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SHORT REPORT

Renal threshold for glucose reabsorption predicts diabetes improvement by sodium-glucose cotransporter 2 inhibitor therapy

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ABSTRACT

In the present study we examined the efficacy of sodium-glucose cotransporter 2 inhibitors on improvement of glycated hemoglobin (HbA1c) in comparison with the renal threshold for glucose reabsorption in patients with type 2 diabetes mellitus. Patients visited the hospital once a month for a regular follow-up examination with the determination of blood glucose and HbA1c levels, and urinary glucose concentration from spot urine samples. Patient samples were compared before and after ipragliflozin administration. We defined the renal threshold for glucose reabsorption as the lowest blood glucose level that correlated with the first detectable appearance of urine glucose. These data showed a significant negative correlation between improvement of HbA1c level and renal threshold for glucose reabsorption in patients treated with the sodium-glucose cotransporter 2 inhibitor. These findings show that patients who have a higher renal threshold for glucose reabsorption can be expected to more effectively respond to sodium-glucose cotransporter 2 inhibitor therapy in terms of lowering HbA1c levels.

INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of diabetic medications for the treatment of patients with type 2 diabetes mellitus[1]. SGLT2 inhibitors reduce filtered glucose reabsorption by epithelial cells of the kidney proximal tubule[1]. The renal threshold for glucose reabsorption of patients with type 2 diabetes mellitus was reported to be between 200 and 250 mg/dL, which is higher than that of normal subjects (170–200 mg/dL)[2–5]. One possible mechanism is the increased expression of SGLT2 in patients with type 2 diabetes mellitus compared with normal subjects[3]. SGLT2 inhibitors typically reduce the renal threshold for glucose reabsorption by approximately 20 mg/dL[5], and are an effective agent in lowering plasma glucose levels in patients with type 2 diabetes mellitus[6]. In the present study, we examined the association between the efficacy of SGLT2 inhibition on the improvement of glycated hemoglobin (HbA1c) relative to the sensitivity of urinary glucose reabsorption in patients with type 2 diabetes mellitus.

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METHODS

Participants

The study protocol used was reviewed and approved by our hospitals' review boards according to the Declaration of Helsinki. Written informed consent was obtained from each participant. The present clinical study involved 22 patients with type 2 diabetes mellitus prescribed ipragliflozin (50 mg/day). As shown in Table 1, six patients were treated with insulin, four patients with biguanide, 12 patients with dipeptidyl peptidase-4 inhibitors and 10 patients with sulfonylurea. Written informed consent was obtained to analyze and present their clinical laboratory data.

Study design

Patients were asked to empty their bladders as much as possible before visiting our clinic, and urinary samples were collected just before drawing blood samples. By this procedure, we

attempted to synchronize the urinary and blood glucose concentrations as best as possible. Patients consistently visited the hospital for follow-up examination once a month, and blood glucose levels and HbA1c were measured from the same casual blood samples. In parallel, urinary glucose levels were determined in spot urine samples at each visit. Bodyweight, blood pressure and estimated glomerular filtration rate (eGFR) were also measured each time. The present study includes patients that were monitored in this manner for a 12-month period.

Venous blood samples were collected into tubes containing ethylenediaminetetraacetic acid and fluoride. Plasma was separated from whole blood within 1 h after collection, and plasma glucose and HbA1c concentrations were determined according to the hexokinase method using a Synchro CX4/CX5 glucose analyzer (Beckman Coulter Inc., Fullerton, CA, USA) and the Glycohemoglobin Analyzer RC20 (Sekisui Medical Co., Ltd, Tokyo, Japan), respectively. Both the intra- and interassay coefficients of variation were ≤2% at plasma glucose values of <126 mg/dL.

Estimation of renal threshold for glucose reabsorption

Renal threshold for glucose reabsorption was defined as the minimum blood glucose concentration that resulted in the presence of measureable urine in at least 12 measurements. In Table 2, one of the typical cases is represented to show how our renal threshold for glucose reabsorption was determined. In this case, we considered this patient's renal threshold for glucose reabsorption was 121 mg/dL, as shown by arrows.

Statistical analysis

The InStat 2 program (GraphPad Software Inc., San Diego, CA, USA) was used for these statistical analyses including Pearson's coefficient test to evaluate the correlation between two parameters, such as renal threshold for glucose reabsorption and improvement of HbA1c by SGLT2 inhibitor administration.

