Effects of dapagliflozin on body weight in patients with type 2 diabetes mellitus: Evidence-based practice

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Abstract. The dose-dependent pharmacological response to dapagliflozin in patients with type 2 diabetes mellitus (T2DM) with regard to weight loss remain unknown. The aim of the present study was to investigate the effects of dapagliflozin on weight loss in patients with T2DM. A total of 8,545 patients with T2DM from 24 randomized controlled trials reported in the literature were selected for inclusion in the study. Data from these trials were analyzed using maximal effect (E_{max}) models with nonlinear mixed effects modeling; the evaluation index was the body weight change rate from baseline values. Patients treated with 2.5 mg/day dapagliflozin exhibited an E_{max} of -3.04%, and the time taken for therapy to reach half of the E_{max} (ET_{50}) was estimated to be 30.8 weeks for patients treated with this dose. Patients treated with 5, 10 and 20 mg/day dapagliflozin exhibited E_{max} values of -6.57, -4.12 and -3.23%, respectively, and their ET_{50} values were estimated to be 27.3, 20.4 and 4.23 weeks, respectively. The data indicated ideal linear relationships between individual predictions and observations, suggesting the optimal fitting of the final models. The present study is the first systematic analysis of the effect of dapagliflozin on weight loss in patients with T2DM. The application of dapagliflozin at 5 mg/day exhibited a greater weight loss effect compared with the other doses used, and the weight loss onset time shortened as the dose of dapagliflozin increased.

Introduction

It is estimated that the global prevalence of diabetes is currently 463 million worldwide and will increase to 700 million by 2045 (1). Type 2 diabetes mellitus (T2DM), a condition in which patients experience hyperglycemia due to impaired insulin action and insufficient insulin secretion, is the most common type of diabetes worldwide (1). In addition, patients with T2DM often present with hypertension, dyslipidemia, atherosclerotic disease and obesity (2,3). It has been reported that >50% of patients with T2DM are obese (3,4). Patients with T2DM who are overweight or obese have a higher risk of cardiovascular disease and higher mortality rate, which are vital determinants of T2DM prognosis (4,5). Therefore, it is crucial to improve the management of T2DM in patients who are overweight or obese (6).

Dapagliflozin is a sodium glucose cotransporter 2 (SGLT2) inhibitor and was the first drug with this mechanism to be approved for the treatment of T2DM. It is considered to be an important treatment option as an adjunct to diet and exercise for the improvement of glycemic control in adult patients with T2DM (7). In addition, dapagliflozin can cause a modest reduction in weight (7). The weight loss achieved with dapagliflozin is clinically meaningful in terms of improving overall health outcomes and reducing the risk of complications associated with T2DM (7).

However, the extent to which dapagliflozin causes weight reduction and the dose-dependent pharmacological response to dapagliflozin in patients with T2DM with regard to weight loss remain unknown. Therefore, the present study aimed to explore the dose-dependent weight loss response to dapagliflozin in patients with T2DM.

Materials and methods

Included data. The data of patients with T2DM treated with dapagliflozin were extracted from published articles, and the

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details of patients assigned to the treatment or control groups were obtained from the selected literature (8-31). These studies had all been approved by the ethics committee of each participating center (8-31). The inclusion criteria for the present study were as follows: i) Patients with T2DM, ii) dapagliflozin treatment, iii) randomized controlled trial (RCT), iv) availability of body weight information and v) availability of the exact dosage and duration of therapy with dapagliflozin. No additional specific criteria were required to be met. The source, grouping, dapagliflozin dosage, duration of treatment, sample size and patient age were extracted from these published articles.

In order to eliminate the potential baseline effect, the present study calculated the body weight change rate from baseline for use as an evaluation index. The equation (I) used was as follows.

$$E\ (\%) = \frac{E_{time} - E_{base}}{E_{base}}\ x\ 100\ \text{(I)}$$

E_{time} is weight at a specific time and E_{base} is weight at baseline.

