Comparison of Ipragliflozin and Pioglitazone Effects on Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Randomized, 24-Week, Open-Label, Active-Controlled Trial

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OBJECTIVE

To compare the efficacy of ipragliflozin versus pioglitazone in patients with type 2 diabetes complicated by nonalcoholic fatty liver disease (NAFLD).

RESEARCH DESIGN AND METHODS

In this open-label, randomized, active-controlled trial, we randomly assigned 66 patients with type 2 diabetes and NAFLD to receive ipragliflozin 50 mg (*n* = 32) or pioglitazone 15–30 mg (*n* = 34) orally once daily. The primary outcome was a change from baseline in the liver-to-spleen attenuation ratio (L/S ratio) on computed tomography at week 24.

RESULTS

At week 24, the mean ± SD L/S ratio had increased by 0.22 (from 0.80 ± 0.24 to 1.00 ± 0.18) in the ipragliflozin group and 0.21 (from 0.78 ± 0.26 to 0.98 ± 0.16) in the pioglitazone group (*P* = 0.90). Serum aspartate and alanine aminotransferase levels, HbA_{1c}, and fasting plasma glucose were similarly reduced in the two treatment groups. Nevertheless, body weight and visceral fat area showed significant reductions only in the ipragliflozin group compared with the pioglitazone group (*P* < 0.0001 and *P* = 0.0013, respectively). There were no serious adverse events in either group.

CONCLUSIONS

Compared with pioglitazone, ipragliflozin exerts equally beneficial effects on NAFLD and glycemic control during the treatment of patients with type 2 diabetes complicated by NAFLD. Furthermore, ipragliflozin significantly reduced body weight and abdominal fat area.

Nonalcoholic fatty liver disease (NAFLD) is a broad disease concept that ranges from nonalcoholic fatty liver, which refers to steatosis affecting hepatocytes, to nonalcoholic steatohepatitis (NASH), the inflammation and fibrosis that occur in addition to steatosis and may result in hepatic cirrhosis and hepatocellular carcinoma (1). Based on underlying insulin resistance and associated hyperinsulinemia, similar to conditions such as impaired glucose tolerance, diabetes, dyslipidemia, and hypertension, NAFLD is

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strongly associated with metabolic syndrome. Therefore, NAFLD can be viewed as the hepatic phenotype for metabolic syndrome (2). The frequency of NAFLD continues to increase worldwide, and its prevalence in Western countries has grown to ~20–40% (3). Even in Japan, ~30% of the population is reported to suffer from NAFLD (4). Moreover, the prevalence of NAFLD as a complication of type 2 diabetes is even higher, reaching 50–80% (5). NAFLD exacerbates insulin resistance and is a major contributor to the worsening of glucose tolerance, as well as having been shown to be an independent risk factor for cardiovascular events closely related to the life expectancies of patients with diabetes (6). Furthermore, diabetes has been reported to contribute to the progression of fibrosis in NASH and the onset of hepatocellular carcinoma (7). Because disorders encompassing NAFLD/NASH are extremely closely related to macrovascular events and hepatocarcinogenesis, which reduce life expectancy in patients with diabetes, it is extremely important to perform early and appropriate therapeutic interventions for type 2 diabetes complicated by NAFLD. Although several reports have described therapeutic interventions for NAFLD/NASH in recent years, the level of evidence remains low, and there is presently no established form of treatment.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are oral hypoglycemic agents with a novel mechanism of action; they prevent the reabsorption of glucose in the proximal renal tubule and increase urinary glucose excretion. This decreases blood glucose levels in a non–insulin-dependent manner. In addition to their excellent hypoglycemic action, SGLT2 inhibitors exert lowering effects on blood glucose and body weight. They have also reportedly shown pleiotropic effects on various complications and regulatory effects on macrovascular events (8,9) as well as beneficial effects on hepatic dysfunction in both clinical trials and animal models (10–12). Accordingly, SGLT2 inhibitors are expected to demonstrate efficacy when used to treat patients with type 2 diabetes complicated by NAFLD.

In this study, we performed a head-to-head comparison of the efficacy and safety of ipragliflozin, an SGLT2 inhibitor, with those of pioglitazone for treating patients with type 2 diabetes complicated by NAFLD.

RESEARCH DESIGN AND METHODS

This was a randomized, 24-week, open-label, multicenter, active-controlled trial. We enrolled patients from three sites in Japan between March 2015 and April 2016. This trial was registered with the UMIN Clinical Trials Registry (reg. no. UMIN000022651).

