JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Favorable effect of sodium–glucose cotransporter 2 inhibitor, dapagliflozin, on non-alcoholic fatty liver disease compared with pioglitazone

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Keywords
Fatty liver, Sodium–glucose cotransporter 2 inhibitor, Type 2 diabetes

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J Diabetes Investig 2021; 12: 1272–1277

doi: 10.1111/jdi.13457

Clinical Trial Registry
University Hospital Medical Information Network Center Clinical Trials Registry
UMIN000022804

ABSTRACT

Aims/Introduction: Sodium–glucose cotransporter 2 inhibitors, as well as thiazolidines, suppress nonalcoholic fatty liver disease (NAFLD); however, few comparative studies have been reported. Dapagliflozin has shown non-inferiority compared with pioglitazone for glycemic control, and superiority regarding weight reduction in patients with type 2 diabetes. We carried out a secondary analysis for the favorable effects of sodium–glucose cotransporter inhibitors for NAFLD.

Materials and Methods: In this multicenter, open-label, prospective, randomized, parallel-group comparison trial, patients taking pioglitazone for ≥12 weeks were randomly switched to dapagliflozin or continued pioglitazone for a further 24 weeks. The fatty liver index (FLI), consisting of body mass index, triglycerides, waist circumference and γ-glutamyl transpeptidase, was used for the evaluation of NAFLD.

Results: A total of 53 participants with NAFLD (27 dapagliflozin; 26 pioglitazone) were included in this analysis. FLI decreased significantly in the dapagliflozin group (48.7 ± 23.4 to 42.1 ± 23.9) compared with the pioglitazone group (49.0 ± 26.1 to 51.1 ± 25.8; $P < 0.01$). Multiple linear regression analysis showed that the changes in FLI had a significantly positive correlation with changes in glycated hemoglobin ($P = 0.03$) and insulin level ($P < 0.01$) in the dapagliflozin group.

Conclusion: Dapagliflozin might be more beneficial than pioglitazone in patients with NAFLD. Improvements in FLI would be closely related to glycemic control.

INTRODUCTION

Diabetes treatments aim to extend life expectancy and improve patient quality of life by suppressing the onset and progression of diabetic complications. Although macro- and microvascular diseases are the main targets of prevention, non-alcoholic fatty liver disease (NAFLD) is also a common and clinically significant complication. NAFLD includes non-alcoholic fatty liver, which refers to steatosis affecting hepatocytes, and non-alcoholic steatohepatitis, mainly involving inflammation and fibrosis, and might progress ultimately to cirrhosis and hepatocellular carcinoma[1]. In addition to various disorders, including hypertension, dyslipidemia and metabolic syndrome, suggested as related etiological factors of NAFLD, insulin resistance based on hyperinsulinemia also requires appropriate therapeutic interventions[2]. Type 2 diabetes frequently coexists with NAFLD, and is an independent risk factor for the development of cirrhosis and liver cancer[3,4]. The thiazolidine, pioglitazone (PIO), has been shown to be a useful treatment for NAFLD in patients with type 2 diabetes, and has been widely used to improve insulin resistance and NAFLD[5]. Sodium–glucose cotransporter 2 (SGLT2) inhibitors have also recently been

Received 10 September 2020; revised 21 October 2020; accepted 30 October 2020

reported to improve NAFLD[5–8]; however, their efficacy in NAFLD has not been proven in large-scale, placebo-controlled studies, and few comparative studies with other antidiabetic drugs have been reported. We recently determined the non-inferiority of dapagliflozin (DAP) for glycemic control, and superiority in terms of weight reduction compared with PIO in patients with type 2 diabetes[9]; bodyweight was dramatically reduced (−4.2 kg in 24 weeks) by switching from PIO to DAP. In the current study, we aimed to compare the efficacies of DAP and PIO in patients with NAFLD.