Model establishment. The effects of dapagliflozin on weight loss in patients with T2DM varied with time and eventually reached a plateau. Maximal effect (E_{max}) models were used to assess these effects. In addition, the actual effects of dapagliflozin on weight loss in patients with T2DM were assessed by subtracting the control effect from the sum effect using equations (II) and (III) as follows:

$$E_{c,i\,j} = E_{a,i,j} - E_{b,i,j}\ \text{(II)}$$

$$E_{c,i\,j} = \frac{E_{max,i,j}\ x\ time}{ET_{50,i,j} + time} + \frac{\varepsilon_{i,j}}{\sqrt{\frac{N_{i,j}}{100}}}\ \text{(III)}$$

$E_{a,i,j}$ represents the sum effect of dapagliflozin on weight loss in patients with T2DM; $E_{b,i\,j}$ represents the weight loss in the control group of patients with T2DM; $E_{c,i,j}$ represents the actual effect of dapagliflozin on weight loss in patients with T2DM; i represents a specific study; j represents the time point of the study; ET_{50} is the duration of treatment required to reach half the E_{max}; $\varepsilon_{i,j}$ represents the residual error of study i with time j; and $N_{i,j}$ represents the sample size in study i at time point j. $\varepsilon_{i,j}$ was weighted by sample size and assumed to be normally distributed, with a mean of 0 and variance of $\sigma^2/(N_{i,j}/100)$.

The variabilities observed between studies were described using additive error or exponential error models. The equations used (IV)-(VII) were as follows:

$$F_{max,m,n} = F_{max} + \eta_{1,n}\ \text{(IV)}$$

$$FT_{50,m,n} = FT_{50} + \eta_{2,n}\ \text{(V)}$$

$$F_{max,m,n} = F_{max}\ x\ \exp(\eta_{1,n})\ \text{(VI)}$$

$$FT_{50,m,n} = FT_{50}\ x\ \exp(\eta_{2,n})\ \text{(VII)}$$

In these equations, F_{max} represent E_{max}, FT_{50} represent ET_{50}, m represents a specific study; n represents the time point of the study; $\eta_{1,n}$ and $\eta_{2,n}$ represent the inter-study variability,

when available, which was assumed to be normally distributed, with a mean of 0 and variance of $\omega_{1,i}^2$, $\omega_{2,i}^2$, respectively.

Furthermore, categorical and continuous covariates (source, weight and age) were evaluated using equations (VIII)-(X):

$$P_{pati} = P_{Typi} + COV\ x\ \theta_c\ \text{(VIII)}$$

$$P_{pati} = P_{Typi} + (COV - COV_m) \cdot \theta_c\ \text{(IX)}$$

$$P_{pati} = P_{Typi}\ x\ (COV/COV_m)^{\theta c}\ \text{(X)}$$

P_{pati} represents the value of an individual parameter; P_{Typi} represents the value of a typical parameter; COV represents the covariate; COV_m represents the median value of COV; and θ_c represents a correction coefficient.

Statistical analysis. Nonlinear mixed effects modeling software (NONMEM®; edition 7; ICON Development Solutions Ltd.) was used to establish the model and conduct statistical analysis. A change in the objective function value (OFV), which is a function that quantifies the difference between predicted values from the model and the actual observed data, was used as the criterion for covariate inclusion, which was the criterion to determine the fitting of the model. When the OFV was decreased [>3.84; χ^2, α=0.05, degrees of freedom (d.f.)=1], the inclusion criterion was met. When the OFV was increased (>6.63; χ^2, α=0.01, d.f.=1), significance was achieved in the final model. Our previous studies were mainly based on the methodology used in the present study, and indicated that the present method was reliable and acceptable (32-35).

Model validation. Individual predictions were compared with observations in individual plots and used to evaluate the final model. Prediction-corrected visual predictive check (VPC) plots were used to assess the predictive effectiveness of the final model.

