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The effectiveness of dapagliflozin for sleep-disordered breathing among Japanese patients with obesity and type 2 diabetes mellitus

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Abstract. Weight reduction is important in patients with sleep-disordered breathing (SDB). In Japanese patients, slight weight reduction is effective for improving the severity of SDB. However, the effect of weight reduction after administration of sodium glucose co-transporter 2 (SGLT2) inhibitor for SDB remains unclear. The aim of this study was to evaluate the improvement of SDB from baseline after administration of dapagliflozin (5 mg) once daily for 24 weeks among Japanese patients with obesity and type 2 diabetes mellitus. Thirty Japanese patients with type 2 diabetes mellitus and SDB were enrolled in a 24-week, prospective, open-label, single-arm, multicentre trial. SDB was defined as at least five 3% oxygen desaturation index (ODI) events per hour, and moderate to severe SDB was defined as at least 15 ODI events per hour. The primary endpoint was the change in 3% ODI between before dapagliflozin administration and at 24 weeks. The prevalence of moderate to severe SDB was 20% in the present study. After administration of dapagliflozin, fasting glucose, HbA1c, aspartate aminotransferase, total cholesterol, low-density lipoprotein cholesterol, and estimated globular filtration rate decreased significantly. The improvement of 3% ODI was observed in patients with moderate to severe SDB but not mild SDB (from 25.0 ± 3.8 at baseline to 18.5 ± 6.1 at 24 weeks, $p = 0.017$). In conclusion, dapagliflozin might improve moderate to severe SDB but not mild SDB in Japanese patients with obesity and type 2 diabetes mellitus.

Key words: Obesity, Sleep apnea syndrome, Sodium glucose co-transporter 2

THE INTERNATIONAL DIABETES FEDERATION TASKFORCE recommended further research regarding the association between sleep-disordered breathing (SDB) and diabetes [1]. SDB was potentially positively associated with cardiovascular diseases [2-4]. Obesity is the primary risk factor for SDB. In East Asian populations, however, including Japanese, patients with type 2 diabetes mellitus are characterized by β cell dysfunction and lesser obesity [5]. Yet although Asians are less obese than other populations, they may have an equivalent or even greater prevalence or severity of SDB [6, 7]. For Japanese patients with type 2 diabetes mellitus, SDB was positively associated with insulin resistance [8] and the onset of type 2 diabetes mellitus [9]. Moreover, a positive association between SDB and microvascular complications among patients with type 2 diabetes mellitus was found [10].

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Weight reduction was found to be effective for mild SDB in both a Finnish study [11] and a US study [12]. In a Japanese study, a weight reduction of only 3% was shown to improve the severity of SDB [13]. Therefore, for Japanese patients with SDB, a slight weight reduction might be effective for treating SDB. Dapagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, reduced body weight compared to a placebo in Japanese patients with type 2 diabetes mellitus [14]. We therefore hypothesized that dapagliflozin might improve SDB *via* slight weight loss among patients with type 2 diabetes mellitus. No evidence exists, however, regarding SGLT2 inhibitor and SDB among patients with type 2 diabetes mellitus. The aim of this study was to evaluate the improvement of SDB from baseline after the administration of dapagliflozin (5 mg) once daily for 24 weeks among patients with obesity and type 2 diabetes mellitus.

Material and Methods

Subjects

Inclusion criteria

Patients were 20 to 80 years old and had previously been diagnosed with type 2 diabetes mellitus. Patients were required to have 1) a body mass index of 23 or more, 2) an estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m^2, and 3) five or more 3% oxygen desaturation index (ODI) events per hour.

Exclusion criteria

Patients with type 1 diabetes were excluded, as were pregnant or breastfeeding women and patients with a past history of severe hypoglycaemia, genital infection, and lower urinary tract infection; ketoacidosis; cerebral infarction; acromegaly; thyroid diseases; otolaryngology disease; cancer; skin diseases; serum hepatic virus marker positive; acute renal dysfunction; alanine aminotransferase (ALT) levels of three or more beyond the upper limit of normal; total bilirubin >2.0 mg/dL; New York Heart Association class-four congestive heart failure; a past history of SGLT2 inhibitor administration; and administration of for the treatment of unstable angina, acute coronary syndrome, acute myocardial infarction, and/or stroke less than 2 months before enrolment.

