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Efficacy and safety of low-dose ipragliflozin, a selective sodium glucose transporter 2 inhibitor, in patients with type 2 diabetes mellitus.

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ABSTRACT

Objective

Few studies have focused on the efficacy and safety of low-dose of selective sodium glucose transporter 2 (SGLT2) inhibitors in patients with type 2 diabetes. Ipragliflozin is an SGLT2 inhibitor licensed in Japan for administration at standard (50mg/day) or high (100mg/day) doses to treat type 2 diabetes mellitus in Japan. However, little is known about low-dose ipragliflozin (25mg/day) on safety and efficacy on the glucose control parameters and the other metabolic parameters. We study the efficacy and safety of low-dose ipragliflozin for the treatment of diabetic patients.

Methods

14 individuals with type 2 diabetes mellitus who had not used SGLT2 inhibitors were recruited and given low-dose ipragliflozin (25mg/day). After 24 weeks, glucose control parameters and the other metabolic parameters were evaluated.

Results

All patients completed the study without any complications. Compared to baseline, HbA1c, fasting glucose, and HOMA- β significantly improved, and in terms of metabolic parameters, body weight, systolic blood pressure, LDL-cholesterol, and BNP significantly improved. In addition, urinary albumin excretion significantly reduced among the patients with microalbuminuria, and for one patient with macroalbuminuria, urinary albumin excretion decreased to half compared to baseline.

Conclusion

Low-dose ipragliflozin (25mg/day) is useful for treatment for type 2 diabetes mellitus on not only glycemic control but also the other metabolic disorders without complications of SGLT2 inhibitors.

Keywords: Selective sodium glucose transporter 2 inhibitors, Type 2 diabetes mellitus

INTRODUCTION

Inhibitors of sodium glucose transporter 2 (SGLT2) are new glucose-lowering agents. SGLT2 is a member of the SGLT family of solute transporters, and highly expressed in proximal tubules in the kidney. SGLT2 plays a key role in glucose reabsorption, and the inhibition of SGLT2 prevents hyperglycemia caused by decreasing glucose reabsorption [1-3]. SGLT2 inhibitors were proposed as an insulin-independent approach for treating hyperglycemia [4] and had effects of reducing body weight and fat mass [5-7]. Furthermore, one report showed one of SGLT2 inhibitors, empagliflozin, reduced the rates of death from cardiovascular cause and hospitalization for heart failure [8]. Another report showed SGLT2 inhibitors improved hypertension by increasing urinary sodium excretion [9]. It was also reported SGLT2 inhibitors improved albuminuria [10]. Thus SGLT2 inhibitors had many merits to patients of type 2 diabetes, but those were also reported to have adverse events. Urinary and genital infection, decreasing eGFR, diabetic ketosis or ketoacidosis [11, 12], and, especially in Japan, toxic skin eruption and stroke were reported as adverse events of SGLT2 inhibitors.

Truly, body weights of Japanese patients of type 2 diabetes were much lower than that of westerners. So we hypothesized low-dose of SGLT2 inhibitors can have sufficient merits and may reduce adverse effects to Japanese patients with type 2 diabetes. In this study, we used low-dose of ipragliflozin (25mg/day), and analyzed the glucose control parameters and the other metabolic parameters and safety.

SUBJECTS AND METHODS

Subjects

We recruited 14 individuals with type 2 diabetes mellitus (42–87 years) at Nagasaki Prefecture Iki Hospital from April to June 2015. We have exclusion criteria of this study; Patients who were or might have been pregnant, those with severe liver dysfunction (including liver cirrhosis), and those who have or had any malignancy were excluded, and all participants provided written informed consent. The study protocol was approved by the Ethics Review Committee of Nagasaki Prefecture Iki Hospital (Japan). Participant characteristics are shown in Table 1 and 2.

Table 1 Participant clinical characteristics at baseline. Data are means ± SD and range or the number of subjects.

	n = 14
Age	62.9 ± 11.9 (42-87)
Gender (male/female)	7/7
BW (kg)	69.6 ± 13.7 (46.4-96.2)
HbA1c (%)	7.55 ± 0.62 (6.7-8.6)
FPG (mg/dl)	148.5 ± 31.6 (113-213)
HOMA-R	2.83 ± 2.08 (0.40-7.53)
HOMA-β	33.1 ± 18.3 (3.6-78.3)
SBP (mmHg)	138.0 ± 19.1 (99-167)
DBP (mmHg)	72.6 ± 11.4 (51-88)
eGFR (ml/min/1.73m ²)	72.3 ± 19.7 (35.6-98.0)
Urinary albumin (mg/gCr)	160.7 ± 396.9 (2.8-1580.2)
BNP (pg/ml)	26.3 ± 16.1 (0.7-94.1)
AST (U/L)	23.4 ± 13.0 (12-67)
ALT (U/L)	28.6 ± 21.6 (11-82)
γ-GTP(U/L)	23.4 ± 13.5 (11-44)
LDL-cholesterol(mg/dl)	105.5 ± 19.8 (65-147)
HDL-cholesterol(mg/dl)	53.5 ± 13.1 (40-85)
triglyceride(mg/dl)	105.1 ± 34.9 (51-164)

