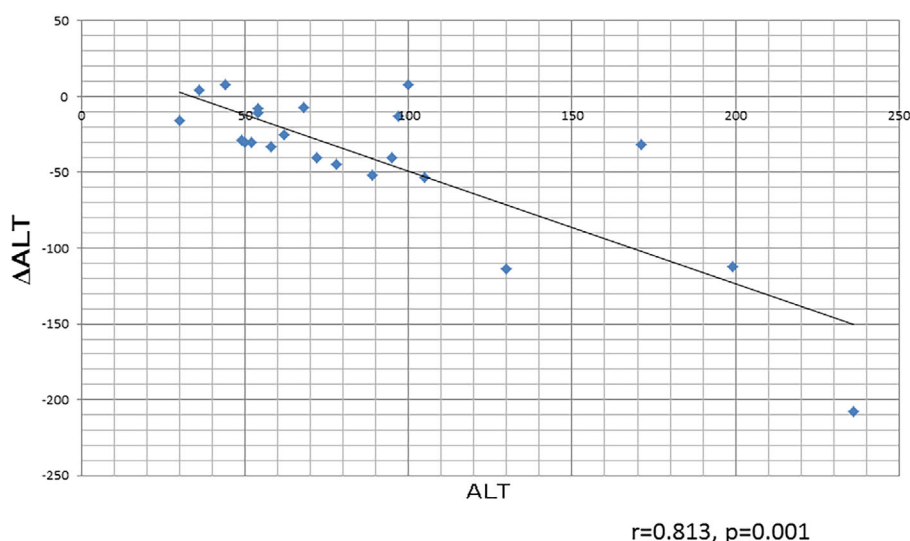


Figure 2. The correlation between the pretreatment levels of aspartate aminotransferase (ALT) and the change in the ALT level (Δ ALT) in NAFLD patients treated with sodium glucose co-transporter 2 inhibitor. Correlations were determined using a Pearson's linear regression analysis.

IU/L, 12 months 48.1 ± 31.5 IU/L, 24 months 45.4 ± 23.6 IU/L), and γ GTP (pre-treatment 84.5 ± 58.6 IU/L, 12 months 51.5 ± 34.9 IU/L, 24 months 55.7 ± 67.2 IU/L).

The ferritin level decreased significantly from pre-treatment to 12 months after treatment (pre-treatment 368 ± 374 ng/mL, 12 months 178 ± 117 ng/mL, $p=0.019, 0.018$).

Metabolic laboratory data

The levels of fasting plasma glucose (FPG), HbA1c, HDL-C at 12 months showed significant improvements compared to the pre-treatment levels: FPG (pre-treatment 132.0 ± 32.2 mg/dL, 12 months 117.4 ± 33.3 mg/dL, $p=0.007$), HbA1c (pre-treatment $6.5\% \pm 0.6\%$, 12 months $6.2\% \pm 0.5\%$, $p=0.001$), and HDL-C (pre-treatment 55.2 ± 11.6 mg/dL, 12 months 60.2 ± 13.1 mg/dL, $p=0.023$).

The T-cho, LDL-C, and TG levels did not change significantly from pre-treatment to 12 and 24 months.

Liver stiffness measurement

SGLT2-i treatment significantly improved the CAP values and Vs measured by ARFI at the end of 1 year: CAP (315.1 ± 43.4 db/mL \rightarrow 293.1 ± 27.2 db/mL, $p=0.027$) and Vs (1.87 ± 0.884 m/s \rightarrow 1.48 ± 0.63 m/s, $p=0.011$). Meanwhile, on the fibroscan, liver stiffness measured by TE did not show significant changes at the end of 1 year.

The correlation between changes in the ALT level and clinical factors

The pre-treatment ALT levels showed a significant correlation with the change in the ALT level (Δ ALT) at 12 and 24 months of therapy ($r=-0.813$, $p=0.001$; $r=-0.867$, $p=0.001$, respectively) (Fig. 2), in the AST level at 12 and 24 months of therapy ($r=-0.745$, $p=0.001$; $r=-0.937$, $p=0.001$, respectively), and in the ferritin level at 12 months ($r=-0.751$, $p=0.001$). However, no significant correlation

was noted with the change in the γ GTP level at 12 and 24 months of therapy.