Study design (Fig. 1)

A 24 weeks, a prospective, open-label, single-arm, multicentre trial was performed. Written informed consent was obtained from all patients, and the protocol was approved by the Institutional Review Board of Ehime University Graduate School of Medicine [UMIN 000018592]. All patients provided informed consent prior to enrolment. After providing informed consent, study patients were monitored for two consecutive overnight periods with pulse oximetry, during which SDB was defined as five or more 3% ODI events per hour [15]. All patients underwent initial screening, and patients who met the inclusion criteria were registered in this study. Diabetic agents were fixed one month prior to the administration of dapagliflozin. Dapagliflozin was initially administered orally in doses of 5 mg one daily for 24 weeks. The physician in charge could increase the dapagliflozin dosage from 5 mg to 10 mg to control plasma glucose levels.

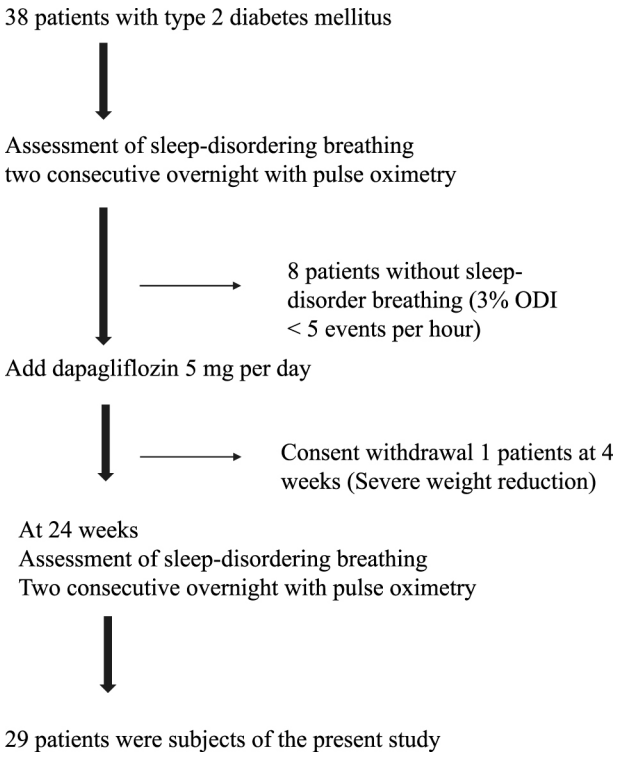

Fig. 1 Study protocol flow diagram

Endpoint

The primary endpoint was the improvement from baseline in the severity of SDB at 24 weeks. Secondary endpoints in this study included the changes from baseline to 24 weeks in neck and waist circumference, HbA1c, fasting glucose level, weight, high-density lipoprotein cholesterol, total cholesterol, and triglycerides.

Measurements

A self-administered questionnaire was used to assess the duration of diabetes mellitus, smoking habits, alcohol

consumption, and medical history. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m). Patients who smoked at least one cigarette per day were classified as current smokers. Patients who drank at least once during the last 12 months were current drinkers. Hypertension was defined as a systolic blood pressure ≥140 mmHg, or a diastolic blood pressure ≥90 mmHg, or both, and/or the use of anti-hypertensive medication. Dyslipidemia was defined as present if serum low-density lipoprotein (LDL) cholesterol concentration was ≥140 mg/dL, triglyceride concentration was ≥150 mg/dL, or high-density lipoprotein (HDL) cholesterol concentration was <40 mg/dL, or if the patients were already being treated with lipid-lowering agents. Stroke and ischemic heart disease were identified from the self-administered questionnaires, medical records, and/or admission data. The definition of microvascular complications was based on the Fukuda standard [16], the Classification of Diabetic Nephropathy 2014 [17, 18], and the abbreviated diagnosis of diabetic neuropathy [19].

Assessment of sleep breathing disorder

For two consecutive nights at home, a pulse oximeter (PULSOX 3Si; Minolta Co., Osaka, Japan) was attached to the left wrist and a sensor probe was fitted to the ring finger and secured with tape. The internal memory of the oximeter stores the values of blood oxygen saturation by performing a moving average for the last 5 seconds, updated every second; the sampling time was short in order to avoid an underestimation of oxygen desaturation [20]. We used the 3% ODI as an indicator of SDB. The value of 3% ODI was taken as the mean value over a period of sleep of at least 4 hours, as estimated by pulse oximetry. In this study, whenever 3% ODI could be evaluated appropriately on two consecutive days, the worse measurement in each pair of consecutive-day measurements was defined as the baseline or 24-week 3% ODI. A sleep diary was used to estimate sleep status. The severity of sleep breathing disorder was defined by the 3% ODI level: normal, <5 events per hour; SDB, ≥5 events per hour; and moderate to severe SDB, ≥15 events per hour [15].