Table 2 Participant complications and treatments at baseline. Data are the number of subjects.

		n = 14
Complications		
Diabetic complications		
Neuropathy		8/14
Retinopathy		4/14
Nephropathy (U-Alb 30-299.9 mg/gCr and eGFR 30-)		7/14
Nephropathy (U-Alb 300- mg/gCr and eGFR 30-)		1/14
Nephropathy (eGFR < 30 or receiving dialysis)		0/14
Cardiovascular disease		
Cerebrovascular disease		0/14
Medical treatment for hypertension		10/14
Medical treatment for hyperlipidemia		5/14
Other diabetic agents		
Only DPP4 inhibitor		1/14
Only Metformin		2/14
DPP4 inhibitor + Metformin		8/14
Sulfonylurea + DPP4 inhibitor		2/14
Sulfonylurea + Metformin		1/14

Study design

The present study was a one-arm, open label, non-randomized clinical trial. To examine efficacy and safety of low-dose ipragliflozin (25mg/day), we added low-dose ipragliflozin and continued for 24 weeks. The following variables were measured at baseline and at 24 weeks after adding low-dose ipragliflozin: the glucose control parameters (HbA1c, fasting plasma glucose (FPG), HOMA-R, HOMA-β), systolic blood pressure (SBP), diastolic blood pressure (DBP), markers of lipid metabolism (low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)), liver enzymes (AST, ALT, and γ-GTP), urinary albumin (U-Alb) and brain natriuretic peptide (BNP). Body weight (BW) and estimated glomerular filtration rate (eGFR) were estimated every 4 weeks during the study. All blood samples were obtained after overnight fasting. Adverse events, including side effects, were examined based on patients' data and interviews to patients. All drugs were not changed throughout the study.

Statistical analysis

Data were expressed as means ± standard deviation (SD) or standard error of the mean (SEM). The statistical significance of differences between means was estimated by paired Student's *t*-test. Values of *p* < 0.05 were considered to indicate statistical significance.

RESULTS

All patients completed the present study without any complication such as urinary and genital infection, diabetic ketosis or ketoacidosis, toxic skin eruption and stroke.

Changes in patients' glycemic parameters (HbA1c, FPG, HOMA-R, HOMA-β), and other metabolic parameters (BW, SBP, DBP, LDL-C, HDL-C, TG, AST, ALT, γ-GTP, and BNP) at baseline and 24 weeks after adding low-dose ipragliflozin is shown in Table 3. Change in urinary albumin at baseline and 24 weeks after adding low-dose ipragliflozin are shown in Table 4, which separated by patients' condition of nephropathy. Changes in eGFR and BW are shown in Figure 1.

Table 3 Patients' data of glucose control parameters and the other metabolic parameters of baseline and 24 weeks after adding low-dose ipragliflozin. Data are expressed as means \pm standard deviation (SD). The significance of differences between means was estimated by paired Student's t-test. Values of $p < 0.05$ were considered to indicate statistical significance (*).

	Baseline	24weeks	p
BW (kg)	69.6 \pm 13.7	67.1 \pm 13.7	0.0078*
HbA1c (%)	7.55 \pm 0.62	7.16 \pm 0.63	0.0001*
FPG (mg/dl)	148.5 \pm 31.6	136.9 \pm 22.9	0.0358*
HOMA-R	2.83 \pm 2.08	2.97 \pm 2.22	0.3200
HOMA- β	33.1 \pm 18.3	43.4 \pm 32.3	0.04740*
SBP (mmHg)	138.0 \pm 19.1	123.0 \pm 13.3	0.00183*
DBP (mmHg)	72.6 \pm 11.4	69.8 \pm 13.5	0.17848
eGFR (ml/min/1.73m ²)	72.3 \pm 19.7	72.3 \pm 20.2	0.48793
BNP (pg/ml)	26.3 \pm 16.1	18.2 \pm 18.8	0.04484*
AST (U/L)	23.4 \pm 13.0	19.0 \pm 3.5	0.09014
ALT (U/L)	28.6 \pm 21.6	23.8 \pm 14.1	0.16188
γ -GTP (U/L)	23.4 \pm 13.5	19.4 \pm 9.0	0.01614*
LDL-cholesterol (mg/dl)	105.5 \pm 19.8	97.5 \pm 19.0	0.02756*
HDL-cholesterol (mg/dl)	53.5 \pm 13.1	54.6 \pm 13.6	0.29769
Triglyceride (mg/dl)	105.1 \pm 34.9	103.3 \pm 44.3	0.43936

