J Gastroenterol (2018) 53:140–151
https://doi.org/10.1007/s00535-017-1364-8

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Effects of canagliflozin, an SGLT2 inhibitor, on hepatic function in Japanese patients with type 2 diabetes mellitus: pooled and subgroup analyses of clinical trials

Yuya Seko[1] · Yoshio Sumida[1] · Kazuyo Sasaki[2] · Yoshito Itoh[1] · Hiroaki Iijima[3] · Toshio Hashimoto[3] · Shinichi Ishii[3] · Nobuya Inagaki[4]

Received: 30 September 2016 / Accepted: 18 June 2017 / Published online: 1 July 2017

Abstract

Background We aimed to investigate the efficacy of canagliflozin (based on its effect on liver function and blood glucose levels) and its safety in high alanine aminotransferase (ALT) patients (ALT >30 U/L).

Methods This post hoc analysis of canagliflozin in type 2 diabetes mellitus (T2DM) patients was divided into Study 1 (pooled analysis of 12- and 24-week placebo-controlled, monotherapy studies) and Study 2 (52-week monotherapy/combination therapy study). The canagliflozin 100 mg group data were compared with placebo or baseline ALT subgroup (baseline ALT >30 or ≤30 U/L) data. The primary endpoint was change in ALT level from baseline. Secondary endpoints were changes in efficacy-related parameters. Adverse events (AEs) were evaluated.

Results The mean ALT change at 12 weeks was -10.3 ± 11.7 and -3.2 ± 17.6 U/L in the canagliflozin vs. placebo group in the high ALT subgroup ($P = 0.0206$); no significant difference was shown in the low ALT subgroup (Study 1). In both ALT subgroups, glycosylated hemoglobin (HbA1c) and body weight were significantly reduced in the canagliflozin vs. placebo group (all $P < 0.0001$). The mean change in ALT at 52 weeks was -16.0 ± 18.8 U/L in the high ALT subgroup ($P < 0.0001$, Study 2). The incidence of AEs or serious AEs in the high ALT subgroup in the canagliflozin group was similar to that in the placebo group (Study 1) or low ALT subgroup (Studies 1 and 2).

Conclusions In T2DM patients with impaired liver function, canagliflozin may improve liver function, reduce HbA1c and body weight, and be well tolerated.

Keywords Alanine aminotransferase · Canagliflozin · Hepatic function · Japan · Type 2 diabetes mellitus

Introduction

Nonalcoholic fatty liver disease (NAFLD), which is the most common chronic liver disease worldwide, is classified into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) [1, 2]. The prevalence of NAFLD has increased with the rise in obesity and metabolic syndrome and is associated with lifestyle changes. In patients with obesity and type 2 diabetes mellitus, the prevalence of NAFLD is as high as 57–98% and 62–69%, respectively [3–5]. Insulin resistance and obesity are closely related to the development and progression of NAFLD [6]. The most common complications of NAFLD are type 2 diabetes mellitus and impaired glucose tolerance [6–9].

A positive correlation between the visceral fat mass and the hepatocyte fat content in NAFLD patients has been reported [10, 11]. The mechanisms through which insulin resistance and obesity contribute to the onset and progression of NAFLD/NASH appear to be those described in the two-hit theory by Day et al. [12, 13] and the multiple parallel hits hypothesis by Tilg et al. [14]. The two-hit

Electronic supplementary material The online version of this article (doi:10.1007/s00535-017-1364-8) contains supplementary material, which is available to authorized users.

✉ Yuya Seko
yuyaseko@koto.kpu-m.ac.jp

[1] Department of Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, Japan

[2] Mitsubishi Tanabe Pharma Corporation, Osaka, Japan

[3] Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan

[4] Department of Diabetes, Endocrinology and Nutrition, Kyoto University Graduate School of Medicine, Kyoto, Japan

theory suggests that the first "hit", steatosis, increases the sensitivity of the liver to the second "hits" that mediate liver injury [13]. In the multiple parallel hits hypothesis, endoplasmic reticulum stress and related signaling networks, adipocytokines, and insulin resistance are suggested as the central pathways responsible for NASH [14]. Cusi et al. recently reported on the beneficial effects of pioglitazone on NASH in patients with prediabetes or type 2 diabetes mellitus [15]. However, the only established therapies for NAFLD are dietary and exercise therapies [1, 2].

Sodium glucose co-transporter 2 (SGLT2) inhibitors, which are used to treat type 2 diabetes mellitus, lower blood glucose levels by inhibiting the reabsorption of glucose in the kidney and promoting the urinary glucose excretion [16]. In addition to a sustained antihyperglycemic effect, SGLT2 inhibitors have also been reported to have a body weight-lowering effect that is accompanied by a reduction in abdominal fat [17]. SGLT2 inhibitors were found to reduce the fat content in the liver, improve inflammation, and prevent progression of fibrosis in NAFLD model mice [18]. The results of phase 3 studies conducted in Japan and overseas suggested that in patients with type 2 diabetes mellitus, liver function parameters might be improved by the administration of the SGLT2 inhibitor canagliflozin [16, 19–21]. However, the effects on liver function and blood glucose levels and the safety of canagliflozin in patients with abnormal hepatic function have not been clarified.

Alanine aminotransferase (ALT), which indicates liver inflammation or injury, is a candidate marker for NAFLD. In recent years, it has been reported that ALT is a useful indicator of the progression of liver fibrosis in NAFLD patients [22, 23]. An ALT level >30 U/L is the criterion established in the guidelines of the Ministry of Health, Labour and Welfare in Japan for the routine health checkup program. Therefore, we conducted a pooled and subgroup analysis of three Japanese clinical studies by baseline ALT [16, 19, 24] to investigate the effects on liver function and blood glucose levels and the safety of canagliflozin in a high ALT subgroup (baseline ALT >30 U/L).

Methods

We carried out a post hoc analysis of three previous studies in Japan: a 12-week monotherapy study [24], a 24-week monotherapy study [16], and a 52-week monotherapy or combination therapy study [19]. This post hoc analysis was divided into two parts: Study 1 (a pooled analysis of the 12- and 24-week studies) and Study 2 (the 52-week study). The aim of Study 1 was to compare the efficacy on liver function and blood glucose levels and the safety of canagliflozin 100 mg with those of placebo at 12 weeks in a high ALT subgroup (baseline ALT >30 U/L). The aims of Study 2, which included a larger number of patients than Study 1, were (1) to evaluate the long-term efficacy and safety of canagliflozin 100 mg at 52 weeks, and (2) to analyze the modulating factors influencing the change of ALT in a high ALT subgroup. The improving effects on liver function and blood glucose levels and safety achieved with the different drugs (placebo and canagliflozin 100 mg) and for the different ALT categories (ALT >30 U/L, ALT ≤30 U/L) were comparatively evaluated. These studies were conducted in compliance with Good Clinical Practice guidelines and the Pharmaceutical Affairs Law in Japan, according to the ethical principles of the Declaration of Helsinki of 1964, as revised in 2008, and were approved by the institutional review boards at all of the participating institutions.

