Gut and Gastroenterology

RESEARCH ARTICLE

# Clinical Efficacy of an SGLT2 Inhibitor in Type 2 Diabetes Complicated By Nonalcoholic Fatty Liver Disease and Changes in Body Composition

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## Abstract

**Background**: Sodium–glucose cotransporter 2 inhibitors (SGLT2is) decrease blood glucose levels by inhibiting glucose reabsorption in the kidneys. These inhibitors may exhibit clinical efficacy in type 2 diabetes mellitus (T2DM) patients with nonalcoholic fatty liver disease (NAFLD). To determine whether SGLT2is are useful for treating these patients, computed tomography (CT) was used to examine changes in the liver/spleen ratio (L/S ratio), liver function, visceral adipose tissue indices (VATI), and subcutaneous adipose indices (SATI) in response to treatment.

**Methods**: Continuous SGLT2i treatment effect was evaluated for at least 6 months on 36 patients (15 males, 21 females) with T2DM complicated by NAFLD. L/S ratio, visceral fat area, and subcutaneous fat area were measured at least twice. These values with liver function tests were compared before and after treatment. Patient characteristics included body mass index, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin (Hb)A1c, and ferritin.

**Results**: The 24-week SGLT2i course significant decreased body weight (65.83 ± 13.21 to 62.15 ± 13.28 kg), HbA1c (decreased to 6.14 ± 0.35), serum ferritin (decreased to 77.70 ± 74.02 ng/ml), ALT (decreased to 22.08 ± 16.38 IU/L), and AST (decreased to 25.64 ± 16.38 IU/L). CT revealed improvements in body composition including increase in L/S ratio (from 0.94 ± 0.13 to 1.35 ± 0.15), and decreases in VATI (from 51.04 ± 18.92 to 44.04 ± 20.07 $cm^2/m^2$) and SATI (from 75.94 ± 41.72 to 67.55 ± 41.79 $cm^2/m^2$).

**Conclusion**: Thus, treatment with SGLT2i improved all parameters associated with T2DM complicated by NAFLD.

## Key points

- Obesity and insulin resistance are common pathologies in T2DM and cause NAFLD.
- In this study, luseogliflozin was administered to patients with T2DM and NAFLD, which significantly improved L/S ratio, visceral fat area, and subcutaneous fat area, as measured by CT.
- Luseogliflozin might improve clinical status and limit pathology of T2DM and NAFLD by improving body composition.

## Introduction

Novel treatment methods are urgently needed to address the problem of nonalcoholic fatty liver disease (NAFLD), also known as the hepatic phenotype of metabolic syndrome. Sodium–glucose cotransporter 2 inhibitors (SGLT2is) are currently in use for the treatment of diabetes; these drugs not only decrease blood glucose levels, they also promote weight loss, decreased blood pressure, and normalized hepatic function test values. Recently, a decrease in serum alanine aminotransferase (ALT) levels linked to the weight loss effect was reported in patients with type 2 diabetes mellitus (T2DM) with NAFLD [1]. However, there are only a few reports that explore this issue quantitatively by examining the ratios of liver fat content and changes in body composition with imaging modalities. As such, the aim of study was to verify the effectiveness of oral SGLT2i therapy in patients with T2DM complicated by NAFLD, notably the impact of 24 weeks of treatment on body composition as determined by computed tomography (CT) scan.

## Materials and Methods

We enrolled 36 patients (15 male, 21 female) diagnosed with T2DM with NAFLD between November 2015 and December 2019. Patient selection was based on the guidelines stipulated in other clinical trials conducted previously [2, 3], and these guidelines are later revised [4]. The following criteria were

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**Accepted:** August 27, 2020