Statistical analysis

The sample size was calculated based on previous data regarding weight reduction and ODI among Japanese patients. A previous study showed that the frequency of 4% ODI events decreased from 6.16 to 4.02 with only a 3% weight loss: an improvement rate of 34.7% [13]. In another study, dapagliflozin decreased the body weight by an average of 3.2% in Japanese patients with type 2 diabetes mellitus [14]. However, participants in this study were not able to achieve a weight loss of 3% or more. Since we needed to establish a strict estimate of the improvement rate of 3% ODI, we assumed that improvement of 3% ODI by weight loss of dapagliflozin was about 60% that of the previous study. In the present study, the frequency of 3% ODI events dropped from 6.16 to 4.87. Precisely 23 patients were needed to provide 90% power and a significance level of 5% to show a significant difference between pre and post treatment, assuming an SD of 1.8. Since we assumed that 25% of patients would discontinue the present study before 24 weeks, the enrolment of 30 patients was needed for the present study. The primary and secondary endpoints were analysed using a paired *t*-test and chi-square test. All analyses were performed by JMP 9.4 (SAS Institute, Inc., Cary, NC, USA). The significance level (two tail) for each test was 0.05.

Results

Table 1 shows the characteristics of this study. The mean age, BMI, fasting glucose, HbA1c, duration of diabetes, and 3% ODI were 58.9 years, 29.43, 152.8 mg/dL, 7.78%, 13.8 years, and 12.4, respectively. The percentages of male and moderate to severe SDB patients were 66.7% and 20.0%, respectively. Table 2 shows physical and laboratory findings before and after administration of dapagliflozin. After 24 weeks of administration of dapagliflozin, fasting glucose, HbA1c, ALT, total cholesterol, LDL cholesterol, and eGFR had decreased significantly. In contrast, creatinine (Cr) had significantly increased. Patients' weight was reduced by 1.9 kg, BMI by 0.74, neck circumference by 0.67 cm, and systolic blood pressure by 7.3 mmHg. The significant changes regarding the SDB parameter were not observed in all patients. Table 3 shows the results according to the severity of SDB. Significant changes in fasting glucose, HbA1c, weight, and BMI were found regardless of the severity of SDB. Among patients with mild SDB, significant changes in ALT, T-chol, LDL-cholesterol, eGFR, Cr, waist, neck circumference, and systolic blood pressure were found. Among patients with moderate to severe SDB, a significant decrease in TG was found. Among patients with moderate to severe SDB, though not among those with mild SDB, a significant improvement in 3% ODI was observed after 24 weeks of administration of dapagliflozin: from 25.0 ± 3.8 at baseline to

Table 1 Patient characteristics at baseline

Variable	Total (n = 30)	Mild SDB (n = 24)	Moderate to severe SDB (n = 6)
Age, years, mean ± SD	58.9 ± 10.7	59.0 ± 10.7	58.3 ± 11.7
Male gender (%)	20 (66.7)	15 (62.5)	5 (83.3)
Body weight, Kg, mean ± SD	79.0 ± 27.1	78.8 ± 29.3	79.6 ± 17.2
BMI, kg/m^2, mean ± SD	29.43 ± 8.54	29.28 ± 8.94	30.05 ± 7.39
Waist, cm, mean ± SD	98.3 ± 14.8	99.4 ± 16.1	94.1 ± 7.4
Neck circumference, cm, mean ± SD	39.39 ± 3.81	39.32 ± 4.03	39.68 ± 3.09
Fasting glucose, mg/dL, mean ± SD	152.8 ± 34.1	150.2 ± 32.0	159.2 ± 42.0
HbA1c, %, mean ± SD	7.78 ± 1.14	7.68 ± 1.10	8.18 ± 1.29
Duration of T2DM, years, mean ± SD	13.8 ± 8.7	13.7 ± 8.8	14.5 ± 9.1
Current drinking (%)	14/30 (46.7)	10/24 (41.7)	4/6 (66.7)
Current smoking (%)	4/30 (13.3)	1/24 (0.04)	3/6 (50.0)
Hypertension (%)	23/30 (76.7)	19/24 (82.6)	4/6 (66.7)
Hyperlipidemia (%)	23/30 (76.7)	19/24 (82.6)	4/6 (66.7)
Diabetic neuropathy (%)	13/30 (43.3)	11/24 (45.8)	2/6 (33.3)
Diabetic retinopathy (%)	4/30 (13.3)	3/24 (12.5)	1/6 (16.7)
Diabetic nephropathy (%)	11/30 (36.7)	8/24 (33.3)	3/6 (50.0)
Stroke (%)	3/30 (10.0)	3/24 (12.5)	0/6 (0.0)
Coronary artery disease (%)	2/30 (6.7)	2/24 (8.3)	0/6 (0.0)
3% ODI, events per hour, mean ± SD	12.4 ± 7.0	9.3 ± 2.4	25.0 ± 3.8