Study 1

Study 1 consists of a pooled analysis of two placebo-controlled studies (the 12-week study and 24-week study). The data from each placebo and canagliflozin 100 mg (the approved dose in Japan) group up to 12 weeks were pooled. Pooling confirmed that the patient backgrounds and the ALT profiles through 12 weeks were nearly identical in these two studies. In the high ALT subgroup of the 12-week study, the mean changes in ALT (±SD) from baseline to 12 weeks were -9.0 ± 10.7 and -2.0 ± 17.0 U/L in the canagliflozin 100 mg and placebo groups, respectively. In the 24-week study, the mean changes were -11.1 ± 12.5 and -3.6 ± 19.8 U/L, respectively.

Study design

The 12-week study [24] was a multicenter, randomized, placebo-controlled, double-blind, parallel-group, phase 2 dose-finding study in Japanese type 2 diabetes mellitus patients. Subjects received monotherapy with canagliflozin (50, 100, 200, or 300 mg) or placebo once a day for 12 weeks. The 24-week study [16] was a multicenter, randomized, placebo-controlled, double-blind, parallel-group phase 3 confirmatory study in Japanese type 2 diabetes mellitus patients. Subjects received monotherapy with canagliflozin (100 or 200 mg) or placebo once a day for 24 weeks. Patients with serious liver disease, defined as those who required hospitalization or surgery for treatment, and those with a medical history of hepatitis B or hepatitis C were excluded, as were patients with ALT or aspartate aminotransferase (AST) > 2.5 × ULN (40 U/L) on the day of screening. The exclusion criteria of ALT and AST levels were set in consideration of the patients' safety and ethics. The amount of alcohol intake was not regulated in these two studies.

Study 2

Study design

The 52-week study [19] was a multicenter, randomized, open-label, long-term, phase 3 study in Japanese patients with type 2 diabetes mellitus. Subjects received canagliflozin (100 or 200 mg) once a day for 52 weeks, either as monotherapy or in combination with another oral antihyperglycemic drug (sulfonylurea, glinide, α-glucosidase inhibitor, biguanide, thiazolidinedione, or dipeptidyl peptidase-4 inhibitor). In combination therapy groups, the antihyperglycemic drugs were given from ≥83 days before the first day of canagliflozin treatment. Patients with serious liver disease, hepatitis B, or hepatitis C were excluded, as were patients with ALT or AST $> 2.5 \times$ ULN (40 U/L) on the day of screening. The amount of alcohol intake was not regulated in this study.

Outcomes

The primary endpoint is the change in ALT level from baseline. The secondary endpoints are the changes in the following parameters: liver function-related parameters (AST and γ-glutamyl transpeptidase [γ-GTP]) and efficacy-related parameters (glycosylated hemoglobin [HbA1c], fasting blood glucose, insulin, body weight, body mass index [BMI], and waist circumference). Adverse events (AEs), serious AEs (SAEs), and laboratory tests (low-density lipoprotein cholesterol [LDL-c], high-density lipoprotein cholesterol [HDL-c], triglyceride [TG], free fatty acid [FFA], uric acid, and total ketone bodies) were also evaluated.

AEs were classified according to system organ class and preferred term using MedDRA/J version 15.1 (Japanese Maintenance Organization, Tokyo, Japan).

Statistical analyses

The full analysis set was used for the analysis of liver function-related parameters (e.g., ALT, AST), efficacy-related parameters (e.g., HbA1c), and laboratory test values. The safety analysis set was used for the analysis of AEs.

In Study 1, the change in ALT after 12 weeks of treatment with canagliflozin 100 mg was compared with that after 12 weeks of treatment with placebo in the high ALT subgroup. The comparisons between treatment groups were performed using analyses of covariance with the baseline value of parameters as a covariate. For reference, similar analyses were also performed for the low ALT subgroup. The last observation carried forward (LOCF) method was used to impute missing values.

In Study 2, the effects of treatment for 52 weeks with canagliflozin 100 mg on liver function-related parameters, efficacy-related parameters, and laboratory test values in each subgroup were assessed by the paired *t* test. Missing values were imputed by the LOCF method. To identify factors affecting a decrease in ALT in the high ALT subgroup, single correlation and multiple regression analyses (stepwise variable selection method; both entry and retention criteria were set at $P = 0.05$) were performed with change in ALT as a dependent variable and related factors as explanatory variables. These were performed in the canagliflozin 100 mg group in Study 2, in which more subjects were observed for a longer period.

Continuous data are summarized based on the number of patients (*n*), mean, and standard deviation (SD), and discrete data are summarized based on the *n* and percentage values for each category. Tests were two-sided with a 5% significance level, and 95% confidence intervals (CIs) were calculated. The statistical analysis was performed by Takumi Information Technology Inc. (Tokyo, Japan), using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study 1

Baseline characteristics

The mean ± SD ALT at baseline was 45.6 ± 13.9 U/L in the canagliflozin 100 mg group and 48.4 ± 14.2 U/L in the placebo group in the high ALT subgroup. The HbA1c levels were 8.07 ± 0.70% in the canagliflozin 100 mg group and 8.10 ± 0.72% in the placebo group in the high ALT subgroup (Table 1). Additionally, the mean HbA1c at baseline did not markedly differ between the high ALT subgroup and the low ALT subgroup, either in the canagliflozin 100 mg group or the placebo group. Conversely, the mean body weight, BMI, waist circumference, and homeostatic model assessment-insulin resistance (HOMA-IR) were all higher in the high ALT subgroup than in the low ALT subgroup, both in the canagliflozin 100 mg group and in the placebo group.