METHODS

Study overview

The present study was a secondary analysis of our original multicenter, open-label, prospective, randomized, parallel-group comparison trial[9]. All patients provided written informed consent before enrollment. The detailed rationale and protocol of the original trial have been described previously[9], and are summarized below. Eligible participants included patients with type 2 diabetes mellitus, aged 20–80 years, 6.5–8.5% of glycated hemoglobin (HbA1c), ≥23 kg/m^2 of body mass index (BMI), estimated glomerular filtration rate ≥45 mL/min/1.73 m^2 and treatment with PIO for >12 weeks undergoing outpatient treatment at seven sites in Hokkaido, Japan. Patients continued with PIO or were switched to DAP for 24 weeks.

Patients who were habitual drinkers were excluded from this secondary analysis. The extent of fatty liver was estimated using the fatty liver index (FLI), consisting of BMI, triglycerides (TG), waist circumference (WC) and γ-glutamyl transpeptidase (γ-GTP), using the following equation: FLI = {exp (0.953 × log (TG) + 0.139 × BMI + 0.718 × log (γ-GTP) + 0.053 × WC − 15.745) / 1 + exp (0.953 × log (TG) + 0.139 × BMI + 0.718 × log (γ-GTP) + 0.053 × WC − 15.745)} × 100[10]. Participants with an FLI <30 were excluded from the analysis, because FLI <30 can be used to rule out hepatic steatosis. The Fibrosis-4 (FIB-4) index, as a marker of hepatic fibrosis, was derived as follows: FIB-4 = age × (aspartate aminotransferase [AST]) / (platelet count × [alanine aminotransferase (ALT)]$^{1/2}$)[11]

The present study was registered with the University Hospital Medical Information Network Center Clinical Trials Registry (UMIN000022804), and the protocol was approved by the institutional review board at Hokkaido University Hospital Clinical Research and Medical Innovation Center (016-0042). The study was carried out in accordance with the Declaration of Helsinki and its amendments.

Statistical analysis

The results are expressed as the mean ± standard deviation, median (range) or number (%). Differences in baseline characteristics between the two groups were evaluated using unpaired *t*-tests or Mann–Whitney *U*-tests for continuous variables, and χ^2-tests or Fisher's exact tests for categorical variables. Correlation coefficients and simple linear regression analyses were used to test for associations between variables. Multivariate analyses were carried out using multiple linear regression to identify factors independently associated with the outcomes. FLI components and their related factors (bodyweight, TG, WC and γ-GTP) were excluded from the multiple linear regression analysis. The results within each group were compared by paired-sample *t*-tests or Wilcoxon's signed-rank tests. Data were analyzed using JMP Pro v14.1.1 software (SAS Institute, Cary, NC, USA), and values of $P < 0.05$ were considered statistically significant.

RESULTS

Characteristics of the participants

A total of 71 patients were randomly assigned to the DAP group ($n = 36$) or PIO group ($n = 35$). All participants had completed the original randomized, controlled trial and their baseline characteristics have been reported previously[9]. Five patients in the DAP group and two patients in the PIO group were excluded from the present analysis because of habitual drinking, and four patients in the DAP group and seven patients in the PIO group were excluded because their FLI was <30. A total of 27 patients were finally included in the DAP group and 26 in the PIO group (Figure 1). There was no significant difference in baseline patient characteristics, including lipid profiles and liver enzymes, between the two groups. However, bodyweight and plasma insulin levels after 24 weeks decreased significantly more in the DAP group compared with the PIO group (Table 1). Only one patient in the DAP group had a decreased sulfonylurea dose during follow up, but the change was not significant.