Results

Included studies. A total of 24 RCTs, which included 8,545 patients with T2DM, were selected for analysis (8-31). These studies included 44 dapagliflozin treatment groups, which comprised 5 with a dose of 2.5 mg/day, 12 with a dose of 5 mg/day, 23 with a dose of 10 mg/day, and 4 with a dose of 20 mg/day. Drug safety at high doses was evaluated and no significant adverse reactions were found; in particular, no serious adverse events associated with the liver, kidney or pancreas were reported in these studies (8-31). In addition, in the included studies, the duration of dapagliflozin treatment was 12-104 weeks, and the mean age range of the patients with T2DM was 49.9-68.0 years (Table I).

Modeling and validation. The actual dapagliflozin effect on weight loss in patients with T2DM is shown in Table II. Four E_{max} models were established, one for each dose of dapagliflozin (2.5, 5, 10 and 20 mg/day) to investigate the effect of the treatment on weight loss in patients with T2DM. The calculated values of E_{max} and ET_{50} were as follows: 2.5 mg/day, -3.04% and 30.8 weeks, respectively; 5 mg/day dapagliflozin, -6.57% and 27.3 weeks, respectively; 10 mg/day dapagliflozin, -4.12% and 20.4 weeks, respectively; and 20 mg/day dapagliflozin,

Table I. Studies identified for analysis.

First author/s, year	Source	Groups	Dapagliflozin, mg/day	Duration of treatment, weeks	Body weight, kg mean median (SD); mean ± SD; (inter-quartile range); median [5-95th percentile]	Patient no.	Age, years	(Refs.)
Iacobellis and Gra-Menendez, 2020	USA	Dapagliflozin	10	24	104 (28)	50	52 (9)	(13)
		Control	-	24	96.9 (23)	50	51 (11)	
Yamakage et al, 2020	Japan	Dapagliflozin	5	24	80.5±22.6	27	58.4±13.0	(28)
		Control	-	24	79.0±16.3	27	60.7±11.9	
Aso et al, 2019	Japan	Dapagliflozin	5	24	73.6 (61.9, 80.8)	33	-	(8)
		Control	-	24	74.9 (65.6, 81.6)	24	-	
Yang et al, 2018	Asia	Dapagliflozin	10	24	71.1±12.0	139	56.5±8.4	(30)
		Control	-	24	72.4±13.1	133	58.6±8.9	
Yang et al, 2016	Asia	Dapagliflozin	5	24	70.8±12.2	147	53.1±9.1	(29)
		Dapagliflozin	10	24	71.4±12.0	152	54.6±9.5	
		Control	-	24	70.9±11.4	145	53.5±9.2	
Matthaei et al, 2015	-	Dapagliflozin	10	52	88.6 (17.6)	108	-	(21)
		Control	-	52	90.1 (16.2)	108	-	
Mathieu et al, 2015	-	Dapagliflozin	10	24	85.8±18.4	160	55.2±8.6	(20)
		Control	-	24	88.2±18.1	160	55.0±9.6	
Cefalu et al, 2015	Europe, Asia, USA, Canada, and Argentina	Dapagliflozin	10	52	92.6 (20.5)	455	62.8 (7.0)	(10)
		Control	-	52	93.6 (19.5)	459	63.0 (7.7)	
Rosenstock et al, 2015	USA	Dapagliflozin	10	24	87.1±18.0	179	53±10	(22)
		Control	-	24	88.0±18.7	176	55±10	
Schumm-Draeger et al, 2015	Europe and South Africa	Dapagliflozin	2.5	16	92.49 (18.632)	100	58.3 (9.0)	(24)
		Dapagliflozin	5	16	93.62 (16.641)	99	55.3 (9.3)	
		Dapagliflozin	10	16	90.58 (15.929)	99	58.5 (9.8)	
		Control	-	16	88.82 (15.327)	101	58.5 (9.4)	
Kaku et al, 2014	Japan	Dapagliflozin	5	24	65.81 (14.37)	86	58.6 (10.4)	(15)
		Dapagliflozin	10	24	69.70 (13.82)	88	57.5 (9.3)	
		Control	-	24	65.96 (12.91)	87	60.4 (9.7)	
Leiter et al, 2014	USA, Canada, Australia, Chile, Argentina and five European countries	Dapagliflozin	10	24	94.5±17.8	480	63.9±7.6	(18)
		Control	-	24	93.2±16.8	482	63.6±7.0	
Grandy et al, 2014	Bulgaria, Czech Republic, Hungary, Poland and Sweden	Dapagliflozin	10	102	92.1 (14.1)	89	60.6 (8.2)	(11)
		Control	-	102	90.9 (13.7)	91	60.8 (6.8)	

Table I. Continued.