Efficacy

At 12 weeks, the ALT level was significantly lower in the canagliflozin 100 mg group than in the placebo group, only in the high ALT subgroup (Fig. 1a). A significant reduction in the AST level was also observed in the canagliflozin 100 mg group, but only in the high ALT subgroup (Fig. 1b). In both ALT subgroups, HbA1c and body weight were significantly lower in the canagliflozin 100 mg group

Table 1 Baseline characteristics of patients (Study 1)

	ALT ≤30 U/L		ALT >30 U/L	
	Placebo ($n = 109$)	Canagliflozin ($n = 117$)	Placebo ($n = 59$)	Canagliflozin ($n = 47$)
Sex				
Male	65 (59.6)	80 (68.4)	49 (83.1)	31 (66.0)
Female	44 (40.4)	37 (31.6)	10 (16.9)	16 (34.0)
Age (years)	59.8 ± 10.1	59.3 ± 10.1	54.7 ± 11.8	55.0 ± 10.7
HbA1c (%)	7.98 ± 0.73	7.99 ± 0.82	8.10 ± 0.72	8.07 ± 0.70
Fasting glucose (mg/dL)	166.0 ± 33.7	159.7 ± 35.6	167.3 ± 30.1	157.9 ± 30.3
Fasting insulin (μIU/mL)	8.042 ± 6.121	7.804 ± 5.956	13.283 ± 8.180	14.564 ± 7.157
HOMA-IR	3.25 ± 2.42	3.06 ± 2.39	5.44 ± 3.31	5.70 ± 2.82
Body weight (kg)	65.31 ± 13.47	66.37 ± 13.16	79.67 ± 14.24	75.11 ± 16.25
BMI (kg/m^2)	24.83 ± 4.01	24.74 ± 3.95	28.44 ± 4.03	27.73 ± 4.74
Waist circumference (cm)	87.73 ± 10.91	88.49 ± 10.51	96.68 ± 8.38	94.91 ± 10.93
ALT (U/L)	19.5 ± 5.2	20.0 ± 5.7	48.4 ± 14.2	45.6 ± 13.9
AST (U/L)	19.8 ± 5.0	19.8 ± 4.5	36.2 ± 15.5	36.1 ± 11.7
γ-GTP (U/L)	39.1 ± 28.3	34.8 ± 25.1	98.8 ± 131.9	52.9 ± 34.1
Platelet ($\times 10^4$/μL)	25.11 ± 7.88	23.23 ± 6.05	21.98 ± 5.66	23.33 ± 6.94
eGFR (ml/min/1.73 m^2)	83.2 ± 15.2	83.8 ± 14.4	85.2 ± 14.8	84.0 ± 15.8
Complications				
Hypertension	51 (46.8)	53 (45.3)	31 (52.5)	29 (61.7)
Hyperlipidemia	59 (54.1)	75 (64.1)	44 (74.6)	33 (70.2)
Hepatic steatosis, diagnosed	17 (15.6)	14 (12.0)	26 (44.1)	22 (46.8)

Data are presented as n (%), or mean ± SD

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycosylated hemoglobin, *HOMA-IR* homeostatic model assessment-insulin resistance, *γ-GTP* γ-glutamyl transpeptidase

than in the placebo group (Fig. 1c, d). Waist circumference was significantly lower in the canagliflozin 100 mg group than in the placebo group, but only in the high ALT subgroup; in the canagliflozin and placebo group, the change from baseline was −1.90 ± 2.78 and −0.51 ± 2.65 cm, respectively, in the high ALT subgroup ($P = 0.0132$) and −1.39 ± 2.93 and −0.70 ± 2.67 cm, respectively, in the low ALT subgroup (no significant difference). Additionally, in both ALT subgroups, fasting insulin level was significantly lower in the canagliflozin 100 mg group than in the placebo group; the change from baseline was −4.056 ± 4.792 and −1.671 ± 5.324 μIU/mL, respectively, in the high ALT subgroup ($P = 0.0163$) and −1.599 ± 3.858 and −0.372 ± 3.228 μIU/mL, respectively, in the low ALT subgroup ($P = 0.0067$) (Suppl. 1).

Safety

The overall incidence of AEs in the high ALT subgroup was similar across treatment groups [canagliflozin 100 mg: 48.9% (95% CI 34.1–63.9), placebo: 50.8% (95% CI 37.5–64.1)]. The incidences of AEs related to the study drug in the high ALT subgroup were 19.1% (95% CI 9.1–33.3) and 11.9% (95% CI 4.9–22.9) with canagliflozin 100 mg and placebo, respectively. In the canagliflozin 100 mg group, no clear difference in the overall incidence of AEs related to the study drug was found between ALT subgroups [19.1% (95% CI 9.1–33.3) and 23.9% (95% CI 16.5–32.7) in the high and low ALT subgroups, respectively]. There was no clear difference in the overall incidence of SAEs in the high ALT subgroup across treatment groups. There were no SAEs related to the study drug in either treatment group in the high ALT subgroup (Table 2).

In the high ALT subgroup, the incidences of symptomatic hypoglycemia (6.4 vs. 0.0%), female genital infections (6.3 vs. 0.0%), and osmotic diuresis (6.4 vs. 1.7%) were higher in the canagliflozin 100 mg group than in the placebo group. Among these AEs, the incidences of symptomatic hypoglycemia (6.4 vs. 0.9%) and osmotic diuresis (6.4 vs. 2.6%) in the canagliflozin 100 mg group were higher in the high ALT subgroup than in the low ALT subgroup. There were no hepatic AEs in the canagliflozin 100 mg group in both subgroups. Total ketone bodies were significantly increased in the canagliflozin 100 mg group in both subgroups (Suppl. 1).