SD, standard deviation; BMI, body mass index; T2DM, type 2 diabetes mellitus; ODI, oxygen desaturation index; SDB, sleep-disordering breathing

18.5 ± 6.1 at 24 weeks (p = 0.017) (Fig. 2). One mild SDB patient whose 3% ODI measurement appeared to worsen over the 24-week period used benzodiazepines on the night of the 24-week measurement only. No patients changed their oral diabetic agents during this study. In two patients, however, insulin dose was down-titrated in order to avoid hypoglycemia. In a sensitivity analysis, neither body weight reduction nor neck circumference reduction was associated with improvement in 3% ODI among all patients.

Discussion

To our knowledge, this is the first study to investigate the effect of dapagliflozin for SDB among Japanese patients with obesity and type 2 diabetes mellitus. Dapagliflozin was effective for moderate to severe SDB but not mild SDB in Japanese patients with obesity and type 2 diabetes mellitus in this study.

Reduced oxygen desaturation stimulates the sympathetic nerve and increases serum catecholamine levels [21, 22]. Inflammatory cytokines in patients with SDB are higher than those in control [23]. Sleep fragmentation due to SDB might activate the hypothalamic-pituitary-adrenal axis [24]. Thus, SDB was thought to be positively associated with insulin resistance. SDB was significantly positively associated with the new onset of type 2 diabetes mellitus in the Japanese general population [9]. Among Japanese patients with type 2 diabetes, SDB was independently positively associated with albuminuria and macroalbminuria [10]. Among patients with type 2 diabetes mellitus, intervention for SDB might be needed to improve clinical outcomes. In a clinical setting, however, the intervention rate for SDB might be low. First, the awareness of SDB might still be low among physicians. Second, the standard therapy for SDB was continuous positive air way pressure (CPAP) therapy to prevent for cardiovascular diseases and death. Long-

Table 2 The changes of physical and laboratory findings before and after administration of dapagloflozin for 24 weeks in 29 patients

	Baseline	24 weeks	*p*-value
All patients (n = 29)			
Fasting plasma glucose, mg/dL, mean ± SD	151.4 ± 34.1	129.4 ± 27.3	0.001
CPR, ng/mL, mean ± SD	1.81 ± 1.03	1.74 ± 1.19	0.68
HbA1c, %, mean ± SD	7.76 ± 1.15	7.28 ± 0.91	0.001
ALT, IU/mL, mean ± SD	32.2 ± 16.9	23.9 ± 14.4	0.002
T-chol, mg/dL, mean ± SD	181.8 ± 28.9	175.1 ± 26.3	0.009
TG, mg/dL, mean ± SD	127.6 ± 67.8	108.1 ± 46.4	0.09
LDL-cholesterol, mg/dL, mean ± SD	104.0 ± 25.8	97.5 ± 24.3	0.032
HDL-cholesterol, mg/dL, mean ± SD	55.6 ± 13.2	56.9 ± 13.3	0.22
Uric acid, mg/dL, mean ± SD	5.94 ± 2.13	5.41 ± 1.36	0.056
Creatinine, mg/dL, mean ± SD	0.81 ± 0.19	0.84 ± 0.21	0.001
eGFR, mean ± SD	73.6 ± 21.1	70.7 ± 21.1	0.006
BNP, ng/mL, mean ± SD	14.8 ± 11.7	14.6 ± 10.5	0.91
Weight, Kg, mean ± SD	79.4 ± 27.4	77.5 ± 27.5	0.001
BMI, mean ± SD	29.64 ± 8.6	28.90 ± 8.7	0.002
Waist, cm, mean ± SD	98.7 ± 14.9	94.8 ± 7.7	0.10
Neck, cm, mean ± SD	39.42 ± 3.88	38.75 ± 4.09	0.012
Systolic blood pressure, mmHg, mean ± SD	135.3 ± 19.9	128.0 ± 15.0	0.002
Diastolic blood pressure, mmHg, mean ± SD	77.8 ± 14.2	77.0 ± 11.3	0.45
Pulse, beats per minute, mean ± SD	78.2 ± 13.4	77.5 ± 10.0	0.43
3% ODI, events per hour, mean ± SD	12.5 ± 7.0	13.5 ± 7.9	0.49
Lowest O_2 saturation, %, mean ± SD	83.5 ± 6.8	83.7 ± 4.7	0.80
Heart rate during night, beats per minute, mean ± SD	69.0 ± 7.5	68.0 ± 7.1	0.43
ESS, mean ± SD	7.8 ± 4.2	7.7 ± 4.7	0.88