First author/s, year	Source	Groups	Dapagliflozin, mg/day	Duration of treatment, weeks	Body weight, kg mean (SD); mean ± SD; (inter-quartile range); median [5-95th percentile]	Patient no.	Age, years	(Refs.)
Ji *et al*, 2014	China, Korea and India	Dapagliflozin	5	24	68.89 (11.43)	128	53.0 (11.07)	(14)
		Dapagliflozin	10	24	70.92 (11.64)	133	51.2 (9.89)	
		Control	-	24	72.18 (13.23)	132	49.9 (10.87)	
Kohan *et al*, 2014	USA, Argentina, Canada, India, Mexico, Peru, Italy, Australia, France, Spain, Denmark, Puerto Rico and Singapore	Dapagliflozin	5	104	95.2±20.9	83	66±8.9	(16)
		Dapagliflozin	10	104	93.2±17.3	85	68±7.7	
		Control	-	10	89.6±20.0	84	67±8.6	
Wilding *et al*, 2014	Worldwide	Dapagliflozin	2.5	104	93.0 (16.7)	202	59.8 (7.6)	(27)
		Dapagliflozin	10	104	94.5 (16.8)	194	59.3 (8.8)	
		Control	-	104	94.5 (19.8)	193	58.8 (8.6)	
Lambers *et al*, 2013	Canada, Netherlands and USA	Dapagliflozin	10	12	93.2 (18.0)	24	53.7 (9.4)	(17)
		Control	-	12	96.2 (19.5)	25	58.0 (9.5)	
Bailey *et al*, 2013	Argentina, Brazil, Canada, Mexico, and USA	Dapagliflozin	2.5	102	84.90 (17.77)	137	-	(9)
		Dapagliflozin	5	102	84.73 (16.26)	137	-	
		Dapagliflozin	10	102	86.28 (17.53)	135	-	
		Control	-	102	87.74 (19.24)	137	-	
Rosenstock *et al*, 2012	Argentina, Canada, India, Mexico, Peru, China, Philippines and USA	Dapagliflozin	5	48	87.8±20.7	141	53.2±10.9	(23)
		Dapagliflozin	10	48	84.8±22.2	140	53.8±10.4	
		Control	-	48	86.4±21.3	139	53.5±11.4	
Henry *et al*, 2012	North America, Latin America, Europe and Asia	Dapagliflozin	5	24	84.1 (19.5)	194	51.7 (9.3)	(12)
		Dapagliflozin	10	24	88.4 (19.7)	211	51.0 (10.1)	
		Control	-	24	87.2 (19.4)	208	52.7 (10.4)	
Strojek *et al*, 2011	Czech Republic, Hungary, Republic of Korea, Philippines, Poland, Thailand and Ukraine	Dapagliflozin	2.5	24	81.89	154	59.9±10.14	(25)
		Dapagliflozin	5	24	81.00	142	60.2±9.73	
		Dapagliflozin	10	24	80.56	151	58.9±8.32	
		Control	-	24	80.94	145	60.3±10.16	
Zhang *et al*, 2010	-	Dapagliflozin	10	12	86.6 [60.6, 115]	45	55.0[41.0,71.0]	(31)
		Dapagliflozin	20	12	86.6 [60.6, 115]	57	55.0[41.0,71.0]	
		Control	-	12	89.8 [59.2, 122]	49	52.0[34.4.70.6]	
		Dapagliflozin	10	12	104 [82.0, 120]	19	57.0[38.0,71.6]	
		Dapagliflozin	20	12	104 [82.0, 120]	25	57.0[38.0,71.6]	
		Control	-	12	95.7 [77.3, 113]	14	60.0[49.6,69.0]	

Table I. Continued.