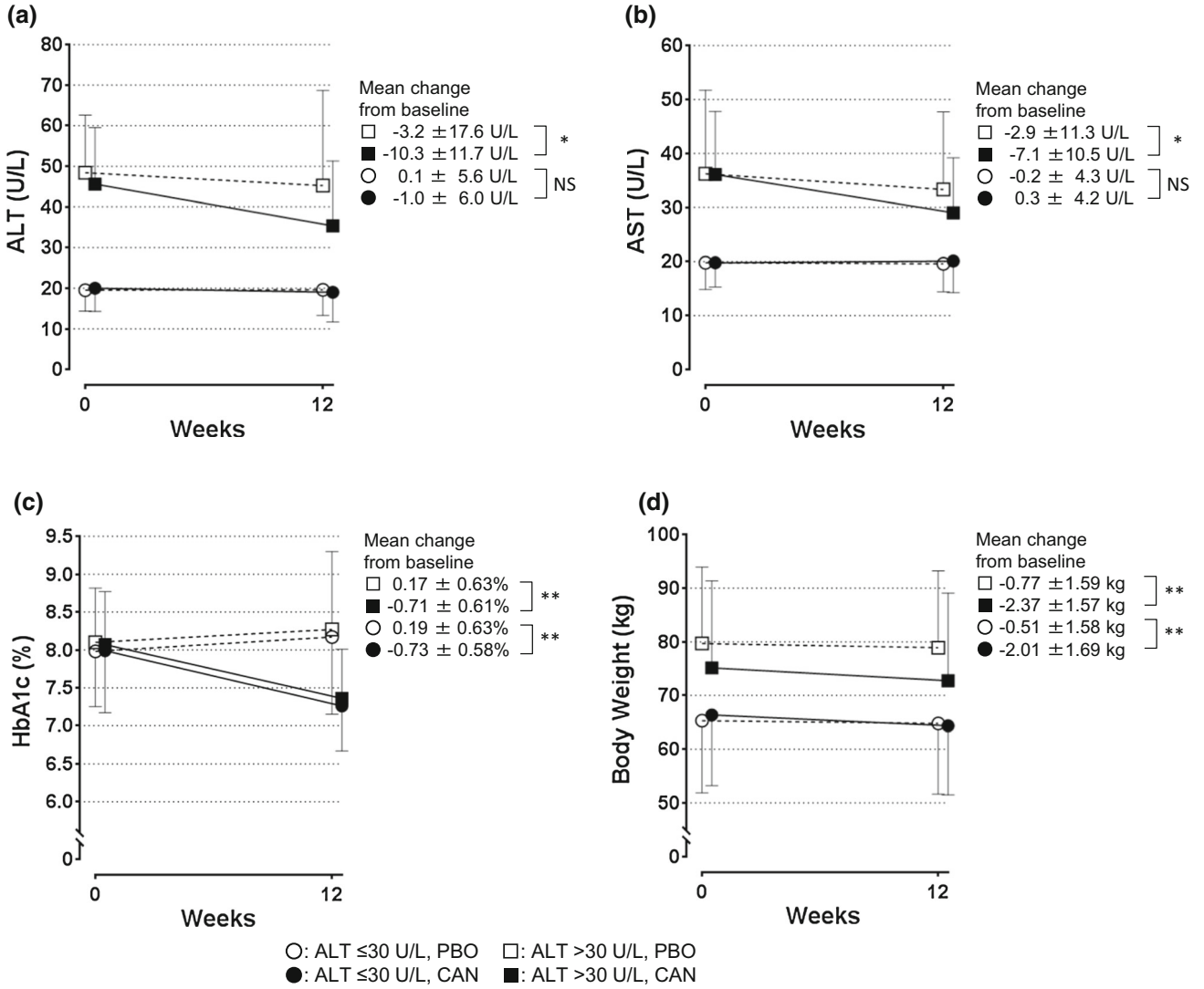

Fig. 1 Change in parameters after administration of canagliflozin (Study 1). ALT (**a**), AST (**b**), HbA1c (**c**), and body weight (**d**) at baseline and 12 weeks. Data are presented as mean ± SD. Low ALT subgroup (*unfilled circle* ALT ≤ 30 U/L; $n = 109$) and high ALT subgroup (*unfilled square*, ALT >30 U/L; $n = 59$) in the placebo group. Low ALT subgroup (*filled circle*, $n = 117$) and high ALT subgroup (*filled square*, $n = 47$) in the canagliflozin 100 mg group. An analysis of covariance by baseline value was performed for the change from before to after treatment for the comparison of the placebo and canagliflozin 100 mg groups. *$P < 0.05$; **$P < 0.0001$. *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *CAN* canagliflozin 100 mg; *HbA1c* glycosylated hemoglobin; *NS* not significant; *PBO* placebo

Study 2

Baseline characteristics

In the canagliflozin 100 mg group, the mean ± SD ALT at baseline was 49.1 ± 18.6 U/L in the high ALT subgroup and 19.3 ± 5.5 U/L in the low ALT subgroup. The AST and γ-GTP levels were both higher in the high ALT subgroup than in the low ALT subgroup. No clear difference in the platelet count was found between the subgroups. The mean ± SD HbA1c at baseline was 8.21 ± 0.91% in the high ALT subgroup and 7.97 ± 0.86% in the low ALT subgroup. The mean age was lower in the high ALT subgroup than in the low ALT subgroup (53.4 ± 10.5 vs. 59.6 ± 10.2 years). The proportion of men, the HOMA-IR, body weight, BMI, waist circumference, and the proportion of subjects with complications of hypertension or hyperlipidemia were higher in the high ALT subgroup (Table 3). The proportion of patients using thiazolidinedione in the low ALT subgroup was higher than that of the high ALT subgroup. Although the relationship between combination of thiazolidinedione and baseline ALT level was not clear, the beneficial effects of pioglitazone were reported in patients with NASH and type 2 diabetes [15].

Table 2 Adverse events (Study 1)

	ALT ≤30 U/L		ALT >30 U/L	
	Placebo ($n = 109$)	Canagliflozin ($n = 117$)	Placebo ($n = 59$)	Canagliflozin ($n = 47$)
Any AE	47 (43.1)	69 (59.0)	30 (50.8)	23 (48.9)
AEs related to study drug	9 (8.3)	28 (23.9)	7 (11.9)	9 (19.1)
Serious AE	0 (0.0)	1 (0.9)	1 (1.7)	0 (0.0)
Serious AEs related to study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation	0 (0.0)	3 (2.6)	2 (3.4)	0 (0.0)
AEs related to study drug leading to discontinuation	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs of special interest				
Hypoglycemia[a]				
Symptomatic hypoglycemia	1 (0.9)	1 (0.9)	0 (0.0)	3 (6.4)
Asymptomatic hypoglycemia	1 (0.9)	5 (4.3)	1 (1.7)	0 (0.0)
Genital infections, males	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Genital infections, females	0 (0.0)	2 (5.4)	0 (0.0)	1 (6.3)
Urinary tract infections	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Volume depletion-related AEs	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Osmotic diuresis-related AEs	2 (1.8)	3 (2.6)	1 (1.7)	3 (6.4)

Data are presented as *n* (%)

AEs adverse events, *ALT* alanine aminotransferase

[a] Symptomatic hypoglycemia: typical hypoglycemic symptoms were present irrespective of the blood glucose level. Asymptomatic hypoglycemia: typical hypoglycemic symptoms were absent but the blood glucose level was low (≤70 mg/dL)

Efficacy

In the high ALT subgroup, the administration of canagliflozin 100 mg resulted in improvement in liver function parameters (ALT, AST) starting from the early stages of treatment, and this improvement persisted through 52 weeks (Fig. 2a, b). The mean change in ALT level at 12 weeks was similar to that in the canagliflozin treatment group in the high ALT subgroup in Study 1.

At 52 weeks in the high ALT subgroup, the mean absolute and percent change ± SD in ALT from baseline was −16.0 ± 18.8 U/L (−30.0 ± 27.9%). The mean changes in AST and γ-GTP levels were −9.0 ± 14.1 and −28.2 ± 73.9 U/L, respectively (Suppl. 2). These changes were appreciably greater than those in the low ALT subgroup (ALT, AST, γ-GTP: 0.4 ± 27.8, 0.2 ± 7.4, and −3.6 ± 38.6 U/L, respectively). Neither the presence nor absence of the concomitant use of another antihyperglycemic drug with canagliflozin nor the type of concomitant drug used resulted in any clear differences in the ALT lowering effect of canagliflozin 100 mg in the high ALT subgroup (data not shown).