Participants

Our subjects were patients with type 2 diabetes, between 20 and 75 years of age, with an HbA_{1c} of 7.0–11.0% (53–97 mmol/mol) and BMI of $\leq$45 kg/m^2 who were receiving diet and exercise therapy alone or with oral hypoglycemic agents other than SGLT2 inhibitors and thiazolidinediones and/or insulin. The inclusion criteria were as follows: NAFLD, findings suggesting hepatic steatosis and hepatic dysfunction on clinical laboratory tests or on imaging studies (e.g., computed tomography [CT] or ultrasound), alcohol consumption volume $<$30 g/day (men) or $<$20 g/day (women), and exclusion of other causes of liver disease (e.g., viral or autoimmune hepatitis). Exclusion criteria included estimated glomerular filtration rate (eGFR) of $<$45 mL/min/1.73 m^2, serum creatinine $>$1.5 mg/dL, history of serious diabetes complications, findings suggestive of insulin dependency, heart failure (New York Heart Association Class III or IV), history of myocardial or cerebral infarction, and findings suggestive of decompensated cirrhosis. This study complied with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by institutional review boards or independent ethics committees of the three participating facilities. All participants provided written informed consent.

Study Design

Eligible patients were randomly assigned (1:1) using a computer-generated randomization sequence to receive ipragliflozin 50 mg once daily or pioglitazone 15–30 mg once daily in an open-label trial for 24 weeks. Ipragliflozin 50 mg or pioglitazone 15–30 mg tablets were taken orally before breakfast. All subjects in the ipragliflozin group received 50 mg/day, and there were no dosage adjustments during the trial. The subjects in the other group were given pioglitazone (15 or 30 mg/day) as an initial dose. If HbA_{1c} was $\geq$6.5% (48 mmol/mol) and the subjects demonstrated tolerability from week four after the start of the trial onward, then the dose could be increased to 30 mg/day. Patients who were already receiving treatment for diabetes at the time of enrollment continued other treatments throughout the study period, and ipragliflozin or pioglitazone was added to the current regimen. During the 24-week observation period, no additions or adjustments were made to the current antidiabetes drugs, antihypertensive medications, or antilipidemic agents. However, reducing the doses of sulfonylurea and insulin, or discontinuing these medications, was allowed as necessary to avoid any risk of hypoglycemia. In addition, patients received diet and exercise counseling at the beginning of the study and were reminded to follow the recommended plan at all study visits.

At the beginning of the study, all patients underwent physical examination and clinical laboratory tests, including measurements of HbA_{1c}, fasting plasma glucose (FPG), fasting plasma insulin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (γ-GT), serum ferritin, serum type IV collagen 7S, serum hyaluronic acid, fasting serum lipids, and serum adiponectin. In addition, eGFR, HOMA of insulin resistance (HOMA-IR), and adipose tissue insulin resistance (Adipo-IR), as an important contributor to both the pathogenesis and the treatment of NASH, values were determined (13). Vital signs and body weight were also recorded. Abdominal CT without contrast was performed to measure the liver-to-spleen attenuation ratio (L/S ratio), visceral fat areas (VFAs), and subcutaneous fat areas (SFAs). Clinical laboratory tests were performed at all outpatient visits during the study period, and CT scans to measure L/S ratio, VFAs, and SFAs were obtained at the end of the 24-week treatment period.

To measure the L/S ratio by CT scan, we specified the regions of interest (ROIs) using circles (2 cm in diameter) in sites that did not contain major vessels and measured the Hounsfield units (CT value) from one ROI each in the right and left hepatic lobes and two ROIs in the spleen. We then determined the L/S ratio on the CT images using the following formula: (mean CT values in the right and left hepatic lobe) ÷ (mean CT value at two ROIs in the spleen). The HOMA-IR index was

calculated as FPG (mg/dL) × fasting plasma insulin (μU/mL) ÷ 405. The Adipo-IR index was calculated as fasting plasma free fatty acids (mmol/L) × fasting plasma insulin (μU/mL). We also determined the NAFLD fibrosis score (14), fibrosis 4 (FIB4) index (15), and NAFIC (NASH, ferritin, IRI, and type IV collagen 7S) score (16) at the start of the trial and after 24 weeks as noninvasive screening for NASH progression. The cutoff value for the NAFLD fibrosis score was calculated using the following formula: −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet ($\times 10^9$/L) − 0.66 × albumin (g/dL), where IFG is impaired fasting glucose. This yielded a value of ≥0.675. The cutoff value for the FIB4 index was calculated using the following formula: [age × AST (units/L)] / {platelet [$\times 10^9$/L] × [ALT (units/L)]$^{1/2}$}. This yielded a cutoff value of ≥2.67. The NAFIC score was rated as follows: serum ferritin ≥200 ng/mL (female) or ≥300 ng/mL (male) = 1 point; fasting insulin ≥10 μU/mL = 1 point; and type IV collagen 7S ≥5.0 ng/mL = 2 points. We selected a cutoff value of ≥2 points to define suspected NASH progression.

Outcomes

The primary outcome was change from baseline in the L/S ratio at week 24. Key secondary outcomes were changes from baseline in AST, ALT, HbA_{1c}, FPG, body weight, abdominal VFA, and SFA at week 24. As another substudy, we compared changes from baseline at week 24 in γ-GT, serum ferritin, serum type IV collagen 7S, NAFLD fibrosis score, FIB4 index, NAFIC score, HOMA-IR, Adipo-IR, lipid profiles, serum adiponectin, serum creatinine, eGFR, and blood pressure values.