First author/s, year	Source	Groups	Dapagliflozin, mg/day	Duration of treatment, weeks	Body weight, kg mean median (SD); mean ± SD; (inter-quartile range); median [5-95th percentile]	Patient no.	Age, years	(Refs.)
Wilding et al, 2009	USA and Canada	Dapagliflozin	10	12	103.4±10.2	24	55.7±9.2	(26)
		Dapagliflozin	20	12	101.2±15.3	24	56.1±10.6	
		Control	-	12	101.8±16.5	23	58.4±6.5	
List et al, 2009	USA, Canada, Mexico and Puerto Rico	Dapagliflozin	2.5	12	90±20	59	55±11	(19)
		Dapagliflozin	5	12	89±17	58	55±12	
		Dapagliflozin	10	12	86±17	47	54±9	
		Dapagliflozin	20	12	88±18	59	55±10	
		Control	-	12	89±18	54	54±9	

Table II. Parameter estimates of the final models.

Model	Parameter	Estimate
A	E_{max}, %	-3.04
	ET_{50}, week	30.8
	ω_{Emax}	1.360
	ω_{ET50}	17.088
	ε	0.062
B	E_{max}, %	-6.57
	ET_{50}, week	27.3
	ω_{Emax}	2.773
	ω_{ET50}	15.460
	ε	0.100
C	E_{max}, %	-4.12
	ET_{50}, week	20.4
	ω_{Emax}	0.585
	ω_{ET50}	7.918
	ε	0.327
D	E_{max}, %	-3.23
	ET_{50}, week	4.23
	ω_{Emax}	-
	ω_{ET50}	3.302
	ε	0.010

Model A, patients treated with 2.5 mg/day dapagliflozin; model B, patients treated with 5 mg/day dapagliflozin; model C, patients treated with 10 mg/day dapagliflozin; D, patients treated with 20 mg/day dapagliflozin. E_{max}, maximal effect; ET_{50}, treatment duration to reach half of the E_{max}; ω_{Emax}, interstudy variability of E_{max}; ω_{ET50}, interstudy variability of ET_{50}; ε, residual error.

-3.23% and 4.23 weeks, respectively. Information was obtained for all 8,545 patients with T2DM and it was not found that the clinicopathological characteristics of the patients may have influenced their weight loss outcomes.

Models were constructed based on the E_{max} and ET_{50} values for the 2.5, 5, 10 and 20 mg/day doses of dapagliflozin. The effects of these doses on weight loss in patients with T2DM are described in equations (XI)-(XIV), respectively:

$$E = \frac{-3.04\% \times time}{30.8 + time} \quad (XI)$$

$$E = \frac{-6.57\% \times time}{27.3 + time} \quad (XII)$$

$$E = \frac{-4.12\% \times time}{20.4 + time} \quad (XIII)$$

$$E = \frac{-3.23\% \times time}{4.23 + time} \quad (XIV)$$

E represents the effect of dapagliflozin on the weight loss of patients with T2DM, and time is the duration of dapagliflozin
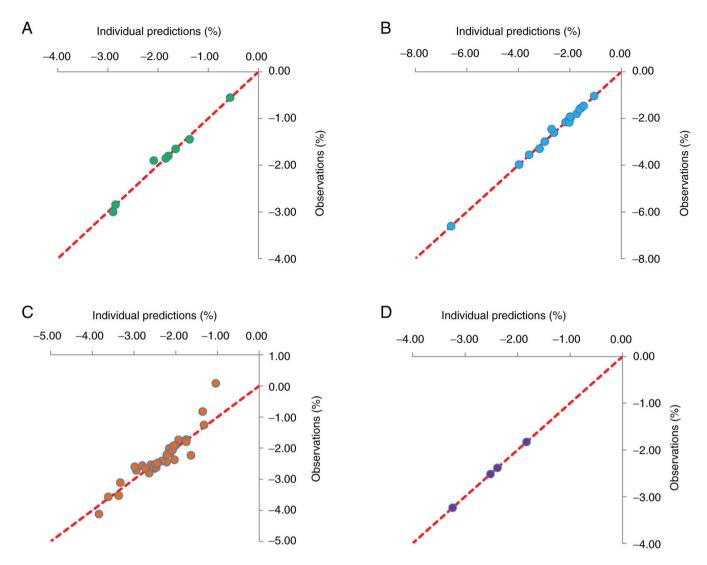
Figure 1. Routine diagnostic plots of predictions and observations for different treatment groups. Plots for patients treated with (A) 2.5 mg/day, (B) 5 mg/day, (C) 10 mg/day and (D) 20 mg/day dapagliflozin are shown.