A reduction in ALT after the use of canagliflozin 100 mg was found in 88.7% of the subjects in the high ALT subgroup (Suppl. 3). In Study 2, a marked increase in ALT was observed at 28 weeks in one subject who discontinued canagliflozin due to jaundice and bile duct carcinoma. It was concluded by the investigator that this patient had been afflicted with bile duct carcinoma prior to enrollment in the study.

The HbA1c and body weight decreased in both subgroups, which persisted through 52 weeks (Fig. 2c, d). The HbA1c, fasting blood glucose, insulin, body weight, and waist circumference were all found to be significantly decreased in both ALT subgroups at 52 weeks (Suppl. 2). At 52 weeks, there were no clear changes in LDL-c levels in either subgroup. The HDL-c level was significantly increased in both subgroups (mean change ± SD from baseline at 52 weeks: 2.9 ± 7.3 and 5.0 ± 8.0 mg/dL in the high and low ALT subgroups, respectively; both $P < 0.0001$). The FFA level was slightly but significantly increased in both subgroups (mean change ± SD from baseline at 52 weeks: 0.075 ± 0.263 and 0.088 ± 0.231 mEq/L, respectively; both $P < 0.0001$). The TG level was not found to be significantly decreased in the high ALT subgroup (Suppl. 2).

Safety

The overall incidence of AEs in the canagliflozin 100 mg group was 80.0% (95% CI 73.7–85.4) and 82.3% (95% CI 78.1–85.9) in the high ALT and low ALT subgroups,

Table 3 Baseline characteristics (Study 2)

	Canagliflozin	
	ALT ≤30 U/L ($n = 389$)	ALT >30 U/L ($n = 195$)
Sex		
Male	265 (68.1)	156 (80.0)
Female	124 (31.9)	39 (20.0)
Age (years)	59.6 ± 10.2	53.4 ± 10.5
Duration of diabetes (years)	7.25 ± 6.38	4.85 ± 4.53
HbA1c (%)	7.97 ± 0.86	8.21 ± 0.91
Fasting glucose (mg/dL)[a]	154.4 ± 31.6	168.1 ± 40.5
Fasting insulin (μIU/mL)[a]	6.620 ± 4.658	12.761 ± 10.114
HOMA-IR[a]	2.54 ± 1.85	5.37 ± 4.92
Body weight (kg)	66.69 ± 13.22	77.94 ± 17.13
BMI (kg/m^2)	24.84 ± 3.90	27.98 ± 5.29
Waist circumference (cm)	88.74 ± 10.14	96.07 ± 11.99
ALT (U/L)	19.3 ± 5.5	49.1 ± 18.6
AST (U/L)	19.8 ± 4.5	36.3 ± 14.6
γ-GTP (U/L)	37.9 ± 28.9	92.9 ± 106.2
Platelet (×10^4/μL)[b]	23.53 ± 5.24	22.80 ± 5.68
eGFR (mL/min/1.73 m^2)	83.9 ± 16.9	87.5 ± 21.1
Monotherapy	89 (22.9)	38 (19.5)
Combination	300 (77.1)	157 (80.5)
Sulfonylurea	80 (26.7)	44 (28.0)
Glinide	39 (13.0)	26 (16.6)
α-glucosidase inhibitor	39 (13.0)	23 (14.6)
Biguanide	44 (14.7)	28 (17.8)
Thiazolidinedione	51 (17.0)	12 (7.6)
Dipeptidyl peptidase-4 inhibitors	47 (15.7)	24 (15.3)
Complications		
Hypertension	190 (48.8)	125 (64.1)
Hyperlipidemia	282 (72.5)	163 (83.6)
Hepatic steatosis, diagnosed	81 (20.8)	81 (41.5)

Data are presented as *n* (%), or mean ± SD

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycosylated hemoglobin, *HOMA-IR* homeostatic model assessment-insulin resistance, *γ-GTP* γ-glutamyl transpeptidase

[a] $n = 389$ and 194 in the low and high ALT subgroups, respectively

[b] $n = 381$ and 195 in the low and high ALT subgroups, respectively

respectively (Table 4). The incidences of AEs related to the study drug were 28.7% (95% CI 22.5–35.6) in the high ALT subgroup and 33.4% (95% CI 28.7–38.3) in the low ALT subgroup. There were no clear differences in the overall incidence of SAEs or SAEs related to the study drug between the two subgroups [SAEs: 4.6% (95% CI 2.1–8.6) in the high ALT subgroup, 5.4% (95% CI 3.4–8.1) in the low ALT subgroup; SAEs related to the study drug: 1.0% (95% CI 0.1–3.7) in the high ALT subgroup, 0.3% (95% CI 0.0–1.4) in the low ALT subgroup]. Although the incidences of AEs associated with symptomatic hypoglycemia, asymptomatic hypoglycemia, female genital infection, and osmotic diuresis were >5%, the incidences in the high ALT subgroup were similar to those in the low ALT subgroup. There was one hepatic AE related to the study drug in the low ALT subgroup only: hepatic function abnormal. Total ketone bodies were significantly increased (97.5 ± 265.2 and 158.9 ± 728.9 μmol/L in the high and low ALT subgroups, respectively; both $P < 0.0001$).

Analysis of modulating factors of the change in ALT

To investigate the subject characteristics and factors associated with the change in ALT levels induced by