Changes in FLI and identification of independent predictors

FLI decreased significantly more in the DAP group (58.3 ± 18.3 to 48.8 ± 19.5) compared with the PIO group (58.4 ± 20.6 to 61.2 ± 20.8) after 24 weeks ($P < 0.01$;

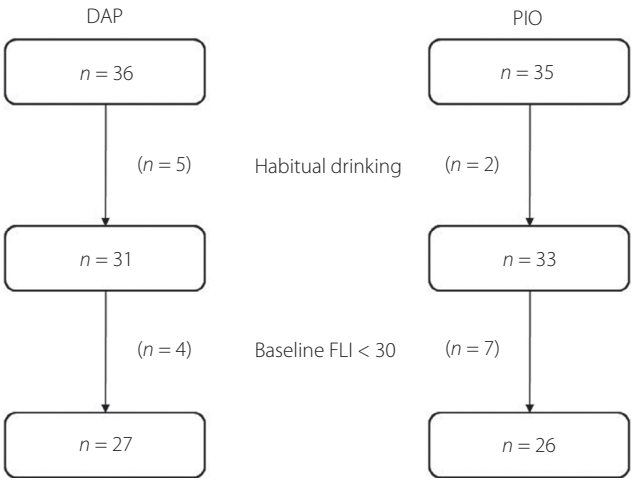

Figure 1 | Flow chart of study participants in this analysis. DAP, dapagliflozin; FLI, fatty liver index; PIO, pioglitazone.

Table 1 | Clinical characteristics and variables in patients treated with dapagliflozin and pioglitazone

	DAP (n = 27)		PIO (n = 26)		P
Age (years)	63.5 ± 7.1		63.4 ± 10.2		0.96
Male, n (%)	15 (55.6)		13 (50.0)		0.59
	0W	24W	0W	24W	
Bodyweight (kg)	75.1 ± 15.8	70.9 ± 16.0**	74.6 ± 13.8	75.1 ± 14.1	<0.01
WC (cm)	99.3 ± 7.9	95.8 ± 8.2**	101.5 ± 8.6	102.4 ± 10.0	0.02
FPG (mmol/L)	7.2 ± 1.2	7.3 ± 1.3	7.0 ± 1.1	7.4 ± 1.4	0.82
HbA1c (%)	6.8 ± 0.6	7.0 ± 0.8	6.9 ± 0.7	7.1 ± 0.8	0.58
Insulin (μIU/mL)	5.8 (3.6–7.0)	5.5 (4.0–6.9)	5.0 (3.3–6.6)	5.6 (4.1–8.5)*	0.02
TC (mg/dL)	175.5 (150.8–199.8)	182.0 (165.3–199.3)	168.5 (151.8–196.0)	175.5 (158.0–193.5)	0.78
LDL-C (mg/dL)	95.5 (82.8–104.0)	97.0 (83.3–12.0)	90.5 (78.5–112.3)	96.0 (81.8–106.3)	0.71
HDL-C (mg/dL)	56.0 (48.8–69.3)	54.0 (46.8–68.8)	54.5 (47.0–65.0)	55.0 (46.8–64.5)	0.53
TG (mg/dL)	108.0 (77.3–134.8)	104.5 (79.8–151.0)	94.5 (58.3–151.3)	103.0 (77.5–164.0)	0.72
AST (IU/L)	23.0 ± 12.0	21.4 ± 10.6	23.6 ± 6.9	23.2 ± 6.5	0.25
ALT (IU/L)	23.1 ± 14.1	21.3 ± 12.4	23.7 ± 12.2	22.3 ± 10.5	0.83
γ-GTP (IU/L)	25.9 ± 15.5	25.2 ± 10.6	23.8 ± 11.2	24.1 ± 11.9	0.48