**Reviewed by:** Justin D, United Kingdom

kept in mind in patient selection. All included patients were with diagnosed type 2 diabetes and poor glycemic control and had elevated serum transaminases (aspartate aminotransferase (AST) and ALT), were not taking insulin secretagogues like sulfonylureas, did not report any symptoms of geriatric syndrome and did not have any kidney disease or urinary tract infections or cancer. Exclusion criteria were patients <55 years and older than 77 years of age, those taking sulfonylureas at the time of recruitment, incidence or history of diabetic complications such as diabetic retinopathy, diabetic nephropathy, and diabetic ketoacidosis. These patients were recruited when they visited the outpatient clinic at our hospital, for diabetes and liver complications. Sample size calculations were done on the basis of earlier reports to achieve an average decrease in hemoglobin A1c (HbA1c) by about 6% due to SGLT2i treatment. A sample size of 36 patients was required at 95% confidence level and 90% power. This sample size was considered representative of larger Japanese population of type 2 diabetic patients.The recruited patients were introduced to the newly available oral SGLT2i (Luseogliflozin; Lusefi tablets, Taisho Pharmaceutical, Co. Ltd, Tokyo, Japan) treatment, and were continued this treatment for at least 6 months and were available for follow-up observation and study. Luseogliflozin treatment is not the routine treatment to NAFLD patients at our hospital. As these patients had established diabetes with elevated HbA1c levels (6.90 ± 0.77), as attending physicians we decided to administer the SGLT2i considering its proven efficacy (prior to our studies) in the treatment of diabetic patients [5] and in improving diet induced diabetes as well as NAFLD in animal studies [6-8]. Liver/Spleen ratio (L/S ratio), visceral fat accumulation (VFA), and subcutaneous fat area (SFA) were measured before and after treatment. Visceral adipose tissue indices (VATI), and subcutaneous adipose indices (SATI) were calculated from the VFA and SFA before and after the treatment based on physical findings, biochemistry, and CT scans. The L/S ratio, liver function, VATI, SATI and visceral to subcutaneous fat ratio (VSR) were compared before and after treatment. The methods and risks of the study were explained to the patients and their written informed consent to participate in the study was obtained.

### Adipose tissue measurement by CT

Adipose tissues were measured by a cross-sectional enhanced-CT imaging (Aquilion ONE; Toshiba Medical Systems Corporation, Tokyo, Japan). Body composition was assessed by analyzing abdominal CT scans taken at the umbilical level. The adipose tissue area was determined using SYNAPSE VINCENT V3.3 software (Fuji Film Medical Co., Ltd., Tokyo, Japan) that enables specific tissue demarcation using previously reported Hounsfield unit (HU) thresholds. The cross-sectional area of each tissue was calculated using standard HU thresholds of −150 to −50 HU for VAT [9] and −190 to −30 HU 84 for SAT) [10]. The VATI and SATI were calculated by dividing the area determined (in $cm^2$) by the square of the patient height in meters ($m^2$) and were reported as indices in $cm^2/m^2$. The VSR was defined as the ratio of the visceral adipose area to the subcutaneous adipose tissue area.

### Statistical analysis

Patient characteristics were summarized with means and standard deviations. Wilcoxon's signed-rank test was used to compare the values obtained before treatment with those obtained at 24 weeks 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. Continuous variables were compared using a Student's t-test or a Mann–Whitney U test. Categorical variables were compared by Fisher's exact test. Values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using EZR ver. 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [11].

### Ethics statement

The study was approved by the Institutional Review Board of Saiseikai Niigata Hospital and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

## Results

We enrolled 36 patients in this study; patient characteristics are shown in (Table 1). The mean age was 65.44 ± 10.94 years (median of 64 years), At the start of the study, body mass index (BMI), ALT, AST, HbA1c and serum ferritin levels were 26.07 ± 4.49 (median 26.13), 40.89 ± 40.07 IU/L, 36.97 ± 25.12 IU/L 6.90% ± 0.77%, and 128.09 ± 115.16 ng/mL, respectively. Likewise, the liver/Spleen ratio was 0.94 ± 0.13, and VATI and SATI were 51.04 ± 18.92 $cm^2/m^2$ and 75.93 ± 42.71 $cm^2/m^2$, respectively. Mean body weight decreased significantly in response to treatment, from 65.83 ± 13.21 kg measured at the start of the study to 62.15 ± 13.28 kg at 24 weeks ( $p < 0.0001$); HbA1c also decreased significantly, from 6.90 ± 0.77 to 6.14 ± 0.35% ($p < 0.0001$).There was also

**Table 1:** Clinical Characteristics of Patients Enrolled in This Study (n = 36)

| Characteristics | Number or mean ± SD |
|---|---|
| Gender (male/female) | 15/21 |
| Age (years) | 65.44 ± 10.94 |
| Body weight (kg) | 65.83 ± 13.21 |
| BMI ($kg/m^2$) | 26.07 ± 4.49 |
| ALT (IU/L) | 40.89 ± 40.07 |
| AST (IU/L) | 36.97 ± 25.12 |
| HbA1c (%) | 6.90 ± 0.77 |
| Ferritin (ng/ml) | 128.09 ± 115.16 |
| VATI ($cm^2/m^2$) | 51.04 ± 18.92 |
| SATI ($cm^2/m^2$) | 75.93 ± 42.71 |
| L/S | 0.94 ± 0.13 |