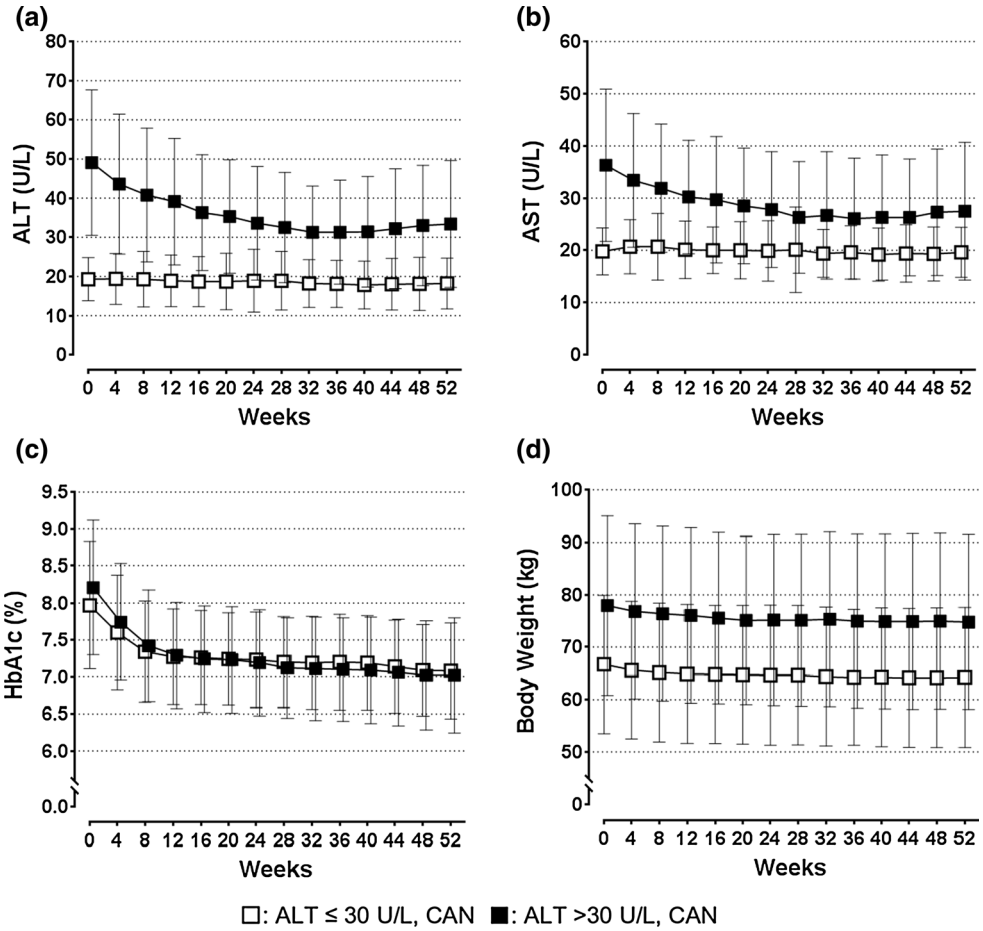

Fig. 2 Change in parameters through 52 weeks (Study 2). Change in ALT (**a**), AST (**b**), HbA1c (**c**), and body weight (**d**) over 52 weeks. Data are presented as mean ± SD. Low ALT subgroup (*unfilled square*, ALT ≤ 30 U/L; $n = 352$–389) and high ALT subgroup (*filled square* ALT >30 U/L; $n = 179$–195) in the canagliflozin 100 mg group. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CAN* canagliflozin 100 mg, *HbA1c* glycosylated hemoglobin

canagliflozin in the high ALT subgroup, correlation and multiple regression analyses were performed for the changes in ALT at 12 and 52 weeks. The results of the correlation analysis in the high ALT subgroup showed a negative correlation between the change in ALT and baseline ALT at both 12 weeks ($r = -0.605$, $P < 0.0001$) and 52 weeks ($r = -0.638$, $P < 0.0001$). The other parameters had low or no correlation with the change in ALT (Table 5). The results of the multiple regression analysis performed with change in ALT at 12 weeks and 52 as the dependent variable and the baseline values of each of the parameters as explanatory variables are shown in Suppl. 4. At 12 weeks, the baseline ALT and HOMA-IR were selected as explanatory variables ($R^2 = 38.3\%$). At 52 weeks, the baseline ALT, baseline HOMA-IR, and baseline LDL-c were selected as explanatory variables ($R^2 = 44.1\%$). From the multiple regression analysis with the change in related parameters containing baseline ALT as explanatory variables, baseline ALT, change in body weight, and change in LDL-c were identified as explanatory variables ($R^2 = 40.9\%$) at 12 weeks, and baseline ALT, change in HbA1c, change in body weight, change in LDL-c, and change in TG were selected as explanatory variables ($R^2 = 47.7\%$) at 52 weeks. In all regression analyses, the baseline ALT accounted for most of the effect, and the contribution of the other variables was small (partial $R^2 = 1.3$–2.4%, Suppl. 4).

Discussion

The present post hoc analysis was performed using the data from Japanese phase 2 and 3 studies of canagliflozin, and the results revealed that canagliflozin improved hepatic function tests in type 2 diabetes mellitus patients with high ALT levels. This effect persisted through 52 weeks. The incidence of AEs or SAEs in the high ALT subgroup in the canagliflozin treatment group was comparable to that of the placebo group and the low ALT subgroup. The results of correlation analysis and multiple regression analysis showed that the baseline ALT was the main influencing factor of the change in ALT.

It was confirmed that in patients with high ALT levels, canagliflozin not only lowers blood glucose levels, body weight, and insulin levels, but also lowers the levels of liver function parameters such as ALT, AST, and γ-GTP.

Table 4 Adverse events (Study 2)

	Canagliflozin	
	ALT ≤30 U/L (n = 389)	ALT >30 U/L (n = 195)
Any AE	320 (82.3)	156 (80.0)
AEs related to study drug	130 (33.4)	56 (28.7)
Serious AE	21 (5.4)	9 (4.6)
Serious AEs related to study drug	1 (0.3)	2 (1.0)
AEs leading to discontinuation	16 (4.1)	4 (2.1)
AEs related to study drug leading to discontinuation	8 (2.1)	2 (1.0)
Deaths	1 (0.3)	1 (0.5)
AEs of special interest		
Hypoglycemia[a]		
Symptomatic hypoglycemia	30 (7.7)	14 (7.2)
Asymptomatic hypoglycemia	41 (10.5)	13 (6.7)
Genital infections (male)	2 (0.8)	1 (0.6)
Genital infections (female)	10 (8.1)	4 (10.3)
Urinary tract infections	17 (4.4)	2 (1.0)
Volume depletion-related AEs	5 (1.3)	1 (0.5)
Osmotic diuresis-related AEs	22 (5.7)	13 (6.7)

Data are presented as n (%)

AEs adverse events, *ALT* alanine aminotransferase

[a] Symptomatic hypoglycemia: typical hypoglycemic symptoms were present irrespective of the blood glucose level. Asymptomatic hypoglycemia: typical hypoglycemic symptoms were absent but the blood glucose level was low (≤70 mg/dL)

To inhibit the progression of NAFLD, it is important to control body weight, HbA1c, and ALT levels [23, 25]. Seko et al. reported that a reduction of 30% or more in the baseline ALT level was associated with amelioration of the NAFLD activity score and progression of liver fibrosis in NAFLD patients [22]. In Study 2 of the present post hoc analysis, the ALT level decreased by approximately 30% by canagliflozin in the high ALT subgroup at 52 weeks. Furthermore, SGLT2 inhibitors have been reported to inhibit the progression of fibrosis or decrease serum ALT levels in NASH and diabetic mouse models, as well as type 2 diabetes mellitus patients with NAFLD [18, 26–29]. Collectively, the results of the present analysis suggest that treatment with SGLT2 inhibitors may provide a clinical benefit to type 2 diabetes mellitus patients with NAFLD.