P-value: mean changes from baseline of the study (0W) to 24 weeks (end of the study; 24W) between the dapagliflozin (DAP) and pioglitazone (PIO) groups, unpaired *t*-tests or Mann–Whitney *U*-tests. **P* < 0.05 and ***P* < 0.01 between 0W to 24W, paired *t*-tests or Wilcoxon's signed rank test. γ-GTP, γ-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Figure 2). Changes in FLI in the DAP group were significantly positively correlated with changes in HbA1c, insulin, homeostasis model assessment as an index of insulin resistance and total cholesterol, whereas changes in the PIO group were positively correlated with changes in ALT and negatively correlated with changes in high-density lipoprotein (HDL)-cholesterol (Table 2). Furthermore, multiple linear regression analysis showed that changes in HbA1c and insulin were significantly positively correlated with changes in FLI in the DAP group (Table 3), but the relationships with ALT and HDL in the PIO group were no longer significant. The FIB-4 index was significantly decreased in the DAP group (1.37 ± 0.59 to 1.20 ± 0.50) compared with the PIO group (1.32 ± 0.50 to 1.35 ± 0.52; $P < 0.01$; Figure 3). Furthermore, there were no predictors for changes in the FIB-4 index. The change in the aspartate aminotransferase : ALT ratio showed no difference between the two groups (DAP, 1.09 ± 0.33–1.09 ± 0.35; PIO, 1.09 ± 0.31–1.14 ± 0.32).

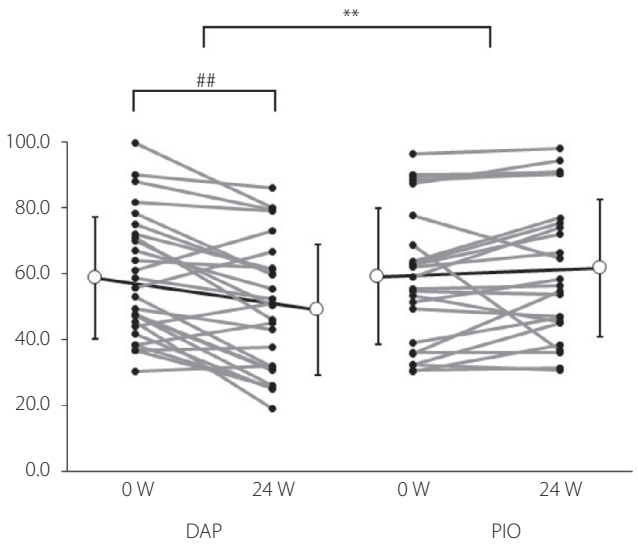

Figure 2 | Changes in fatty liver index between 0 and 24 weeks. White circles are the mean ± standard deviation. ***P* < 0.01 between the dapagliflozin (DAP) and pioglitazone (PIO) groups, unpaired *t*-tests; ##*P* < 0.01 between 0 and 24 weeks in each group, paired *t*-tests. 0W, baseline of the study; 24W, 24 weeks (end of the study).

DISCUSSION

This secondary analysis of our previous randomized, controlled trial showed that DAP ameliorated FLI, as a surrogate measure for fatty liver, compared with PIO in patients with type 2 diabetes complicated by NAFLD. The change in FLI in patients treated with DAP was significantly positively correlated with changes in insulin and HbA1c, in accordance with previous reports[6,7]. Elevated plasma glucose and insulin levels promote fatty acid synthesis, and influence the development of hepatic steatosis[12]. DAP is a rational treatment for improving hepatic steatosis by improving glucose metabolism and reducing hepatic lipogenesis, related to lower insulin levels. In addition to improving glycemic control and hyperinsulinemia, SGLT2 inhibitors can also slow or even reverse the progression of NAFLD as a result of their beneficial effects on insulin resistance through weight loss, especially visceral fat[13], associated

Table 2 | Relationships between changes in fatty liver index and clinical parameters

	DAP		PIO	
	Correlation coefficient	*P*	Correlation coefficient	*P*
ΔFPG	0.0586	0.74	0.1867	0.31
ΔHbA1c	0.3493	0.04	0.2569	0.16
ΔInsulin	0.4244	0.03	0.0379	0.85
ΔHOMA-IR	0.4237	0.03	0.0287	0.89
ΔTC	0.3590	0.04	0.0872	0.64
ΔHDL-C	−0.1238	0.49	−0.3877	0.03
ΔLDL-C	0.1075	0.55	0.0541	0.77
ΔAST	0.0114	0.95	0.1510	0.41
ΔALT	0.1872	0.29	0.3647	0.04

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAP, dapagliflozin; PG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment as an index of insulin resistance; LDL-C, low density lipoprotein-cholesterol; PIO, pioglitazone; TC, total cholesterol.