SD, standard deviation; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bA1c, hemoglobin A1c; VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index; L/S, liver-to-spleen ratio

significant decline in serum ferritin (to 77.70 ± 74.02 ng/ml, $p$ = 0.0008), ALT (to 22.08 ±16.38 IU/L, $p$ = 0.0023), and AST (to 25.64 ± 8.53 IU/L; $p$ = 0.0017; (Table 2). The changes in body composition evaluated by CT scan from baseline to 24 weeks are as indicated in (Figure 1). Among these, we report a significant increase in the L/S ratio (to 1.35 ± 0.15; p < 0.0001) and significant decreases in VAT1 (to 44.04 ± 20.07 $cm^2/m^2$; p=0.0001) and SAT1 (to 67.55 ± 41.79 $cm^2/m^2$; p=0.0007). The improvements in the liver-to-spleen (L/S) ratio and in VATI were more marked than that observed in SATI. However, VSR showed no significant change in response to therapy (p = 0.4268). We report no significant adverse events associated with this study. Among the 36 patients, three reported mild itchiness and one reported constipation. However, worsening of liver disorder was not detected in any of the patients.

## Discussion

Sodium–glucose co-transporters (SGLTs) are expressed on the membranes of numerous cells and in various tissues [12]. SGLT2 is found in the S1 and S2 segments of the renal proximal tubules where it mediates the reabsorption of filtered glucose via its actions within the glomeruli [13] and plays a major role in the reuptake of glucose from urine. SGLT2i is a novel oral antidiabetic drug that inhibits the reuptake of glucose in proximal renal tubules and increases urinary glucose excretion, thereby inducing calorie loss [14]. Among seven types of oral antidiabetic drugs, SGLT2i is the only one that consistently promotes weight loss in this population. The SGLT2i, luseogliflozin, inhibits the actions of the transporter in a selective manner which results in the inhibition of the sodium and glucose reuptake and promotes excretion of

**Table 2.** Biochemical Parameters of Patients with T2DM and NAFLD Treated with SGLT-2I (n =36)

| Characteristics | Pretreatment | 24 Weeks | *p* value |
|---|---|---|---|
| **Body weight (kg)** | 65.83 ± 13.21 | 62.15 ± 13.28 | <0.0001 |
| **ALT (IU/L)** | 40.89 ± 40.07 | 22.08 ± 16.38 | 0.0023 |
| **AST (IU/L)** | 36.97 ± 25.12 | 25.64 ± 8.53 | 0.0017 |
| **HbA1c (%)** | 6.90 ± 0.77 | 6.14 ± 0.35 | <0.0001 |
| **Ferritin (ng/ml)** | 128.09 ± 115.16 | 77.70 ± 74.02 | 0.0008 |

Data are shown as the mean ± SD, *p* values from Wilcoxon`s signed test.

SD, standard deviation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, hemoglobin A1c