Obesity, insulin resistance, and enhanced expression of inflammatory adipocytokines, such as IL-6 and TNFα, in adipose tissue are among the factors associated with NAFLD as suggested by the two-hit theory [12, 13] and the multiple parallel hits hypothesis [14]. SGLT2 inhibitors have been reported to reduce abdominal visceral fat [17], improve insulin sensitivity [30], and suppress the genetic expression of inflammatory markers in the liver of mice fed a high-fat diet [27]. In our study, body weight, waist circumference, and fasting insulin level were significantly reduced in the canagliflozin 100 mg group, which suggests abdominal visceral fat reduction and improvement of insulin sensitivity. Hence, the body weight lowering effect and the subsequent improvement of insulin resistance and expression of inflammatory adipocytokines by canagliflozin treatment may result in the improvement of liver function.

Leiter et al. reported that the liver function improving effects of canagliflozin were related to decreases in blood glucose levels and body weight [21]. In contrast, Komiya et al. reported that the decrease in ALT by 24-weeks administration of ipragliflozin in type 2 diabetes patients with impaired hepatic function did not depend on the decrease in body weight [27]. The results of our multiple regression analysis between the subject characteristics or the change in related factors and the change in ALT level at 12 and 52 weeks by canagliflozin suggested that the baseline ALT value was the main explanatory factor for the ALT lowering effect of canagliflozin. These results indicate that canagliflozin further lowered ALT in patients with higher baseline ALT values. The change in body weight was identified as one of the explanatory factors for the change in ALT at 12 and 52 weeks. These results support the liver function improving mechanisms of SGLT2 inhibitors through the body weight lowering effect, which were hypothesized above and reported by Leiter et al. However, there were some parameters for which the underlying

Table 5 Relationship between the change in ALT after the administration of canagliflozin and various parameters in the high ALT subgroup (Study 2)

Parameters	*n*	Change in ALT from baseline (Pearson's correlation coefficient)			
		12 weeks		52 weeks	
		r	*P*	*r*	*P*
Baseline					
Age	195	0.063	0.3834	0.114	0.1131
HbA1c	195	−0.030	0.6820	0.005	0.9400
Fasting glucose	194	−0.025	0.7249	−0.014	0.8473
Fasting insulin	194	0.016	0.8295	−0.013	0.8521
HOMA-IR	194	0.015	0.8336	−0.018	0.8059
Body weight	195	−0.045	0.5334	−0.034	0.6321
BMI	195	−0.054	0.4510	−0.029	0.6872
Waist circumference	195	−0.042	0.5601	−0.027	0.7123
ALT	**195**	**−0.605**	**<0.0001**	**−0.638**	**<0.0001**
HDL-c	195	−0.012	0.8647	0.048	0.5067
LDL-c	195	−0.063	0.3809	−0.149	0.0378
TG	194	−0.061	0.3990	−0.097	0.1798
FFA	194	−0.047	0.5183	0.034	0.6381
Platelet	195	−0.093	0.1943	−0.170	0.0172
Uric acid	195	0.040	0.5812	0.060	0.4008
Total ketone bodies	195	−0.015	0.8355	0.068	0.3476
Change from baseline at 12 weeks or 52 weeks[a]					
HbA1c	195	0.145	0.0437	0.210	0.0032
Fasting glucose	194	0.111	0.1245	0.111	0.1243
Fasting insulin	192, 194	−0.027	0.7128	−0.042	0.5572
Body weight	195	0.200	0.0050	0.147	0.0407
BMI	195	0.199	0.0054	0.143	0.0455
Waist circumference	195	0.133	0.0643	0.142	0.0470
HDL-c	195	0.180	0.0120	0.086	0.2335
LDL-c	195	0.206	0.0039	0.170	0.0174
TG	194	0.004	0.9588	0.100	0.1634
FFA	194	0.188	0.0088	0.219	0.0022
Platelet	195	−0.149	0.0373	−0.106	0.1396
Uric acid	195	0.081	0.2577	0.101	0.1604
Total ketone bodies	195	0.058	0.4196	0.127	0.0769

[a] Data for analysis were matched to the same weeks

ALT alanine aminotransferase, *BMI* body mass index, *FFA* free fatty acid, *HbA1c* glycosylated hemoglobin, *HDL-c* high-density lipoprotein cholesterol, *HOMA-IR* homeostatic model assessment-insulin resistance, *LDL-c* low-density lipoprotein cholesterol, *TG* triglyceride

Bold texts indicate the most highly correlated parameter in each week

mechanisms explaining the relationship with the change in ALT remain unclear. Except for the baseline ALT value, the contributions of the parameters identified as the explanatory factors for the change in ALT were small in the multiple regression analysis. These results may derive from other unknown mechanisms.

In Studies 1 and 2, the incidence of AEs or SAEs in the high ALT subgroup in the canagliflozin treatment group was similar to that of the placebo group and the low ALT subgroup. Consistent with previous reports [31, 32], the incidences of genital infection and osmotic diuresis were higher in the canagliflozin 100 mg group. The increase of free fatty acids and ketone bodies were observed in the canagliflozin 100 mg group, probably due to enhance lipolysis in adipose tissue and hepatic ketogenesis that is attributed to energy loss by urinary glucose excretion [33].

The present study has some limitations. In this analysis, impaired liver function was defined as ALT >30 U/L. Patients

with ALT or AST >2.5 × ULN, serious liver disease, or a history of hepatitis B or hepatitis C infection were excluded from this analysis. In addition, patients did not always have a confirmed NAFLD diagnosis [2] because histological diagnosis by liver biopsy or ultrasonography was not always performed for all patients in the high ALT subgroup. Furthermore, the amount of alcohol intake was not regulated in patients in this study. In the high ALT subgroup, the mean platelet count value, a marker of liver fibrosis, was in the normal range at baseline. In the future, it will be necessary to conduct a more detailed investigation in patients with confirmed diagnoses of NAFLD.

In conclusion, the results of this post hoc analysis suggest that in type 2 diabetes mellitus patients with impaired liver function, such as those with NAFLD, canagliflozin may improve liver function, reduce both HbA1c and body weight, and also be well tolerated.

Acknowledgements The authors wish to thank Michelle Belanger, MD, on behalf of Springer Healthcare Communications for providing medical writing assistance, which was funded by Mitsubishi Tanabe Pharma Corporation. The authors thank Ms. Nobuko Maruyama and Mr. Chikao Ishikawa for insightful discussions. The authors thank all investigators, study team, and patients for participating in this study, as listed in Suppl. 5.