Safety variables included adverse events, hypoglycemic episodes, and the findings of standard laboratory analyses, physical examination, vital signs, and electrocardiography.

Statistical Analysis

The planned sample size was 60 subjects, with equal assignment to each of the two study groups (30 per group). With this sample size, the study would have 90% power to detect a difference in the mean of the L/S ratio of 0.15 on the assumption of an SD of 0.17 (17,18), a discontinuation rate of 7%, and a two-sided type 1 error of 0.05.

The statistical analyses were performed on an intention-to-treat population. We selected an intention-to-treat design for this study from the standpoints of safety and side effects and enrolled regular outpatients in accordance with actual clinical practice. Baseline characteristics of the two study groups were summarized with means and SDs for continuous variables and frequencies and percentages for categorical variables. First, we performed the Shapiro-Wilk test to evaluate the assumption of normality. A two-sample *t* test was used to assess differences between the two study groups for continuous variables and the χ^2 test (or Fisher exact test) for categorical variables. Data for the primary outcome and secondary outcomes were presented as means and SDs for continuous variables. A two-sample *t* test was also used to assess differences in the primary outcome and secondary outcomes between the study groups at baseline and at week 24 and in their respective changes from baseline. Nonparametric methods were used for non–normally distributed values. The Wilcoxon rank-sum test was used to assess differences in serum ferritin, serum type IV collagen 7S, serum hyaluronic acid, the NAFLD fibrosis score, FIB4 index, NAFIC score, and Adipo-IR between the study groups at baseline and at week 24 and in their respective changes from baseline. In addition, changes in continuous measures between baseline and after the 24-week treatment period were tested using a paired *t* test or the Wilcoxon signed-rank test for non–normally distributed values in each group. Data pertaining to the major clinical events of interest were presented as frequencies and percentages for categorical variables. The χ^2 test (or Fisher exact test) was used to identify differences between the two study groups in categorical variables. A *P* value <0.05 was regarded as statistically significant. All analyses were performed with SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY).

RESULTS

Supplementary Fig. 1 outlines the trial. In total, 81 patients were screened and 66 were randomly assigned to receive ipragliflozin 50 mg (*n* = 32) or pioglitazone

Table 1—Baseline characteristics of the intention-to-treat population

	Pioglitazone group (*n* = 34)	Ipragliflozin group (*n* = 32)	*P*
Age (years)	59.1 ± 9.8	57.3 ± 12.1	0.499
Male, *n* (%)	18 (53)	14 (44)	0.455
Body weight (kg)	76.7 ± 15.2	79.6 ± 17.9	0.484
BMI (kg/m^2)	29.9 ± 6.2	30.7 ± 5.0	0.578
Waist circumference (cm)	96.7 ± 13.6	99.5 ± 11.9	0.379
Duration of diabetes (years)	9.5 ± 5.8	8.7 ± 5.8	0.559
HbA_{1c} (%)	8.3 ± 1.4	8.5 ± 1.5	0.491
HbA_{1c} (mmol/mol)	67 ± 15.1	69 ± 15.9	0.491
FPG (mg/dL)	169.4 ± 50.9	160.1 ± 38.7	0.406
AST (units/L)	43.3 ± 20.5	39.7 ± 16.7	0.442
ALT (units/L)	53.1 ± 26.6	57.4 ± 27.3	0.524
Medications, *n* (%)			
Metformin	17 (50.0)	20 (62.5)	0.307
DPP-4 inhibitor	25 (73.5)	19 (59.4)	0.223
Sulfonylurea	10 (29.4)	4 (12.5)	0.093
Insulin	4 (11.8)	7 (21.9)	0.271
ARB or ACE inhibitor	13 (38.2)	22 (68.8)	0.013
Statin	19 (55.9)	20 (62.5)	0.585
Clinical scoring systems			
NAFLD fibrosis score ≥0.675	4 (11.8)	3 (9.4)	0.753
FIB4 index ≥2.67	4 (11.8)	2 (6.3)	0.436
NAFIC score ≥2 points	10 (29.4)	6 (18.8)	0.448

Data are mean ± SD unless otherwise indicated. ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase 4.

15–30 mg (n = 34). Sixty-one patients completed the trial (ipragliflozin group, n = 30; pioglitazone group, n = 31). The reasons for discontinuation in the ipragliflozin group included the patient deciding to withdraw and loss to follow-up (one each). There were two adverse events (edema in both cases) in the pioglitazone group, and one subject was lost to follow-up. Table 1 shows demographic and baseline characteristics of the study participants. Baseline characteristics were similar in the two groups. The only significant differences at baseline between the two groups were the percentage of patients taking an angiotensin receptor blocker or an ACE inhibitor (P = 0.013) and the serum type IV collagen 7S values (P = 0.013). The mean dose of pioglitazone at 24 weeks was 21.2 ± 7.5 mg/day. The changes in the insulin dose at the end of the 24 weeks, compared with those at baseline, were −2.9 and 3.4 units in the ipragliflozin and pioglitazone groups, respectively—not significantly different. There were no subjects in either group whose sulfonylurea doses were reduced or who discontinued sulfonylurea agents during the observation period. In addition, there were no subjects in either group receiving treatment with glucagon-like peptide 1 receptor agonists.