Table 3 | Relationships between changes in fatty liver index and clinical parameters in the dapagliflozin group according to multiple linear regression analysis

	Regression coefficients	95% CI	*P*
ΔInsulin	1.31	0.38, 2.14	<0.01
ΔHbA1c	7.32	0.38, 4.26	0.03
ΔTC	0.02	−0.15, 0.19	0.86

Multiple linear regression was adjusted for age, sex, insulin, glycated hemoglobin (HbA1c) and total cholesterol (TC). 95% CI, 95% confidence interval.

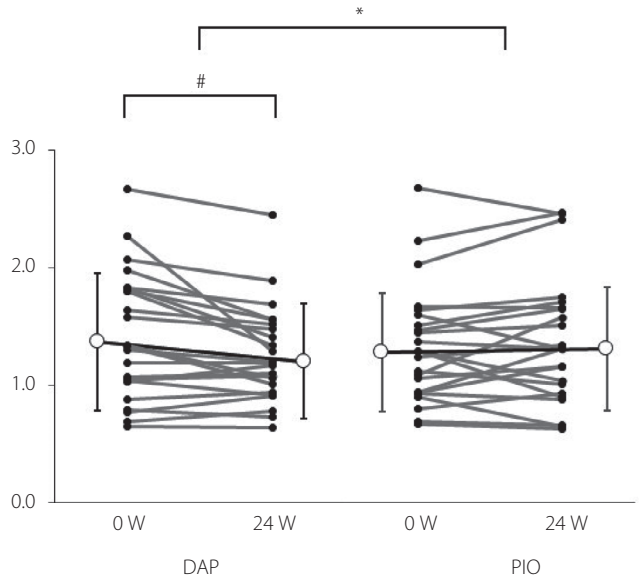

Figure 3 | Changes in the Fibrosis 4 index between 0 and 24 weeks. White circles are the mean ± standard deviation. **P* < 0.05 between the dapagliflozin (DAP) and pioglitazone (PIO)groups, unpaired *t*-tests; #*P* < 0.05 between 0 and 24 weeks in each group, paired *t*-tests. 0W, baseline of the study; 24W, 24 weeks (end of the study).

with hepatic inflammation leading to exacerbation of NAFLD[14].

Furthermore, DAP improved the FIB-4 index, as a marker of liver fibrosis. PIO was shown to improve fibrosis in a rodent model and meta-analysis; however, the Pioglitazone, Vitamin E or Placebo of Non-Alcoholic Steatohepatitis (PIVENS) trial, which was the first to show a convincing histological benefit in patients with non-alcoholic steatohepatitis, did not show any improvement of fibrosis in patients treated with PIO[15,16]. In contrast, SGLT2 inhibitors improved hepatic fibrosis in terms of both pathological examination[17] and surrogate markers[8]. The mechanism of SGLT2 inhibitors, which improves liver fibrosis, has not been fully elucidated. However, there is histological evidence that treatment with SGLT2 inhibitors improves liver fibrosis in mouse models of non-alcoholic steatohepatitis and diabetes, which suggests that administration of SGLT2 inhibitors prevents the progression of liver fibrosis by reducing inflammation in the liver[18]. SGLT2 inhibitors have thus been suggested to improve a wider range of NAFLD characteristics, including fibrosis and inflammation.