Furthermore, there was no significant correlation between the change in ALT and body weight at 12 and 24 months.

Adverse events

Adverse events (AEs) were seen in three cases. One patient had a urinary tract infection, while the two others had genital infections. There were no serious AEs.

Discussion

In this study, we investigated the long-term effects of SGLT-2i on the liver function test results and liver stiffness using TE and ARFI. Several previous studies have shown the efficacy of SGLT-2i in patients with NAFLD; however, the observation period in those studies was relatively short (11-13). In the present study, we showed for the first time the long-term effects of SGLT-2i at 12 and 24 months of therapy.

SGLT-2i treatment for 12 and 24 months significantly decreased the levels of liver enzymes and body weight. These results indicated that SGLT-2i continued to improve the liver function test results and body weight over a long duration. Several previous reports have shown that SGLT-2i treatment leads to the eventual regaining of body weight by increasing the appetite (14, 15). However, in the present study, none of the 22 cases at 12 months and only one of 15 cases at 24 months regained body weight compared to the pretreatment level.

The detailed mechanism underlying the improvement in the liver function is controversial, although several have been hypothesized. One mechanism suggests the involvement of improved liver steatosis with body weight reduction (14).

Of note, a positive correlation between the reduction in ALT and body weight was not seen at 12 or 24 months in our study. According to a previous study, despite no reduction in body weight, SGLT-2i markedly improved hepatic steatosis in the mouse model (15). Therefore, the maintenance of improvement in the liver function parameters at 12 and 24 months might not be due to the reduction in the body weight. Recent research suggests that lipolysis and fatty acid oxidation may be involved in this underlying mechanism (16).

Serum ferritin is an oxidative stress marker in patients with NAFLD and chronic hepatitis C and is associated with the severity of NAFLD (17, 18). A previous study showed that phlebotomy was an effective treatment in patients with NASH (19). We found a significant correlation between the level ALT before treatment and the reduction in ferritin levels. Therefore, the reduction in the level of serum ferritin following SGLT-2i therapy might indicate an improvement in hepatic inflammation.

The CAP values for assessing liver steatosis improved with SGLT-2i treatment for 12 months. However, while liver stiffness was significantly improved on ARFI, no such improvements were noted on TE. This difference may be because of the characteristics of the two modalities. A previous meta-analysis reported that the assessment of liver fibrosis by ARFI is less influenced by steatosis than TE. ARFI may thus be more efficient for monitoring the liver fibrosis in NAFLD patients than TE (20). In several previous studies, six-month treatment with SGLT-2i did not change the liver stiffness. As seen in our study, long-term SGLT-2i treatment might be necessary to ameliorate liver fibrosis.

The level of ALT before treatment was significantly correlated with the decrease in the ALT level at 12 and 24 months following SGLT-2i therapy. A previous study in patients with type 2 diabetes also reported that SGLT-2i improved the liver function in patients with higher ALT values at baseline compared to those with lower values (21). To stop the progression of NAFLD, it is important to control the body weight, diabetes, and ALT levels (22). According to a previous report, a reduction of $\geq 30\%$ in the pretreatment ALT level was associated with a reduction in the NAFLD activity score and the inhibition of the progression of liver fibrosis in NAFLD patients (23). Our results suggest that SGLT-2i treatment may provide clinical benefit in NAFLD patients with high ALT levels.

In terms of the safety profile, urinary and genital infections were seen in three cases. The urinary tract should be examined during SGLT-2i treatment in order to detect infection in the early stage.

This study has several limitations. First, the number of patients enrolled was too small. A study in a larger number of patients will be necessary to confirm the outcomes. Second, a liver biopsy was not performed in all cases. In addition, we were unable to compare the differences in the efficacy among SGLT-2i drugs because many of the patients were treated with Ipragliflozin.

In conclusion, this retrospective study shows that long-term SGLT-2i treatment improves the liver function, steatosis, and liver fibrosis in patients with NAFLD as well as type 2 diabetes. Patients with higher ALT levels show a greater improvement in the liver function than those with lower levels and may benefit from SGLT-2i therapy.

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

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