Table 2 shows the changes in the primary and secondary outcomes and other parameters at the end of 24 weeks compared with those at baseline. The changes in the mean ± SD L/S ratio at the end of 24 weeks, compared with those at baseline, were 0.22 (0.80 ± 0.24 to 1.00 ± 0.18) and 0.21 (0.78 ± 0.26 to 0.98 ± 0.16) in the ipragliflozin and pioglitazone groups, respectively. Although this demonstrated significant improvement within both groups, there were no significant differences between the two groups (P = 0.90) (Table 2; Fig. 1*C*). Next, the changes in serum aminotransferase levels at the end of 24 weeks were compared with those at baseline in the ipragliflozin and pioglitazone groups. The AST (mean ± SE change, ipragliflozin group vs. pioglitazone group, −12.6 ± 2.1 vs. −11.6 ± 3.2 units/L; P = 0.802) and ALT (−20.0 ± 3.4 vs. −17.5 ± 4.0 units/L; P = 0.642) values both decreased significantly compared with baseline and did not differ markedly between the two groups (Table 2; Fig. 1*A* and *B*). There were also similar decreases in the glycemic parameters, particularly HbA_{1c} (−0.94 ± 0.20 vs. −1.11 ± 0.18%; P = 0.522) and FPG (−23.6 ± 6.0 vs. −26.1 ± 6.7 mg/dL; P = 0.785). There were no significant differences between the two groups, such that the efficacies reflected by glycemic parameters were identical (Table 2).

Compared with the baseline, body weight decreased by −2.3 ± 0.5 kg

Table 2—Changes in NAFLD, glycemic, and metabolic parameters compared between baseline and week 24 by treatment group

	Pioglitazone group (n = 34)	Ipragliflozin group (n = 32)	P
L/S ratio			
Baseline	0.78 ± 0.26	0.80 ± 0.24	0.752
Week 24	0.98 ± 0.16	1.00 ± 0.18	0.527
Change from baseline	0.21 ± 0.03*	0.22 ± 0.04*	0.90
VFA (cm^2)			
Baseline	158.7 ± 68.2	154.5 ± 52.4	0.785
Week 24	154.0 ± 74.0	122.0 ± 47.0	0.053
Change from baseline	−2.6 ± 4.9	−26.1 ± 4.9*	0.0013
SFA (cm^2)			
Baseline	227.5 ± 134.4	249.6 ± 105.7	0.468
Week 24	243.4 ± 148.8	222.0 ± 108.9	0.533
Change from baseline	15.7 ± 6.0*	−23.0 ± 6.2*	<0.0001
Body weight (kg)			
Baseline	76.7 ± 15.2	79.6 ± 17.9	0.484
Week 24	77.6 ± 15.5	76.7 ± 18.1	0.833
Change from baseline	0.9 ± 0.4*	−2.3 ± 0.5*	<0.0001
HbA_{1c} (%)			
Baseline	8.28 ± 1.38	8.52 ± 1.46	0.491
Week 24	7.07 ± 0.89	7.57 ± 1.02	0.041
Change from baseline	−1.11 ± 0.18*	−0.94 ± 0.20*	0.522
FPG (mg/dL)			
Baseline	169.4 ± 50.9	160.1 ± 38.7	0.437
Week 24	139.0 ± 26.6	136.5 ± 26.7	0.727
Change from baseline	−26.1 ± 6.7*	−23.6 ± 6.0*	0.785
AST (units/L)			
Baseline	43.3 ± 20.5	39.7 ± 16.7	0.442
Week 24	32.4 ± 15.4	27.3 ± 8.9	0.113
Change from baseline	−11.6 ± 3.2*	−12.6 ± 2.1*	0.802
ALT (units/L)			
Baseline	53.1 ± 26.6	57.4 ± 27.3	0.524
Week 24	36.8 ± 15.1	38.2 ± 20.5	0.765
Change from baseline	−17.5 ± 4.0*	−20.0 ± 3.4*	0.642
γ-GT (units/L)			
Baseline	71.6 ± 54.1	62.8 ± 58.3	0.524
Week 24	48.8 ± 61.2	44.0 ± 38.3	0.765
Change from baseline	−24.5 ± 5.8*	−19.4 ± 5.4*	0.642
Fasting plasma insulin (μU/mL)			
Baseline	14.2 ± 8.8	13.3 ± 5.9	0.641
Week 24	12.9 ± 7.4	13.6 ± 12.4	0.809
Change from baseline	−1.8 ± 1.2	−0.1 ± 1.9	0.400
HOMA-IR			
Baseline	5.69 ± 3.42	5.16 ± 2.51	0.530
Week 24	4.45 ± 2.70	4.82 ± 5.45	0.759
Change from baseline	−1.37 ± 0.58*	−0.43 ± 1.00	0.401
Adipo-IR			
Baseline	10.99 ± 8.20	9.03 ± 5.87	0.353
Week 24	8.73 ± 6.27	9.49 ± 8.93	0.732
Change from baseline	−2.56 ± 0.90*	0.25 ± 1.79	0.134
Serum ferritin (ng/mL)			
Baseline	159.0 ± 141.1	175.9 ± 116.7	0.259
Week 24	113.5 ± 80.7	110.2 ± 80.1	0.885
Change from baseline	−42.1 ± 13.1*	−72.8 ± 13.1*	0.036