Table.4 Patients' data of urinary albumin excretion of baseline and 24 weeks after adding low-dose ipragliflozin. Without nephropathy (U-Alb -29.9 mg/gCr and eGFR 30-); n=6, Nephropathy (U-Alb 30-299.9 mg/gCr and eGFR 30-); n=7, and Nephropathy (U-Alb 300- mg/gCr and eGFR 30-); n=1. Data are expressed as means \pm standard deviation (SD). The significance of differences between means was estimated by paired Student's t-test. Values of $p < 0.05$ were considered to indicate statistical significance (*).

Urinary albumin (mg/gCr)	baseline	24weeks	p
Without nephropathy (U-Alb -29.9 mg/gCr and eGFR 30-)	12.1 \pm 7.7	13.6 \pm 7.3	0.3263
Nephropathy (U-Alb 30-299.9 mg/gCr and eGFR 30-)	84.7 \pm 50.9	53.4 \pm 42.3	0.0076*
Nephropathy (U-Alb 300- mg/gCr and eGFR 30-)	1580.2	794.2	

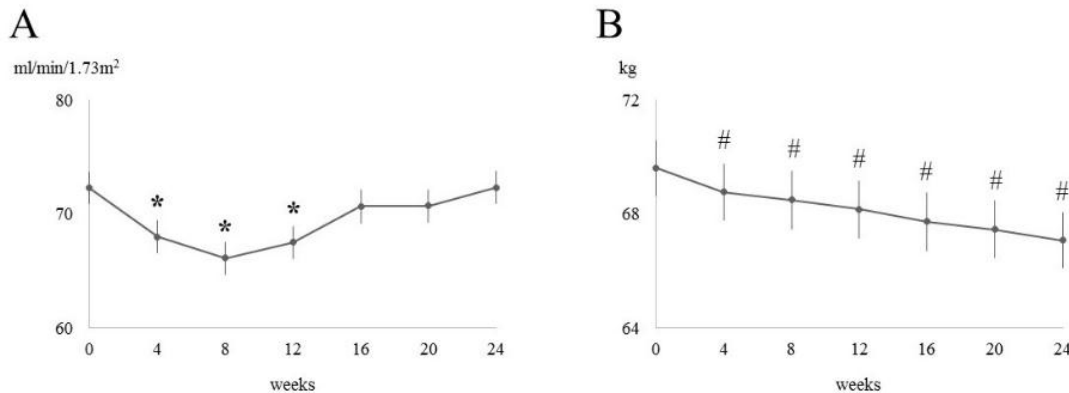


Figure 1
A. Change in eGFR(ml/min/1.73m²) during 24 weeks after adding low-dose ipragliflozin.
B. Change in BW(kg) during 24 weeks after adding low-dose ipragliflozin.
 Data are expressed as means \pm standard error of the mean (SEM). The significance of differences between baseline and every 4weeks were estimated by paired Student's t-test. Values of $p < 0.05$ (*) and $p < 0.01$ (#) were considered to indicate statistical significance.

In terms of glycemic parameters, HbA1c was significantly reduced by adding low-dose

ipragliflozin (7.16 \pm 0.63 %) compared to baseline (7.55 \pm 0.62 %) ($p = 0.0001$) and FPG was also