treatment. Notably, these equations show that the only factor that ultimately affects body weight is the dose and duration of dapagliflozin.

Fig. 1 presents plots of individual predictions compared with observations for patients treated with 2.5, 5, 10 and 20 mg/day dapagliflozin. The data indicate ideal linear relationships between individual predictions and observations, suggesting the optimal fitting of the final models. Plots for individuals treated with 2.5, 5, 10 and 20 mg/day dapagliflozin are shown in Fig. 2. These also demonstrate the optimal predictive ability of the models. VPC plots (Fig. 3) were established using data derived from patients treated with 2.5, 5, 10 and 20 mg/day dapagliflozin. The majority of the observed data fell within the 95% prediction intervals generated from the simulated data, which indicated the predictive power of the final models.

Dose-dependent pharmacological response to dapagliflozin. Fig. 4 indicates a dose-dependent pharmacological effect of dapagliflozin on weight loss in patients with T2DM. Fig. 4A indicates the relationship between E_{max} and dapagliflozin dosage, and Fig. 4B that between ET_{50} and dapagliflozin dosage. Based on these results, it can be deduced that among the four

doses, 5 mg/day dapagliflozin exhibited the greatest weight loss effect, and the order of efficacy from high to low was as follows: 5 mg/day >10 mg/day >20 mg/day >2.5 mg/day. The onset time of weight loss reduced as the dose increased, and the order of onset from fast to slow was as follows: 20 mg/day >10 mg/day >5 mg/day >2.5 mg/day.

Discussion

Dapagliflozin is a SGLT2 inhibitor, which is used as a therapeutic strategy for the treatment of diabetes (7). The SGLT2 protein is specifically expressed in the renal tubular proximal S1 segment, where it mediates glucose reabsorption in the early proximal tubule; it is responsible for ~90% of glucose reabsorption in the kidney (7). SGLT2 inhibitors specifically inhibit the activity of SGLT2 and lower renal glucose reabsorption in the proximal convoluted tubule leading to increased urinary glucose excretion (7,36-38). The recommended initial dosage of dapagliflozin in the United States and China is 5 mg, which is rapidly absorbed following oral administration and enables the maximal plasma concentrations to be achieved in 2 h (7). In addition, the oral bioavailability following the
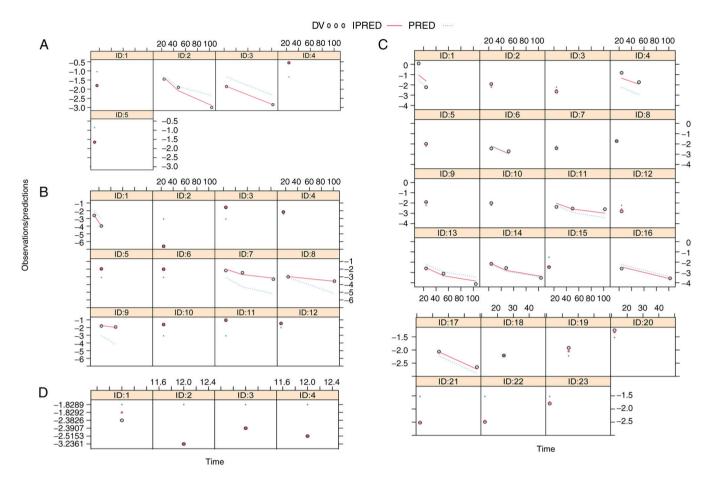
Figure 2. Individual plots of predictions and observations for different treatment groups. Plots for patients treated with (A) 2.5 mg/day, (B) 5 mg/day, (C) 10 mg/day and (D) 20 mg/day dapagliflozin are shown. DV, observed value; IPRED, individual predicted value; PRED, population predicted value; ID, study identity.