Continued on p. 1368

Table 2—Continued

	Pioglitazone group (n = 34)	Ipragliflozin group (n = 32)	P
Serum type IV collagen 7S (ng/mL)			
Baseline	4.51 ± 1.64	3.60 ± 0.95	0.013
Week 24	4.27 ± 1.13	3.37 ± 0.88	0.0010
Change from baseline	−0.15 ± 0.20	−0.30 ± 0.18	0.516
FIB4 index			
Baseline	1.84 ± 1.13	1.44 ± 0.64	0.130
Week 24	1.71 ± 1.19	1.22 ± 0.55	0.067
Change from baseline	−0.16 ± 0.09	−0.22 ± 0.06*	0.596
Serum adiponectin (μg/mL)			
Baseline	5.61 ± 2.04	5.54 ± 1.71	0.922
Week 24	12.64 ± 6.87	6.56 ± 1.94	0.0064
Change from baseline	6.98 ± 1.34*	1.02 ± 0.42*	0.0009
Total cholesterol (mg/dL)			
Baseline	181.3 ± 43.4	184.0 ± 42.7	0.802
Week 24	192.8 ± 41.4	187.1 ± 45.0	0.601
Change from baseline	8.9 ± 5.5	2.0 ± 3.0	0.282
LDL cholesterol (mg/dL)			
Baseline	104.0 ± 27.9	108.3 ± 36.2	0.591
Week 24	114.6 ± 29.5	110.7 ± 40.1	0.661
Change from baseline	10.5 ± 3.5*	1.9 ± 2.7	0.057
HDL cholesterol (mg/dL)			
Baseline	47.4 ± 11.6	48.9 ± 9.3	0.568
Week 24	52.7 ± 13.5	54.7 ± 10.4	0.514
Change from baseline	5.0 ± 1.4*	5.5 ± 1.5*	0.820
Triglycerides (mg/dL)			
Baseline	188.4 ± 148.8	166.9 ± 76.4	0.466
Week 24	169.3 ± 131.3	143.4 ± 81.4	0.350
Change from baseline	−22.8 ± 18.7	−24.5 ± 10.3*	0.938
Fasting free fatty acids (mmol/L)			
Baseline	0.76 ± 0.31	0.73 ± 0.32	0.657
Week 24	0.71 ± 0.41	0.77 ± 0.26	0.546
Change from baseline	−0.06 ± 0.05	0.05 ± 0.07	0.184
Systolic blood pressure (mmHg)			
Baseline	138.4 ± 19.4	133.7 ± 13.3	0.256
Week 24	141.1 ± 19.6	132.7 ± 13.3	0.052
Change from baseline	2.4 ± 2.5	−0.7 ± 3.3	0.445
Diastolic blood pressure (mmHg)			
Baseline	85.7 ± 12.9	81.8 ± 11.4	0.200
Week 24	86.7 ± 12.5	83.2 ± 10.6	0.224
Change from baseline	1.2 ± 1.7	1.5 ± 1.6	0.896

Data are mean ± SD and, at week 24, mean ± SE change. *$P \leq 0.05$ compared with baseline.

(−2.9%) in the ipragliflozin group and increased by 0.9 ± 0.4 kg (1.2%) in the pioglitazone group after 24 weeks. Inverse changes in body weight were observed in the two groups ($P < 0.0001$) (Table 2). We then examined the changes in abdominal fat area at the end of 24 weeks compared with those at baseline. The VFA in the ipragliflozin group decreased significantly, by −26.1 ± 4.9 cm^2 (−16.9%), but there was only a slight decrease in the pioglitazone group of −2.6 ± 4.9 cm^2 (−1.6%) (P = 0.0013) (Table 2; Fig. 1*E*). The SFA also decreased significantly, by −23.0 ± 6.2 cm^2 (−9.2%), in the ipragliflozin group, while increasing significantly, by 15.7 ± 6.0 cm^2 (6.9%), in the pioglitazone group ($P < 0.0001$) (Table 2; Fig. 1*F*). Inverse changes in abdominal fat area resembling those in body weight were also observed.

The changes in the mean HOMA-IR and Adipo-IR values at the end of 24 weeks, though not differing significantly between the two groups, showed significant improvement compared with baseline in the pioglitazone group (Table 2). Moreover, although serum adiponectin levels improved significantly compared with baseline values in both groups, the beneficial effects were greater in the pioglitazone than in the ipragliflozin group (P = 0.0009) (Table 2; Fig. 1*D*).