SD, standard deviation; CPR, c-peptide immunoreactivity; ALT, aspartate aminotransferase; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; SD, standard deviation; SDB, sleep-disordering breathing; BMI, body mass index; ODI, oxygen desaturation index; ESS, Epworth Sleepiness Scale

term treatment intervention for SDB is important for improving the prognosis of patients with type 2 diabetes mellitus. However, a low adherence rate of CPAP therapy was reported compared to that for patients using oral medication [25].

Limited evidence regarding the association between weight reduction and severity of SDB exists. In a US interventional study of obese patients with type 2 diabetes and sleep apnea syndrome (mean BMI: 36.7), weight reduction (10.8 kg) in a lifestyle intervention group significantly improved the severity of SDB [12]. In a Finnish study of overweight patients with mild SDB (mean BMI: 33.4), weight reduction (10.7 kg) through a very low-calorie diet improved the severity of SDB [11]. In obese Asian patients with SDB (mean BMI: 31.2), the apnea-hypopnea index values were significantly decreased in a 3% weight reduction group, while 4% ODI values also decreased, but not significantly [13]. The findings in the present study are partially consistent with results in these previous studies regarding the relationship between weight reduction and SDB. The composition of weight reduction following SGLT2 inhibitor

Table 3 The changes of physical and laboratory findings before and after administration of dapagloflozin for 24 weeks, according to the severity of SDB at baseline

	Baseline	24 weeks	*p*-value
Mild SDB (n = 23)			
Fasting plasma glucose, mg/dL, mean ± SD	149.3 ± 32.5	129.7 ± 26.6	0.001
CPR, ng/mL, mean ± SD	1.83 ± 1.14	1.84 ± 1.31	0.74
HbA1c, %, mean ± SD	7.65 ± 1.12	7.24 ± 0.82	0.008
ALT, IU/mL, mean ± SD	34.6 ± 17.7	23.7 ± 13.6	0.001
T-chol, mg/dL, mean ± SD	182.5 ± 30.8	175.1 ± 26.9	0.010
TG, mg/dL, mean ± SD	129.5 ± 71.3	111.5 ± 47.7	0.21
LDL-cholesterol, mg/dL, mean ± SD	105.7 ± 27.3	98.0 ± 22.7	0.016
HDL-cholesterol, mg/dL, mean ± SD	54.7 ± 13.3	56.0 ± 13.2	0.23
Uric acid, mg/dL, mean ± SD	5.69 ± 1.62	5.34 ± 1.41	0.08
Creatinine, mg/dL, mean ± SD	0.81 ± 0.18	0.85 ± 0.19	0.002
eGFR, mean ± SD	71.77 ± 18.42	68.65 ± 18.31	0.013
BNP, ng/mL, mean ± SD	15.4 ± 12.3	14.7 ± 11.3	0.73
Weight, Kg, mean ± SD	79.4 ± 29.9	77.7 ± 30.0	0.010
BMI, mean ± SD	29.53 ± 9.05	28.93 ± 9.19	0.019
Waist, cm, mean ± SD	99.9 ± 16.2	94.9 ± 7.4	0.049
Neck, cm, mean ± SD	39.36 ± 4.11	38.68 ± 4.30	0.046
Systolic blood pressure, mmHg, mean ± SD	136.7 ± 21.4	129.4 ± 22.9	0.046
Diastolic blood pressure, mmHg, mean ± SD	78.9 ± 15.6	77.1 ± 15.7	0.47
Pulse, beats per minute, mean ± SD	79.7 ± 14.5	78.7 ± 10.1	0.73
3% ODI, events per hour, mean ± SD	9.3 ± 2.5	12.2 ± 7.9	0.06
Lowest O_2 saturation, %, mean ± SD	85.7 ± 3.9	85.1 ± 3.6	0.39
Heart rate during night, beats per minute, mean ± SD	68.4 ± 6.6	68.3 ± 7.3	0.95
ESS, mean ± SD	7.0 ± 4.1	6.7 ± 3.9	0.61
Moderate to severe SDB (n = 6)			
Fasting plasma glucose, mg/dL, mean ± SD	159.2 ± 42.0	128.0 ± 32.7	0.012
CPR, ng/mL, mean ± SD	1.73 ± 0.57	1.35 ± 0.53	0.08
HbA1c, %, mean ± SD	8.18 ± 1.29	7.42 ± 1.31	0.001
ALT, IU/mL, mean ± SD	23.2 ± 9.6	24.8 ± 18.7	0.82
T-chol, mg/dL, mean ± SD	179.0 ± 22.5	175.0 ± 26.5	0.56
TG, mg/dL, mean ± SD	120.2 ± 53.9	94.8 ± 42.4	0.013
LDL-cholesterol, mg/dL, mean ± SD	97.5 ± 19.0	95.5 ± 32.1	0.82
HDL-cholesterol, mg/dL, mean ± SD	59.3 ± 13.9	60.3 ± 14.5	0.74
Uric acid, mg/dL, mean ± SD	6.90 ± 3.52	5.65 ± 1.25	0.31
Creatinine, mg/dL, mean ± SD	0.81 ± 0.26	0.83 ± 0.29	0.20
eGFR, mean ± SD	80.78 ± 30.30	78.70 ± 30.48	0.32
BNP, ng/mL, mean ± SD	12.6 ± 9.8	14.4 ± 7.1	0.51