significantly reduced by adding low-dose ipragliflozin (136.9 ± 22.9 mg/dl) compared to baseline (148.5 ± 31.6) ($p = 0.0358$). There was no significant difference in HOMA-R, but HOMA- β was significantly increased by adding low-dose ipragliflozin (43.4 ± 32.3) from baseline (33.1 ± 18.3) ($p = 0.04740$). In terms of other metabolic parameters, SBP, LDL-C, γ -GTP, and BNP were significantly reduced by adding low-dose ipragliflozin ($p < 0.05$). DBP, TG, AST, ALT were reduced and HDL-C was increased, but there was no significant difference. Urinary albumin of patients with nephropathy (U-Alb 30-299.9 mg/gCr and eGFR 30-) was significantly reduced by adding low-dose ipragliflozin (53.4 ± 42.3 mg/gCr) compared to baseline (84.7 ± 50.9 mg/gCr) ($p = 0.0076$, $n=7$) and that of a patient with nephropathy (U-Alb 30-299.9 mg/gCr and eGFR 30-) was reduced by adding low-dose ipragliflozin (795.2 mg/gCr) to baseline (1580.2 mg/gCr) ($n=1$). Although it was reported administration of SGLT2 inhibitor reduced eGFR because of dehydration, eGFR was significantly reduced until only 12 weeks after adding low-dose ipragliflozin and recovered to same level to baseline at 24 weeks after adding low-dose ipragliflozin. It was reported administration of SGLT2 inhibitors quickly reduced BW because of dehydration and succeeding fat burn, but our data showed BW gradually decreased (there were significant difference between baseline and all periods of checking BW ($p < 0.01$)).

DISCUSSION

Increasing prevalence of type 2 diabetes worldwide [13] comes growing importance of preventing its complications [14]. Type 2 diabetes has been characterized by hyperglycemia due to the failure in glucose homeostasis, which is controlled by the concerted secretion of pancreatic hormones such as insulin and glucagon, and concomitant with insulin resistance in peripheral tissues [15]. There are many kinds of antihyperglycemic agents, but it is difficult to maintain long-term glycemic control in majority of patients, even when used in combination [16]. It is important to maintain good glycemic control and a new drug is expected all over the world. SGLT2 inhibitors are new antihyperglycemic agents and expected to improve glycemic control [4]. SGLT2 inhibitors prevent

hyperglycemia caused by decreasing glucose reabsorption [3]. In addition, many reports showed SGLT2 inhibitors decreased body weight and fat mass, then improved insulin resistance [5-7]. Some reports also showed SGLT2 inhibitors have the possibility to improve β cell function and insulin secretion [17-19]. Furthermore, SGLT2 inhibitors have other metabolic efficacy such as improvement of hypertension [9] and hyperlipidemia [20, 21]. Zinman B, et al. reported one of SGLT2 inhibitor, empagliflozin, improved the rates of death from cardiovascular cause and hospitalization for heart failure [8]. Some studies also demonstrated significant reduction in albumin excretion in various experimental models [10, 22]. Thus SGLT2 inhibitors have many merits, but also have some adverse effects. Urinary and genital infection, decreasing eGFR, diabetic ketosis or ketoacidosis were well known all over the world [11,12]. Furthermore, especially in Japan, toxic skin eruption and stroke were reported as adverse events of SGLT2 inhibitors. Thus, to avoid adverse events of SGLT2 inhibitors, we designed the present study to reveal the efficacy on the glucose control parameters and the other metabolic parameters and safety of low-dose ipragliflozin (25mg/day). In regard to safety, all patients completed the study without any complication such as urinary and genital infection, diabetic ketosis or ketoacidosis, toxic skin eruption and stroke. The eGFR was significantly reduced until only 12 weeks after adding low-dose ipragliflozin and recovered to the baseline level at 24 weeks, although there have been no reports eGFR was recovered in such a short span of time when any SGLT2 inhibitor was administered. Our data showed BW gradually decreased, though it was reported administration of SGLT2 inhibitor quickly reduced BW because of dehydration probably and then because of fat resolution [23]. Thinking through the position of the data of eGFR and BW, low-dose ipragliflozin has little risk of severe dehydration, and it may be the reason why all patients finished our study perfectly without any complication. In terms of efficacy, we showed HbA1c, fasting glucose, and HOMA- β improved significantly. Considering BW was reduced significantly, we think it is possible HOMA-R will improve if we continued to use low-dose ipragliflozin over a long period of time. As for metabolic parameters, not only body weight, but also systolic blood pressure, LDL-cholesterol, and

BNP significantly decreased. In addition, urinary albumin excretion significantly reduced among the patients with microalbuminuria, and for one patient with macroalbuminuria, urinary albumin excretion decreased dramatically. These data indicated low-dose ipragliflozin have an adequate efficacy and can prevent many kinds of complications such as heart failure, renal dysfunction, and disorders caused by hypertension and hyperlipidemia.

In conclusion, we recommend that low-dose ipragliflozin should be a potent treatment alternative for patients with type 2 diabetes to attain good efficacy of glucose control and metabolic parameters with safety. It should be

noted that the limitations of our study include the small number of cases and the short duration of the period of investigation. Thus, further randomized control studies including larger numbers of cases, with longer-term monitoring are required to confirm the beneficial effects of low-dose of ipragliflozin and other SGLT2 inhibitors in patients with type 2 diabetes.

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