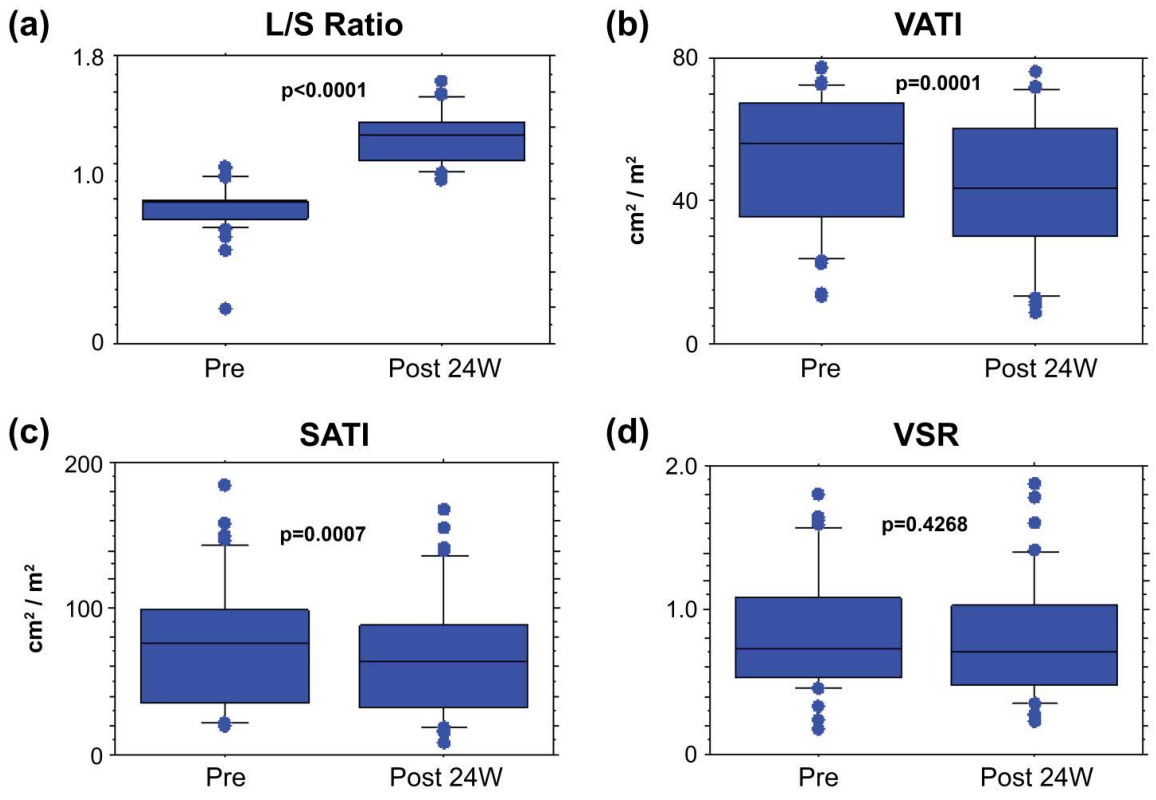


**Figure 1:** Changes in Parameters Measured From Baseline through Week 24 of Treatment

A) L/S ratio, B) VATI, C) SATI and D) VSR measured at baseline and again at week 24

glucose in the urine. Luseogliflozin may reduce blood glucose levels in an insulin-independent manner; it may also be effective in treating hyperinsulinemia and NAFLD [15]. In addition, hepatic disorders associated with luseogliflozin treatment are reported to be few in number. Obesity and insulin resistance are common pathologies in T2DM and are underlying causes of NAFLD. As such, there is a high rate of NAFLD among patients with T2DM. Furthermore, nonalcoholic steatohepatitis (NASH) may also advance readily due to inflammation and fibrosis of the liver in T2DM complicated by NAFLD. Therefore, effective drug therapy for obesity and insulin resistance is a very important clinical issue with far-reaching implications. In animal studies, SGLT2i had an impact on both obesity and insulin resistance and was capable of suppressing the development of NASH. This result was confirmed by recent clinical studies focused on the SGLT2i and its role in treating T2DM and its associated complications (NAFLD/NASH) [16, 17]. In one of the few previous clinical studies that focused on the impact of SGLT2is in these patients, canagliflozin was administered for 24 weeks to five