administration of 10 mg dapagliflozin is 78%, and the mean half-life is 12.9 h (7). Dapagliflozin has been accepted as a monotherapy or adjuvant therapeutic strategy for T2DM in the European Union, United States and China (7).

Various clinical trials have verified that dapagliflozin is effective in reducing glycated hemoglobin, fasting plasma glucose and body weight with a low incidence of hypoglycemic events (7,39,40). In addition, dapagliflozin monotherapy (5-10 mg/day) is effective in achieving glucose control, and patients exhibit optimal adherence to the treatment due to it being easy to use (7,41-43). However, patients with T2DM often develop obesity (2,3); obese patients have an elevated risk of cardiovascular disease and mortality. Therefore, it is crucial to improve the management of overweight or obese patients with T2DM (6). Fortunately, in addition to improving the control of blood glucose, dapagliflozin is also able to reduce the weight of patients with T2DM, thus providing benefits to patients with T2DM from multiple perspectives.

However, the dose-dependent pharmacological response to dapagliflozin with regard to weight loss in patients with T2DM is unknown; specific clinical guidance for dapagliflozin in the promotion of weight loss in patients with T2DM is lacking. Therefore, the purpose of the present study was to probe the effects of dapagliflozin on weight loss in patients with T2DM. A total of 24 RCT studies containing 8,545 patients with T2DM were included for analysis in the present study. These included 44 dapagliflozin dose groups, of which 5 received a dose of 2.5 mg/day, 12 a dose of 5 mg/day, 23 a dose of 10 mg/day, and 4 a dose of 20 mg/day.

The E_{max} model was used to evaluate the dose-dependent pharmacological response of weight loss to dapagliflozin in patients with T2DM. In addition, in order to determine the actual weight loss effect of dapagliflozin in T2DM, the control effect was subtracted from the sum effect. Moreover, since RCTs were included, the experimental and control groups from the same source were essentially identical in terms of patient demographics, comorbidities and other factors that may influence weight loss in patients with T2DM. The literature data were processed by subtracting the possible effect on weight in the control group from that in the experimental group in order to obtain the actual weight loss effect of dapagliflozin in T2DM.

Finally, four E_{max} models were established, one for each dose of dapagliflozin (2.5, 5, 10 and 20 mg/day). The models represent the effect of dapagliflozin on weight loss in patients with T2DM. Patients treated with 2.5, 5, 10 and 10 mg/day dapagliflozin demonstrated E_{max} values of -3.04, -6.57, -4.12 and 3.23%, respectively and ET_{50} values of 30.8, 27.3, 20.4 and 4.23 weeks, respectively. The efficacy of dapagliflozin in the induction of weight loss in patients with T2DM was highest with a 5 mg/day dose, followed by 10, 20 and 2.5 mg/day, respectively. We hypothesize that the reason for the least
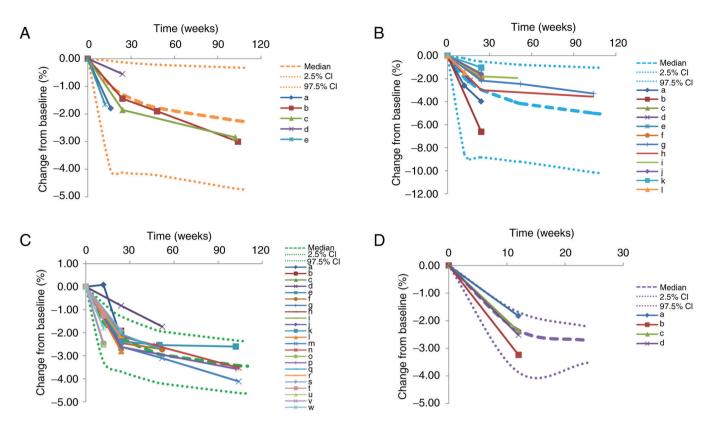
Figure 3. Prediction-corrected visual predictive check plots. Plots for patients treated with (A) 2.5 mg/day, (B) 5 mg/day, (C) 10 mg/day and (D) 20 mg/day dapagliflozin are shown. The median, 2.5 and 97.5% CI were simulated by the Monte Carlo method (n=1,000). CI, confidence interval; a-w, 44 dapagliflozin dose groups from 24 randomized controlled trials (8-31).
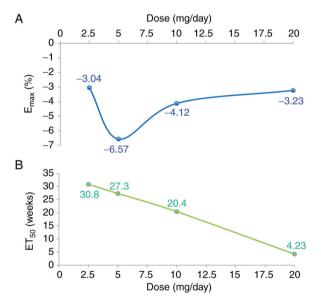