The scoring systems used for the evaluation at the start of the study, aiming to perform noninvasive screening for the progression of NASH, consisted of the NAFLD fibrosis score, FIB4 index, and NAFIC score. The results of a subanalysis performed in cases that exceeded the cutoff values are presented in Table 3. The changes in the NAFLD parameters at the end of 24 weeks, compared with those at baseline, were as follows for the ipragliflozin versus pioglitazone groups: L/S ratio 0.20 ± 0.06 vs. 0.23 ± 0.05, P = 0.737; AST −20.1 ± 5.0 vs. −13.5 ± 6.1 units/L, P = 0.443; and ALT −19.0 ± 4.6 vs. −15.9 ± 6.0 units/L, P = 0.708. Improvements were observed in both groups for these and other parameters, including indicators of fibrosis and scoring system values (Table 3).

The extent of changes resulting from these treatments and their respective correlations with NAFLD parameters (including scoring system values), the fat distribution, and metabolic parameters are shown in the Supplementary Table 1. We identified significant correlations between the NAFLD parameters (i.e., the L/S ratio, ALT, and γ-GT) and the amount of change in body weight only in the ipragliflozin group. In addition, in the ipragliflozin group, improvement in the L/S ratio correlated significantly with both serum adiponectin levels and decreased HbA_{1c} levels. In contrast, in the pioglitazone group, there was no significant correlation between any of the NAFLD parameters and the amounts of change in body weight, abdominal fat areas, or glycemic parameters. However, serum adiponectin level improvement correlated significantly with the L/S ratio, γ-GT, and the FIB4 index, an indicator of fibrosis (Supplementary Table 1). In addition, we performed a multiple linear regression analysis wherein we defined changes in primary and secondary outcomes after 24 weeks versus baseline as the dependent variables and defined values at baseline (i.e., assigned drug [pioglitazone = 0, ipragliflozin = 1], age, sex, height, BMI, L/S ratio, VFA, SFA, HbA_{1c}, FPG, HOMA-IR, free fatty acids, and Adipo-IR) as the independent variables. After adjustment for these independent variables, we identified no significant differences between the two drugs in NAFLD parameters including the L/S ratio and glycemic parameters. While body weight, VFA, and SFA improved significantly with ipragliflozin,

