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1,5-anhydroglucitol is a good predictor for the treatment effect of the Sodium-Glucose cotransporter 2 inhibitor in Japanese patients with type 2 diabetes mellitus

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ABSTRACT

Background and Aims: The suitable selection of appropriate medicines is one of important factor in successful diabetes care. We looked for clinical indicators that could predict the effects of SGLT2 inhibitors in advance.
Methods and Results: In a single-center, this retrospective study was designed to examine predictive indices of the effectiveness of SGLT2 inhibitors. Using the medical records of 169 patients, we investigated the differences in clinical data between a group with improved glycemic control and a group with less improved glycemic control. 32 weeks of treatment with SGLT2 inhibitors decreased the HbA1c levels by 0.71%. The glucose-lowering effect was associated with improvement of the liver function. The maximum BMI change was independent of the rate of the HbA1c reduction. The HbA1c reduction was greater in patients with low 1,5-AG. This determination was unaffected by the use of anti-diabetic medication. Limiting HbA1c from 7.0% (52 mmol/mol) to 8.4% (68 mmol/mol) did not change this tendency. The maximum sum of sensitivity and specificity for patients with an HbA1c improvement of more than 0.7% was obtained with a 1,5-AG cutoff level of 7.65 μg/mL.
Conclusion: The use of SGLT2 inhibitors in patients with T2DM, 1,5-AG was identified as the most reliable indicator for predicting HbA1c reduction.

Introduction

Glucose homeostasis is achieved by sharing information of metabolic conditions in organs throughout the body and coordinating each organ closely. Based on the body's metabolic needs, insulin is secreted precisely at a level and appropriate time to act on its target organs and stabilize the circadian rhythm of the plasma glucose levels. Diabetes mellitus is a result of a dissonance in these mechanisms. When glycemic control is insufficient, pancreatic beta cells are overloaded promoting a further reduction in the beta-cell mass and function. The tuning method for metabolic disharmony is different for each individual. Therefore, in the treatment of type 2 diabetes (T2DM), it is necessary to grasp the state of each element constituting the deterioration of glucose tolerance. Based on the findings, optimal therapy and oral hypoglycemic agents need to be selected to approximate the normal circadian rhythm of the plasma glucose. In T2DM, the expression of Sodium-Glucose cotransporter 2 (SGLT2) is enhanced and the glucose reabsorption ability in the proximal renal tubule is elevated, thereby accelerating the deterioration of the blood glucose level [1]. SGLT2 inhibitors improve the glucose profile by inhibiting glucose reabsorption in the proximal tubules of the kidney and enhancing urinary glucose excretion [2]. The mechanism of action of SGLT2 inhibitors does not depend on the insulin secretion. It has been reported to result in improved insulin sensitivity and beta-cell protection [3],[4].

However, in clinical practice, there are some patients who cannot obtain a sufficiently effective of improvement in the glucose level by SGLT2 inhibitors. We speculated individual differences were involved in the effect of SGLT2 inhibitors. For glycemic control, we decided to search for indices to determine which patients can benefit most by using SGLT2 inhibitors. We conducted a single-center, retrospective study designed to examine useful indices to determine the effect of SGLT2 inhibitors in the real-world clinical practice. In the current study, we retrospectively investigated the relevance between the effects of the SGLT2 inhibitors and clinical indices before and during medication with SGLT2 inhibitors using predefined inclusion and exclusion criteria.