Table 3 Cont.

	Baseline	24 weeks	*p*-value
Weight, Kg, mean ± SD	79.6 ± 17.2	77.0 ± 16.4	0.033
BMI, mean ± SD	30.05 ± 7.39	29.08 ± 6.95	0.036
Waist, cm, mean ± SD	94.1 ± 7.4	94.3 ± 9.7	0.92
Neck, cm, mean ± SD	39.68 ± 3.09	39.03 ± 3.49	0.12
Systolic blood pressure, mmHg, mean ± SD	130.3 ± 12.7	133.0 ± 14.3	0.57
Diastolic blood pressure, mmHg, mean ± SD	73.7 ± 5.35	84.2 ± 10.7	0.08
Pulse, beats per minute, mean ± SD	72.7 ± 6.5	72.2 ± 5.8	0.84
3% ODI, events per hour, mean ± SD	25.0 ± 3.8	18.5 ± 6.1	0.017
Lowest O_2 saturation, %, mean ± SD	74.8 ± 8.9	78.5 ± 5.0	0.33
Heart rate during night, beats per minute, mean ± SD	71.3 ± 10.8	66.9 ± 6.9	0.17
ESS, mean ± SD	10.5 ± 3.9	11.5 ± 5.9	0.61

SD, standard deviation; CPR, c-peptide immunoreactivity; ALT, aspartate aminotransferase; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; SD, standard deviation; SDB, sleep-disordering breathing; BMI, body mass index; ODI, oxygen desaturation index; ESS, Epworth Sleepiness Scale