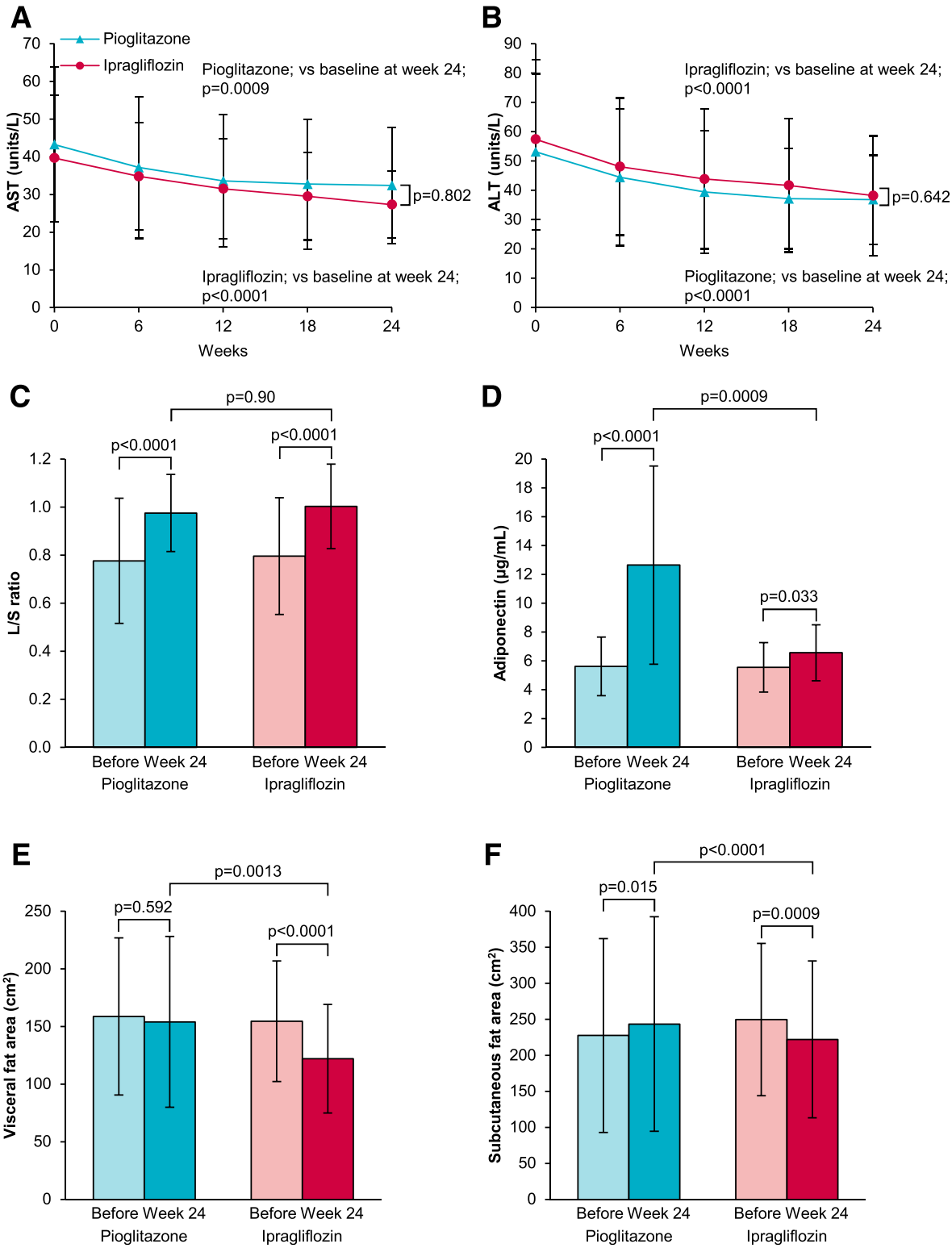

Figure 1—Changes in aminotransferase levels, L/S ratio, serum adiponectin, abdominal VFA, and SFA from baseline to week 24. *A*: Serum AST. *B*: Serum ALT. *C*: L/S ratio, as assessed by CT. *D*: Serum adiponectin. *E*: VFA assessed by CT. *F*: SFA assessed by CT. Error bars show SDs.

serum adiponectin markedly improved with pioglitazone (Supplementary Table 2). Based on these results, although the principal effects exerted by ipragliflozin—causing weight loss and improving blood glucose levels—contribute to NAFLD amelioration, our results also suggest that the marked improvement in serum adiponectin levels produced by pioglitazone ameliorates NAFLD/NASH, including reductions in the indicators of fibrosis.

Adverse events occurred in the ipragliflozin and pioglitazone groups during the 24 weeks of this trial, differing minimally

Table 3—Changes in NAFLD parameters from baseline to week 24 according to subanalysis by clinical scoring systems for suspected NASH and for advanced fibrosis

	Pioglitazone group (n = 11)	Ipragliflozin group (n = 8)	P
L/S ratio			
Baseline	0.72 ± 0.18	0.78 ± 0.27	0.535
Week 24	0.94 ± 0.12	0.98 ± 0.26	0.661
Change from baseline	0.23 ± 0.05*	0.20 ± 0.06*	0.737
AST (units/L)			
Baseline	49.9 ± 23.8	51.9 ± 21.8	0.856
Week 24	36.4 ± 17.1	31.8 ± 12.3	0.526
Change from baseline	−13.5 ± 6.1*	−20.1 ± 5.0*	0.443
ALT (units/L)			
Baseline	55.8 ± 21.5	56.8 ± 16.1	0.919
Week 24	39.9 ± 17.3	37.8 ± 20.5	0.806
Change from baseline	−15.9 ± 6.0*	−19.0 ± 4.6*	0.708
γ-GT (units/L)			
Baseline	73.3 ± 42.6	54.9 ± 32.1	0.319
Week 24	45.4 ± 24.5	37.0 ± 22.2	0.456
Change from baseline	−27.9 ± 6.7*	−17.9 ± 5.5*	0.290
Serum ferritin (ng/mL)			
Baseline	186.2 ± 90.2	248.3 ± 153.4	0.545
Week 24	152.9 ± 85.7	144.4 ± 80.0	0.717
Change from baseline	−33.4 ± 13.1*	−103.9 ± 35.5*	0.062
Serum type IV collagen 7S (ng/mL)			
Baseline	5.72 ± 1.80	4.21 ± 0.70	0.016
Week 24	4.75 ± 1.36	3.78 ± 1.34	0.238
Change from baseline	−0.96 ± 0.36*	−0.44 ± 0.46	0.442
Serum hyaluronic acid (ng/mL)			
Baseline	70.7 ± 52.6	65.0 ± 50.9	0.990
Week 24	90.3 ± 96.2	50.5 ± 22.1	0.600
Change from baseline	19.6 ± 20.1	−14.5 ± 15.2	0.600
FIB4 index			
Baseline	2.06 ± 1.24	2.12 ± 0.72	0.657
Week 24	1.70 ± 1.19	1.61 ± 0.70	0.717
Change from baseline	−0.36 ± 0.15*	−0.51 ± 0.10*	0.492

Data are mean ± SD and, at week 24, mean ± SE change. *$P \leq 0.05$ compared with baseline.

between the two groups (Supplementary Table 3). However, there were differences between the two groups regarding the details of these adverse events. Two women and one man in the ipragliflozin group developed urinary tract infections, and one woman developed vaginal candidiasis. However, these adverse effects resolved with appropriate administration of antibiotics or antifungals, and the patients were able to continue the study. None of these patients experienced a recurrent infection. There were no other adverse events in either group; i.e., none of the patients experienced severe hypoglycemia, dehydration, ketoacidosis, cardiac failure, or severe infection that necessitated treatment interruption or termination.