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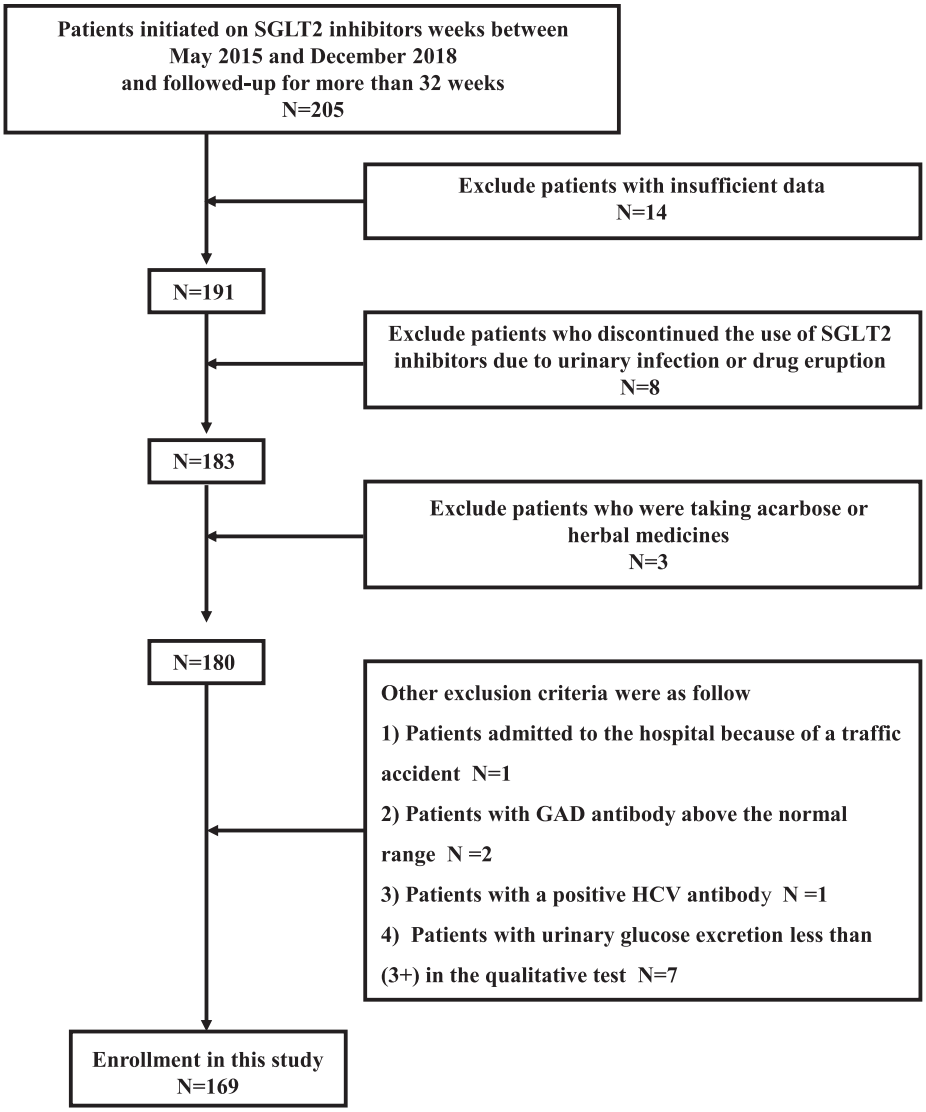

Fig. 1. Flow diagram of study participants.

Materials and methods

Subjects and study design

The medical records of 205 Japanese T2DM patients between May 2015 and December 2018 were analyzed retrospectively. Patients medicated with SGLT2 inhibitors due to poor glycemic control were extracted from the medical records.

They started SGLT2 inhibitors (canagliflozin,dapagliflozin,empagliflozin,ipragliflozin, luseogliflozin, or tofogliflozin) during the period and received regular ambulatory treatment more than 32 weeks in Osaki Citizen Hospital Division of Metabolism and Diabetes. All out-patients were visited the hospital for glycemic control and diabetes education.

Bodyweight was measured at each outpatient visit. Blood samples (HbA1c, glycoalbumin(GA), 1,5- anhydroglucitol(1,5-AG), Total bilirubin, AST, ALT, gamma GTP(γGTP), triglyceride(TG),HDL-cholesterol (HDL-C), LDL-cholesterol(LDL-C) and estimated glemerular filtration rate(eGFR) were also collected at all outpatient visits. Serum levels of 1,5-AG were measured using a colorimetric assay (BML, Tokyo, Japan). The eGFR was calculated with the equation provided by the Japanese Society of Nephrology [5]. Diet therapy and exercise therapy were not newly started, discontinued, or altered during the study period. Concomitant administration of other SGLT2 inhibitors was prohibited. The decision to add, increase or decrease the dose of oral hypoglycemic agents and insulin was made by the physicians in charge but unnecessary changes were avoided.