Figure 4. Pharmacological effect of dapagliflozin on weight loss. Relationships between (A) E_{max} and dapagliflozin dosage and (B) ET_{50} and dapagliflozin dosage. E_{max}, maximal effect; ET_{50}, time taken to reach half the E_{max}.

favorable effect being achieved with 2.5 mg is that this dose is insufficient, while the optimal efficacy was obtained at 5 mg. However, the underlying mechanism of the effects of dapagliflozin on body weight require further study in the future. The onset time of weight loss was fastest with a dosage of 20 mg/day and slowed gradually as the dosage decreased from 10 to 2.5 mg/day. In addition, information was obtained

from all 8,545 patients with T2DM and it was not found that different methodology, data collection methods, sample sizes, generalizability or other factors had any influence on weight loss outcomes.

The present study has certain objective limitations. Firstly, the included studies were all published, and included those with negative results or studies that did not show a significant effect of dapagliflozin on weight loss; However, unpublished literature data were not included, which may result in potential bias. Secondly, the deviations from the mean were not analyzed. Thirdly, the safety profile of the drug, particularly that associated with the liver, kidney and pancreas was not included or thoroughly considered. However, the doses explored were all administered in clinical trials or as recommended in the instructions of use, and the general safety was optimal and acceptable. It is important to note that the long-term effects require further assessment. Nevertheless, the security of long-term dapagliflozin use appears to be acceptable. Fioretto *et al* (44) reported that dapagliflozin treatment for ≤104 weeks was well tolerated in older patients. Although older patients treated with dapagliflozin, experienced more renal adverse events than placebo-treated patients, the majority of these events were non-serious small transient changes in serum creatinine. Durán-Martínez *et al* (45) reported that dapagliflozin had an appropriate safety profile in patients with T1DM following the careful selection of participants and implementation of strategies to reduce the risk of diabetic ketoacidosis, and the treatment also led to clinical improvements in this population.

In conclusion, to the best of our knowledge, the present study is the first to analyze the dose-dependent pharmacological

effect of dapagliflozin on weight loss in patients with T2DM. Of the four doses used, 5 mg/day dapagliflozin exhibited the greatest weight loss effect, and the onset time of weight loss accelerated with increasing dose. The detailed mechanism underlying the effects of dapagliflozin on body weight will be investigated in future studies. In particular, proteomic investigations may be carried out using animal experiments to determine the specific signaling pathway of dapagliflozin.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

The study was conceived and designed by SMH and DDW. Collection of data was performed by YH, YFL, CWY, YYG, XC, QG, QQX and XMW. Data analysis and interpretation were performed by DDW, YH, YFL, CWY and YYG. The manuscript was written by YH, YFL, CWY and YYG. All authors read and approved the final version of the manuscript: YH and DDW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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