Compliance with ethical standards

Conflict of interest K Sasaki, H. Iijima, T. Hashimoto, and S. Ishii are employees of Mitsubishi Tanabe Pharma Corporation.; Y. Sumida received lecture fees from Mitsubishi Tanabe Pharma Corporation; Y. Itoh received research grants from MSD K. K., Otsuka Pharmaceutical Co., Ltd, Astellas Pharma Inc., Eisai Co., Ltd and Bristol-Myers Squibb, and received lecture fees from Bristol-Myers Squibb.; N Inagaki received research grants/scholarship grants from Mitsubishi Tanabe Pharma Corporation, MSD K. K., Eli Lilly Japan K. K., Roche Diagnostics K.K., Shiratori Pharmaceutical Co., Ltd., Astellas Pharma Inc., Sanofi K. K., Takeda Pharmaceutical Co., Ltd, Japan Tobacco Inc., Nippon Boehringer Ingelheim Co., Ltd., AstraZeneca K.K., Kyowa Hakko Kirin Co., Ltd., Daiichi Sankyo Company, Ltd., Sumitomo Dainippon Pharma Co., Ltd, Ono Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Pfizer Japan Inc., and Taisho Toyama Pharmaceutical Co., Ltd., and received lecture fees from Nippon Boehringer Ingelheim Co., Ltd.. The clinical studies were funded by Mitsubishi Tanabe Pharma Corp. N. Inagaki has received consulting fees for Mitsubishi Tanabe Pharma Corp with regard to the clinical studies. Y. Seko, Y. Sumida, Y. Itoh, and N. Inagaki have not received honoraria from Mitsubishi Tanabe Pharma Corp for writing promotional material with regard to this manuscript.

Funding This post hoc analysis was funded by Mitsubishi Tanabe Pharma Corporation. The article processing charges and open access fee for this publication were funded by Mitsubishi Tanabe Pharma Corp.

References

1. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012;55:2005–23.
2. Watanabe S, Hashimoto E, Ikejima K, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. J Gastroenterol. 2015;50:364–77.
3. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274–85.
4. Leite NC, Salles GF, Araujo AL, et al. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. Liver Int. 2009;29:113–9.
5. Jimba S, Nakagami T, Takahashi M, et al. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med. 2005;22:1141–5.
6. Reid AE. Nonalcoholic steatohepatitis. Gastroenterology. 2001;121:710–23.
7. Nakahara T, Hyogo H, Yoneda M, et al. Type 2 diabetes mellitus is associated with the fibrosis severity in patients with nonalcoholic fatty liver disease in a large retrospective cohort of Japanese patients. J Gastroenterol. 2014;49:1477–84.
8. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011;140:124–31.
9. Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med. 1999;107:450–5.
10. Eguchi Y, Eguchi T, Mizuta T, et al. Visceral fat accumulation and insulin resistance are important factors in nonalcoholic fatty liver disease. J Gastroenterol. 2006;41:462–9.
11. Koda M, Kawakami M, Murawaki Y, et al. The impact of visceral fat in nonalcoholic fatty liver disease: cross-sectional and longitudinal studies. J Gastroenterol. 2007;42:897–903.
12. Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology. 1998;114:842–5.
13. Day CP. Pathogenesis of steatohepatitis. Best Pract Res Clin Gastroenterol. 2002;16:663–78.
14. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology. 2010;52:1836–46.
15. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or Type 2 diabetes mellitus: a randomized, controlled trial. Ann Intern Med. 2016;165(5):305–15.
16. Inagaki N, Kondo K, Yoshinari T, et al. Efficacy and safety of canagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled. Phase III study. Expert Opin Pharmacother. 2014;15:1501–15.
17. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013;382:941–50.
18. Honda Y, Imajo K, Kato T, et al. The selective SGLT2 inhibitor ipragliflozin has a therapeutic effect on nonalcoholic steatohepatitis in mice. PLoS One. 2016;11:e0146337.

19. Inagaki N, Kondo K, Yoshinari T, et al. Efficacy and safety of canagliflozin alone or as add-on to other oral antihyperglycemic drugs in Japanese patients with type 2 diabetes: a 52-week open-label study. J Diabetes Investig. 2015;6:210–8.
20. Inagaki N, Goda M, Yokota S, et al. Safety and efficacy of canagliflozin in Japanese patients with type 2 diabetes mellitus: post hoc subgroup analyses according to body mass index in a 52-week open-label study. Expert Opin Pharmacother. 2015;16:1577–91.
21. Leiter LA, Forst T, Polidori D, et al. Effect of canagliflozin on liver function tests in patients with type 2 diabetes. Diabetes Metab. 2016;42:25–32.
22. Seko Y, Sumida Y, Tanaka S, et al. Serum alanine aminotransferase predicts the histological course of non-alcoholic steatohepatitis in Japanese patients. Hepatol Res. 2015;45:E53–61.
23. Ballestri S, Nascimbeni F, Romagnoli D, et al. The independent predictors of NASH and its individual histological features. Insulin resistance, serum uric acid, metabolic syndrome, ALT and serum total cholesterol are a clue to pathogenesis and candidate targets for treatment. Hepatol Res. 2016;46(11):1074–87.
24. Inagaki N, Kondo K, Yoshinari T, et al. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab. 2013;15(12):1136–45.
25. Vilar-Gomez E, Yasells-Garcia A, Martinez-Perez Y, et al. Development and validation of a noninvasive prediction model for nonalcoholic steatohepatitis resolution after lifestyle intervention. Hepatology. 2016;63:1875–87.
26. Nishimura N, Kitade M, Noguchi R, et al. Ipragliflozin, a sodium-glucose cotransporter 2 inhibitor, ameliorates the development of liver fibrosis in diabetic Otsuka Long-Evans Tokushima fatty rats. J Gastroenterol. 2016;51(12):1141–9.
27. Komiya C, Tsuchiya K, Shiba K, et al. Ipragliflozin improves hepatic steatosis in obese mice and liver dysfunction in Type 2 diabetic patients irrespective of body weight reduction. PLoS One. 2016;11:e0151511.
28. Ohki T, Isogawa A, Toda N, et al. Effectiveness of ipragliflozin, a sodium-glucose co-transporter 2 inhibitor, as a second-line treatment for non-alcoholic fatty liver disease patients with Type 2 diabetes mellitus who do not respond to incretin-based therapies including glucagon-like peptide-1 analogs and dipeptidyl peptidase-4 inhibitors. Clin Drug Investig. 2016;36(4):313–9.
29. Hayashizaki-Someya Y, Kurosaki E, Takasu T, et al. Ipragliflozin, an SGLT2 inhibitor, exhibits a prophylactic effect on hepatic steatosis and fibrosis induced by choline-deficient l-amino acid-defined diet in rats. Eur J Pharmacol. 2015;754:19–24.
30. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest. 2014;124(2):509–14.
31. Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. Trends Pharmacol Sci. 2011;32:63–71.
32. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159:262–74.
33. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab. 2015;100:2849–52.