Japanese patients with T2DM complicated by NAFLD/NASH who presented with NAFLD activity scores (NASs) ≥3 points on liver biopsy [18]. In this study, all patients undergoing treatment with the SGLFT2 inhibitor demonstrated improved NAS with improvements in fibrosis observed in two patients. These results demonstrated that the SGLT2i is likely to be effective against NASH that can complicate T2DM [19]. Re-evaluation of these patients is particularly important. However, frequent liver biopsies are associated with complications including hemorrhage; this modality can be effectively replaced with non-invasive imaging and analysis. In this study we investigated the impact of SGLT2i (Luseogliflozin; Lusefi tablets, Taisho Pharmaceutical, Co. Ltd, Tokyo, Japan) on liver function via image analysis in patients with T2DM complicated by NAFLD. The onset of fatty liver involves two distinct mechanisms, specifically, increased in the influx of fatty acids and increased fatty acid synthesis *in situ*. As part of the first mechanism, increased lipolysis or excess ingestion of fat increases the influx of fatty acids to the liver from the portal vein. Likewise, via the second mechanism, continuous over-ingestion of carbohydrates and fructose, especially during hyperinsulinemia, increases the synthesis of fatty acids in the liver. Administration of SGLT2i results in decreased accumulation of fat in the liver by decreasing intrinsic fat and thus fatty acid influx. In addition, there is a possibility that SGLT2i decreases fatty acid synthesis in the liver promoted by insulin due to its capacity to address hyperinsulinemia by improving insulin resistance. These mechanisms, working together, can result in suppression of hepatic steatosis [19]. In a recently reported comparative/randomization ratio study, 50 patients with T2DM complicated with NAFLD were treated with 10 mg of the SGLT2i, empagliflozin, or control in addition to standard treatment for 20 weeks; changes in liver lipids were quantified using MRI [20]. The lipid ratio in the livers of those in the empagliflozin-treated group decreased by 4% compared to that observed in the control group; interestingly, the change in the lipid ratio did not correlate with weight loss. In this study, changes in body composition included weight loss as well as marked improvement in the L/S ratio and VATI. The decrease in VATI was more marked than that measured in SATI; when these parameters are measured in response to weight loss achieved by diet and exercise, the same results are obtained. These findings suggest that SGLT2is promote weight loss via a physiological mechanism. It is also noteworthy that the study identified improvements in serum ferritin levels, which are findings that reflect liver inflammation, notably as related to NASH. SGLT2i (Luseogliflozin) has been reported to decrease the accumulation of fat in the liver, evaluated as the L/S ratio on CT in T2DM patients with NAFLD. There are also reports that the improvement in liver function are directly attributable to improvements in fatty acid metabolism and reduction of the inflammation promoted by adipose tissue [21]. Hepatic fat content was evaluated as the MRI hepatic fat fraction (MRI-HFF); this value also decreased significantly in T2DM patients with NAFLD after treatment with luseogliflozin for 24 weeks. The reduction of hepatic fat content correlated with body weight, BMI, AST, ALT, triglycerides (TGs), fasting plasma glucose, and serum ferritin levels [22]. Moreover, after administration of luseogliflozin to T2DM patients with hepatic impairment, the area under the concentration-time curve (AUC), revealed nearly equivalent Pugh-Child severity scores. We note that the pharmacokinetics of luseogliflozin is affected by the severity of hepatic impairment. Among the limitations of this study, variation in individual measures of VSR was high, a fact that may relate to the relatively short observation period. Nonetheless, our results suggest that SGLT2 is may be critically useful for the treatment of fatty liver.

## Conclusions

In conclusion, treatment with the SGLT2i, luseogliflozin, improved the L/S ratio, serum ALT, AST and ferritin levels, as well as VATI, and SATI. SGLT2is are likely to improve the clinical status and limit pathology associated with T2DM with NAFLD by improving parameters associated with body composition.

## Declarations

### Funding

Taisho Pharmaceutical Co., Ltd provided editorial funding. Grant Number not available.

The funder played no role in the manuscript preparation and study design and execution.

### Conflicts of interest/Competing interests

There are no conflicts of interest to declare.

### Ethics approval

The study was approved by the Institutional Review Board of Saiseikai Niigata Hospital (E17-27) and was conducted in accordance with the principles of the Declaration of Helsinki.

### Consent to participate

All patients provided written informed consent.

**Consent for publication**

Not applicable

**Availability of data and material**

Not applicable

**Code availability**

Not applicable

**Authors' contributions**

Conceptualization: TI.

Data curation: TI, SE, MA, MI, YN, AI, TS, TH, and TY.

Formal analysis: TI.

Funding acquisition: TI.

Investigation: TI, SE, MA, MI, YN, AI, TS, TH, and TY.

Methodology: TI.

Project administration: TI and MI.

Resources: TI, SE, MA, MI, YN, AI, TS, TH, and TY.

Software: Toru Ishikawa.

Supervision: TI.

Visualization: TI.

Writing – original draft: TI.

Writing – review & editing: TI and MI

## Acknowledgments

Taisho Pharmaceutical Co., Ltd provided editorial funding.

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**Citation:** Ishikawa T, Imai M, Endo S, Azumi M, Nozawa Y, Sano T, et al. (2020) Clinical Efficacy of an SGLT2 Inhibitor in Type 2 Diabetes Complicated By Nonalcoholic Fatty Liver Disease and Changes in Body Composition. Gut Gastroenterol 3: 001-006.