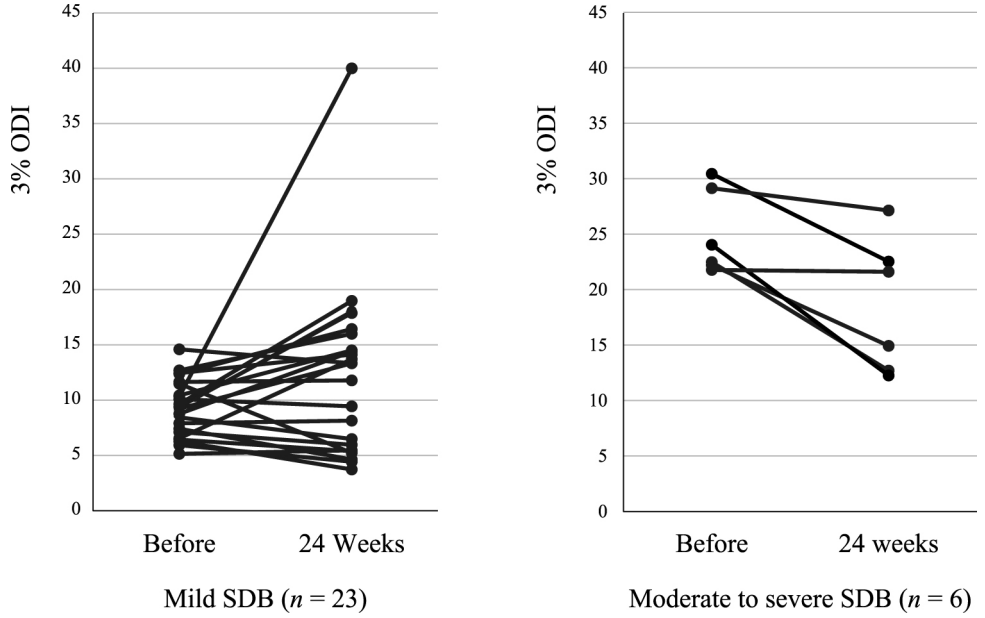

Fig. 2 The improvement of 3% ODI among patients with moderate to severe SDB.
Among patients with mild SDB, the effect of dapagliflozin for SDB was not found. The improvement of 3% ODI was observed in all six patients with moderate to severe SDB.

was reported in two previous studies of Japanese patients with type 2 diabetes mellitus [26, 27]. The majority of body weight reduction was due to a loss of fat mass in both studies, and 22% of weight reduction was from water loss in both studies [23, 24]. Among patients with diabetes, hyperinsulinemia was common. The effects of insulin on sodium metabolism relates to common clinical situations such as sodium retention and edema [28].

Fluid retention and fluid shift in the body affected onset and worsened SDB [29]. Thus, the loss of fat and water due to SGLT2 inhibitor might contribute to the improvement of the severity of SDB. Long-term administration of SGLT2 might affect the prognosis of patients with type 2 diabetes mellitus and SDB by improving SDB.

The EMPA-REG OUTCOME trial reported a renal protective effect of long-term use of SGLT2 inhibitors [30]. In the EMPA-REG OUTCOME trial, however, an initial decrease in eGFR was observed among patients treated with SGLT2 inhibitors. As the duration of the present study was only 24 weeks, which is within the period of the previously reported initial decrease in eGFR, the decrease in eGFR in this study is partially consistent with the renal function results in the EMPA-REG OUTCOME trial.

The administration of dapagliflozin appears to improve moderate to severe SDB but not mild SDB in this study. Mean BMI at baseline was similar between patients with mild SDB and those with moderate to severe SDB. The pathogenesis of SDB is multifactorial. There is evidence that fluid retention and overnight rostral fluid shift, both of which are stronger in men than in women, may contribute to the pathogenesis of SDB [31]. The proportions of male sex were 62.4% and 83.3% among patients with mild SDB and those with moderate to severe SDB, respectively (not significant). After 24 weeks of dapagliflozin administration, weight reductions were 1.70 kg and 2.56 kg among patients with mild SDB and those with moderate to severe SDB, respectively (not significant). One patient with mild SDB had used benzodiazepines to fall asleep. Benzodiazepines might worsen ODI *via* their muscle relaxant action. The discrepancies between the results in patients with mild SDB and those with moderate to severe SDB may be explained, at least in part, by use of benzodiazepines, BMI at baseline, sex, and weight reduction.

There were several limitations in this study. First, the sample size was small. Further studies are needed to confirm our findings. Second, this study have no control group. Third, we could not use polysomnography to estimate the status of SDB. The assessment of SDB in the present study was achieved through the home use of pulse oximetry on two consecutive nights. A pulse oximeter might be useful for estimating the severity of SDB at home. Finally, the distribution of body fluids before administration of dapagliflozin was not available in the present study.

In conclusion, the administration of dapagliflozin might improve moderate to severe SDB but not mild SDB in Japanese patients with obesity and type 2 diabetes mellitus. Further clinical studies regarding the association between SGLT2 inhibitor and SDB are needed to confirm our findings.

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Disclosures

SF has received honoraria for lectures from AstraZeneca, Eli Lilly, Sanofi, Boehringer Ingelheim, Mochida pharmaceutical Co., Ltd. and Dainippon Parma Co. Other authors declare no conflicts of interest.

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