RESULTS

Participant characteristics

All measured values are shown in Tables 1 and 3. The medians are also shown in Table 3. The median age was 64 years (range 46–83 years). The median eGFR of these patients was 67.3 mL/min/1.73 m^2 (range 43.0–95.3 mL/min/1.73 m^2). The median systolic blood pressure was 131.0 mmHg (range 109–156 mmHg), the median diastolic blood pressure was 72.5 mmHg (range 60–90 mmHg), and the median bodyweight was 66.65 kg (range 54.0–98.5 kg). The initial median HbA1c level before the addition of SGLT2 inhibitor therapy was 8.4%

Table 1 | Characteristics of patients (all measured values)

Number	Threshold	ΔHbA1c	eGFR (before)	eGFR (after)	ΔeGFR	BW (before)	BW (after)	ΔBW	SP (before)	SP (after)	ΔSP	DP (before)	DP (after)	ΔDP	Age	Sex
1	206	−0.4	70.6	81.5	10.9	82	78.5	−3.5	141	108	−33	70	51	−19	81	M
2	197	−0.8	77.2	77.2	0	96.2	90.6	−5.6	124	128	4	66	73	7	59	M
3	173	−0.8	61.4	70.2	8.8	74.5	70.2	−4.3	156	139	−17	73	81	8	57	M
4	268	−1.3	66.6	66.3	−0.3	90.6	85.6	5	136	127	−9	82	81	−1	63	M
5	243	−1.3	63.9	52.3	−11.3	61.5	63.1	1.6	144	148	4	81	82	1	48	M
6	237	−1	69.7	68.8	0.9	54	53.6	−0.4	120	120	0	60	66	6	72	M
7	185	−0.3	88	88	0	79.9	79.6	−0.3	130	110	−20	80	70	−6	46	M
8	160	−0.6	66.9	75.6	8.7	65.5	66.6	1.1	140	136	−4	90	84	−6	83	M
9	178	−0.6	58.9	71.5	12.6	69.9	64.7	−5.2	130	131	1	89	79	−10	65	M
10	240	−0.5	95.3	89.1	−6.2	98.5	90.4	−8.1	120	130	10	70	74	4	50	M
11	146	0.3	73.4	74.1	0.7	73	72.4	−0.6	120	130	10	70	78	8	63	M
12	252	−0.6	67.8	60.1	−7.7	60	58	−2	120	130	10	60	70	10	56	F
13	121	0.5	69.2	73.6	4.4	84.9	82.9	−2	120	147	27	84	82	−2	52	M
14	206	−0.9	60.6	64.1	3.5	76	75	−1	155	137	−18	73	76	3	77	M
15	178	−0.4	60.9	64.9	4	61	61.5	0.5	126	134	8	73	81	8	73	F
16	242	−0.5	51.2	53.8	2.6	63.5	66	2.5	130	140	10	70	70	0	81	M
17	263	−0.4	43	48.4	5.8	55.5	54.2	−1.3	140	144	4	80	80	0	82	F
18	212	−1.5	76.8	79	2.2	81	77	−4	120	130	10	70	70	0	50	M
19	224	−0.3	67.7	70.1	2.4	64	64.9	0.9	150	161	11	90	100	10	75	F
20	175	0.2	56.2	56.2	0	65.1	63.7	−1.4	123	125	2	72	78	6	73	M
21	196	−0.4	51.9	43.6	−8.3	68.7	63	−5.7	130	140	10	70	70	0	75	M
22	191	−0.4	76.1	76.1	0	66.2	66.7	0.5	109	112	3	66	60	−6	62	M

All measured values are shown. Δ, Subtraction of value of before from value of after; After, 1 year after sodium-glucose cotransporter 2 inhibitor treatment condition; Before, before start of sodium-glucose cotransporter 2 inhibitor treatment condition; BW, bodyweight (kg); DP, diastolic blood pressure (mmHg); eGFR, estimated glomerular filtration rate (mL/min/1.73 $m^{2)}$; F, female; HbA1c, glycated hemoglobin; M, male; SP, systolic blood pressure (mmHg); Threshold, renal threshold for glucose reabsorption (mg/dL).

Table 2 | How renal threshold for glucose reabsorption was estimated

															↓	
Blood glucose (mg/dL)	306	292	281	253	229	211	198	194	191	187	178	176	155	124	121	63
Urinary glucose	+++	+++	+++	++++	+++	+++	++	+++	++	++	++	+++	++	++	+	–

Blood glucose levels are placed as descending order of powers in a left to right direction with urinary glucose concentration results. The renal threshold for glucose reabsorption is shown by an arrow as the minimum blood glucose level as the turning point of urinary glucose from absence to presence. Thus, we estimated 121 mg/dL in this patient. –, Not detectable; +, 100–249 mg/dL; ++, 250–499 mg/dL; +++, 500–999 mg/dL; ++++, 1000–1999 mg/dL.

Table 3 | Characteristics of patients

Threshold (mg/dL)	201.5
ΔHbA1c (%)	–0.5
eGFR (before) (mL/min/1.73^2)	67.3
eGFR (after) (mL/min/1.73^2)	70.15
ΔeGFR (mL/min/1.73^2)	1.55
Body weight, before (kg)	69.3
Body weight, after (kg)	66.65
ΔBody weight (kg)	–1.15
Systolic blood pressure, before (mmHg)	130
Systolic blood pressure, after (mmHg)	130.5
ΔSystolic blood pressure (mmHg)	4
Diastolic blood pressure, before (mmHg)	72.5
Diastolic blood pressure, after (mmHg)	77
ΔDiastolic blood pressure (mmHg)	0.5
Age (years)	64
Other antibiotic medications	
Insulin	6
Biguanide	4
DPP4 inhibitors	12
Sulfonylurea	10

The median values and antidiabetic medications of patients are shown. DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