Only one previous study has compared the efficacies of SGLT2 inhibitors and PIO on NAFLD in patients with type 2 diabetes[19]. In that report, ipragliflozin exerted similar beneficial effects to PIO, based on the liver : spleen attenuation ratio on computed tomography. The apparent discrepancy between these and the current results might be caused by differences in the study designs and evaluation methods. The previous study started both medications additively at the same time, whereas the present study switched from PIO to DAP, and NAFLD in our participants was therefore likely to have been improved to some extent by PIO before the start of the study. Interestingly, the previous study reported that the marked improvement in serum adiponectin levels produced by PIO ameliorated NAFLD[19]. Adiponectin decreases hepatic and systematic insulin resistance, and attenuates liver inflammation and fibrosis[20]. In the PIO group of this study, improved FLI was associated with elevated HDL. Adiponectin increases HDL cholesterol by promoting reverse transport of cholesterol. The association of the changes in HDL and NAFLD might suggest the involvement of adiponectin[21]. The main mechanism underlying the amelioration of NAFLD by SGLT2 inhibitors is probably due to lower circulating glucose and insulin levels; however, adiponectin might also be involved, given that bodyweight was reduced in the DAP group, and SGLT2 inhibitors have been reported to increase adiponectin levels[22,23]. Unfortunately, we did not have a chance to measure adiponectin during this study, and the relationship therefore was not investigated.

The present analysis had two main limitations. It was a secondary analysis and might therefore have lacked statistical strength. However, approximately 75% of the participants from the original randomized, controlled trial were included in this analysis, and their backgrounds were matched. In addition, NAFLD was evaluated indirectly by calculating FLI, and pathological examination, as the standard method for measuring liver steatosis and fibrosis, was not carried out. FLI is a value calculated by BMI, WC, TG, and γ-GTP, and it was difficult to evaluate the relationship between FLI and these individual factors. A further randomized, comparative trial of SGLT2 inhibitors versus PIO, based on pathophysiological examination, is therefore required.

In conclusion, DAP might ameliorate NAFLD compared with PIO, and improvements in FLI as a result of DAP treatment might depend on glycemic control.

ACKNOWLEDGMENTS

The authors thank Naoki Nishimoto PhD for advice on statistical analysis, and Susan Furness PhD from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

DISCLOSURE

A Nakamura, SN Taneda, Y Kurihara, T Atsumi and H Miyoshi have received honoraria for lectures, and received research funding from some organizations as described below. A Nakamura obtained research support from Mitsubishi Tanabe Pharma Co., Daiichi Sankyo Co. Ltd., MSD, Novo Nordisk Pharma, Novartis Pharma, AstraZeneca, LifeScan Japan and Taisho Pharmaceutical. S Taneda received honoraria for lectures from Takeda Pharmaceutical Co., Ltd., Novo Nordisk Pharma and Ono Pharmaceutical Co., Ltd. Y Kurihara received honoraria for lectures from AstraZeneca, Mitsubishi Tanabe Pharma Co., Ltd., MSD, Ono Pharmaceutical Co., Ltd., Sanofi, Taisho Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co. Ltd., Eli Lilly, Sumitomo Dainippon pharma Co. and Takeda Pharmaceutical Co., Ltd. T Atsumi received honoraria for lectures from Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Pfizer Inc., AbbVie Inc., Eisai Co. Ltd., Daiichi Sankyo Co. Ltd., Bristol-Myers Squibb Co., UCB Japan Co. Ltd. and Eli Lilly Japan K.K., and received research funding from Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co. Ltd., Otsuka Pharmaceutical Co., Ltd., Pfizer Inc. and Alexion Inc. H Miyoshi received honoraria for lectures from Astellas Pharma Inc., AstraZeneca, Sumitomo Dainippon Pharma Co, Eli Lilly, Kissei, Mitsubishi Tanabe Pharma Co., MSD, Novartis Pharma, Novo Nordisk Pharma, Takeda Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd. and Sanofi, and received research funding from Astellas Pharma Inc., AstraZeneca, Daiichi Sankyo Co. Ltd., Sumitomo Dainippon Pharma Co., Eli Lilly, Mitsubishi Tanabe Pharma Co., MSD, Novo Nordisk Pharma, Sanofi, Takeda Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd. and Taisho Toyama Pharmaceutical Co., Ltd. The other authors declare no conflict of interest.

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