CONCLUSIONS

In the present trial, ipragliflozin was shown to exert beneficial effects on NAFLD that were identical to those of pioglitazone during the 24-week trial period. We observed an amelioration of hepatic steatosis as evaluated using the L/S ratio, reduced serum aminotransferase levels, and lowering of other NAFLD parameters, with equivalent beneficial effects observed for glycemic parameters. Compared with pioglitazone, there were significant decreases in body weight and abdominal fat area. Tolerability was also favorable.

Our study also revealed ipragliflozin and pioglitazone to have different effects on several metabolic parameters. Pioglitazone treatment improves the characteristics of adipose tissue, which improves insulin resistance (19). Because there are also reports of VFA-lowering effects of pioglitazone (20), we expected that it might exert a parallel beneficial effect on hepatic ectopic steatosis and visceral fat mass. However, the present results indicate that pioglitazone caused no significant visceral fat mass reduction, while the subcutaneous fat mass and body weight increased significantly. These results are opposite those of ipragliflozin, with a 3% decrease in body weight, 17% decrease in VFA, and 9% decrease in SFA documented at 24 weeks. Despite these differences, pioglitazone exhibited the same beneficial effects on NAFLD as ipragliflozin, suggesting that these two drugs have different NAFLD-improving mechanisms. Therefore, ipragliflozin appears to cause caloric loss by enhancing urinary glucose excretion and consistently and efficiently decreases the visceral fat mass. We thus speculate that ipragliflozin corrects insulin resistance and the associated hyperinsulinemia, thereby improving NAFLD. By comparison, although pioglitazone causes increases in body weight and the subcutaneous fat mass, marked activation of peroxisome proliferator–activated receptor-γ induces adipocyte differentiation and ameliorates hepatic ectopic steatosis. It also reduces chronic inflammation and improves insulin resistance, particularly in adipose tissue, through beneficial effects on adiponectin secretion (21). We herein conducted a comparison of the pioglitazone group and the ipragliflozin group and found a significant increase in the secretion of serum adiponectin in the former. In addition, we observed significant improvement of adipose tissue insulin resistance, as assessed by the Adipo-IR, only in the pioglitazone group. We concluded that pioglitazone contributes to improving the characteristics of adipose tissue, which in turn ameliorates the hyperinsulinemia primarily associated with NAFLD and thereby improves the features of NAFLD/NASH.

In comparison with ipragliflozin, which reduces body weight and visceral fat mass as well as improving glycemic control and NAFLD, pioglitazone does not reduce either body weight or visceral fat mass. This report has clarified that pioglitazone exerts beneficial effects on NAFLD by qualitatively improving adipose tissue. Therefore, considering specifically adipose tissue, we believe that ipragliflozin exerts "quantitative improvement effects" on NAFLD, while pioglitazone exerts "qualitative improvement effects."

Pioglitazone has previously been reported to act beneficially on hepatic fibrosis in

NASH (22–27). Moreover, it is noteworthy that case subjects in the current study suspected of experiencing progression of NASH during noninvasive screening follow-up and who used ipragliflozin also exhibited improved NAFLD parameters, including reductions in fibrosis markers. Unlike pioglitazone, ipragliflozin does not mediate direct beneficial qualitative effects on adipose tissue through marked activation of peroxisome proliferator–activated receptor-γ and anti-inflammatory actions. However, in addition to improving glycemic control and reducing body weight, as observed with SGLT2 inhibitors in general, it appears that ipragliflozin might be capable of slowing or even reversing the progression of NASH through beneficial effects on insulin resistance resulting from reduced ectopic steatosis. This possibility is supported by a meta-analysis that revealed that lifestyle-induced weight loss ≥5% improved hepatic steatosis and weight loss ≥7% reduced the histological disease activity of NASH (28).

Our findings indicate that it is extremely important to treat obesity, particularly visceral fat obesity, which is the pathology underlying the onset of NAFLD. An SGLT2 inhibitor that can simultaneously correct hyperglycemia and efficiently decrease visceral fat might be extremely useful for treating patients with type 2 diabetes complicated by NAFLD. On the other hand, there are reports of increased appetite and increases in body weight due to SGLT2 inhibitors. Thus, we may need to perform ongoing and very detailed observations focusing on patient outcomes as well as long-term efficacy and safety, including the beneficial effects on NAFLD. The limitations of this study include that it was performed at a small number of facilities, the sample size was small, and an open-label design was used. In this trial, the L/S ratio was set as the primary outcome, and histological evaluation, which is the gold standard for measuring liver steatosis, was not performed. In addition, the pioglitazone dose was set to a maximum of 30 mg/day with the intention of minimizing the risk of adverse reactions. As a result, many participants, particularly females, remained on the 15 mg/day dose. In the future, we hope to conduct a long-term, large-scale investigation including histological evaluations.

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