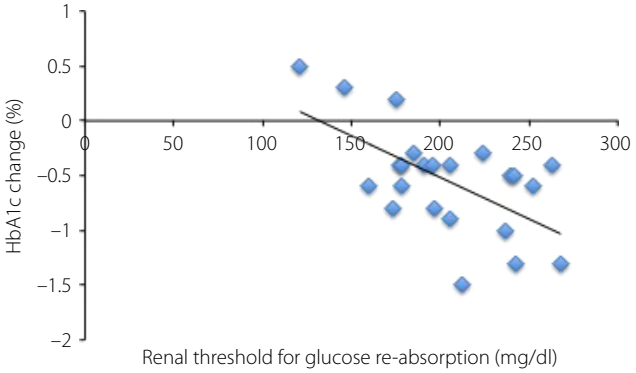

Figure 1 | Correlations between renal thresholds for glucose re-absorption and improvement of glycated hemoglobin (HbA1c) levels by sodium-glucose cotransporter 2 inhibitor administration. The mean values of HbA1c levels 3 months after starting sodium-glucose cotransporter 2 therapy are shown on the *y*-axis and renal threshold for glucose reabsorption is shown on the *x*-axis. There was a significant negative correlation between renal threshold for glucose reabsorption and improvement of HbA1c levels by sodium-glucose cotransporter 2 inhibitor therapy (r = –0.6011, P = 0.0031).

(range 7.9–10.5%). The median duration with type 2 diabetes mellitus was 5.6 years (range 3–18 years).

Efficacy of SGLT2 inhibitor and renal threshold for glucose reabsorption

The median renal threshold for glucose reabsorption in this patient population was 201.5 mg/dL (range 121–268 mg/dL; Tables 2 and 3). The median improvement of HbA1c levels by SGLT2 inhibitor administration was –0.5% (range –1.5–0.5%; Tables 2 and 3). We did not observe any significant change in eGFR, bodyweight, and systolic and diastolic blood pressure before and after SGLT2 administration. As shown in Figure 1, there was a significant negative correlation between renal threshold for glucose reabsorption and the improvement of HbA1c (correlation coefficient, r = –0.6011; coefficient of determination, r^2 = 0.3613, the two-tailed P-value, P = 0.0031). In contrast, there was no statistically significant correlation between eGFR and HbA1c or between bodyweight and HbA1c levels in the absence of SGLT2 inhibitor therapy (data not shown).

DISCUSSION

Defronzo *et al.*[5] used a pancreatic clamp approach to estimate renal threshold for glucose reabsorption in type 2 diabetes mellitus patients, and reported an average of 196 ± 63 mg/dL. More recently, Nakamura *et al.*[7] utilized continuous glucose monitoring approach with 1 day of SGLT2 inhibitor administration and estimated renal threshold for glucose reabsorption of 151 mg/dL in type 2 diabetes mellitus patients. Alternatively, we estimated renal threshold for glucose reabsorption by a very simple method using ordinary clinical data. Based on the established concept of maximal glucose reabsorption threshold in the kidney, we predicted that the lowest detectable concentration of glucose in urine for a given patient provides a reasonable estimate of the glucose renal threshold. Using this criteria, we found an average renal threshold for glucose reabsorption in our patient population as 204.2 ± 38.9 mg/dL (range 121–268 mg/dL), which is similar to that reported by Defronzo *et al.*[5]

The results of the present study showed a significant negative correlation between the renal threshold for glucose reabsorption and HbA1c levels after treatment with the SGLT2 inhibitor, ipragliflozin. The efficacy of SGLT2 inhibitor was poorer for patients with lower renal threshold for glucose reabsorption. As patients with higher renal threshold for glucose reabsorption have a greater capacity to reabsorb urinary glucose at epithelial cells of the kidney proximal tubule, these patients do not excrete urinary glucose at the lower ranges of blood glucose. In contrast, patients with lower renal threshold for glucose reabsorption have a lower capacity to reabsorb urinary glucose. These patients tend to excrete urinary glucose at lower ranges of blood glucose.

Previous studies examining the renal threshold for glucose reabsorption with SGLT2 inhibitor administration were carried out over relative short time frames[5,7]. However, clinically, the majority of patients remain on diabetic therapies for prolong periods of time. Thus, we examined the relative effectiveness of SGLT2 inhibitor therapy over a 1-year time-period. Nakamura *et al.*[7] reported that in younger type 2 diabetes mellitus patients, despite lower renal threshold for glucose reabsorption, they showed better improvement of HbA1c with SGLT2 inhibitor administration compared with patients with higher renal threshold for glucose reabsorption. The difference in conclusions between the two studies could be attributed to the duration of SGLT2 inhibitor administration.

The present findings show that estimating the renal threshold for glucose reabsorption before prescribing SGLT2 inhibitors can predict diabetes improvement by SGLT2 inhibitor therapy. Through this approach, physicians can select patients that will have a greater response to SGLT2 inhibitors vs patients who would be better treated with other glucose-lowering therapies. However, it is important to note that the present study only examined a limited number of patients, and larger cohort studies are now necessary to confirm these results.

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DISCLOSURE

The authors declare no conflict of interest.

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