Furthermore, medications such as antihypertensive drugs and lipid-lowering agents were not changed in dose, discontinued, or newly added if possible. All patients were instructed to follow a 25–30 kcal/kg/day diet calculated on their ideal body weight. That SGLT2 inhibitors were properly taken was confirmed by urine glucose excretion. A flow diagram of the study participants and other exclusion criteria is shown in Fig. 1.

A total of thirty-six patients were excluded from the analysis. The remaining 169 patients were enrolled in our data analysis.

Table 1
Patient clinical characteristics and concomitant medications for treating diabetes.

Age (years)			57.0 ± 13.7		AST (IU/L)				33.5 ± 21.7	
Male (%)			53.8		ALT (IU/L)				41.0 ± 30.2	
Body weight (kg)			77.4 ± 17.4		γGTP (IU/L)				55.43 ± 60.96	
Body Mass Index (kg/m^2)			29.14 ± 5.11		TG (mg/dl)				176.5 ± 120.7	
HbA1c (%)			7.92 ± 1.03		HDL-C (mg/dl)				48.5 ± 15.1	
GA (%)			20.13 ± 5.28		LDL-C (mg/dl)				104.2 ± 34.7	
1,5-AG (mg /mL)			7.67 ± 6.24		eGFR (ml/min/1.73 m2)				79.01 ± 25.96	
Concomitant drug -Statin- (%)			45.0		Concomitant drug -Antihypertensive drug- (%)				64.5	
Insulin (%)	Sulfonylurea (%)	Glinide (%)	dipeptidyl peptidase-4 inhibitor (%)		glucagon like peptide-1 receptor agonist (%)		Thiazolidine (%)	Biguanide (%)	α-glucosidase inhibitor (%)	None (%)
39.6	20.1	7.1	62.1		13.6		11.2	72.2	13.6	5.9

Statistical analysis

All data were expressed as mean ± standard error. All data were analyzed using JMP, version 12.0.0 (SAS Institute Inc., Cary, NC, USA).

To identify clinically significant predictors, our study used a p-value of < 0.001 instead of 0.05 as a statistically highly significant difference. The graphs other than ROC curves are shown as a boxplot. Error bars represent by the standard error.

Results

The baseline characteristics of the patients enrolled in this study are shown in Table 1. One hundred and sixty-nine patients with a median age of 59.0 years were enrolled during the study period. The study population had a mean HbA1c of 7.92% (63 mmol/mol), GA of 20.13%, body mass index(BMI) of 29.14 kg/m^2, and eGFR of 79.0 ml/min/1.73 m^2.

An average of 2.4 drugs was administered as an oral concomitant medicine in the diabetes treatment. 39.6 percent of these patients were medicated with insulin therapy. 62.1% of these were medicated with DPP-4 inhibitors. 72% of these were medicated with biguanide. Among SGLT2 inhibitors, ipragliflozin was used in 45.6% of patients, empagliflozin was used in 28.7%, and tofogliflozin was used in 15.8% of patients. The use of canagliflozin was 7.6%, of dapagliflozin 1.8%, and that of luseogliflozin was 0.6%. Glycemic control improved at 32 weeks after the dosage with a mean reduction from the baseline HbA1c of −0.71%. The BMI of the patients decreased by an average of 1.13 kg/m^2 (Fig. 2a, b). No patients showed severe adverse effects during the study. The individuals whose records were examined were stratified into two groups. Patients who achieved an HbA1c reduction of more than 0.7% compared to baseline were defined as drug effective patients (Group A). On the other hand, patients with an HbA1c reduction of ≤ 0.7% compared to baseline were defined as patients with no drug effect (Group B). We analyzed the differences between the clinical indices of these two groups. There were no patients whose defined group had changed due to the influence in the discontinuation and/or change of dose of other oral hypoglycemic agent and insulin. Regardless of data, patients with an increased insulin dose or who added sulfonylurea agents (SU) were defined as group B. Group A had higher baseline HbA1c, GA. The baseline 1,5-AG of group A was lower than that of group B. Group A tended to have a higher baseline insulin/SU usage and TG compared to group B. The baseline eGFR of Group A tended to be higher than that of Group B. This difference in baseline BMI and liver function between the two groups was not statistically significant (Table 2). 32 weeks of treatment with SGLT2 inhibitors led to a significant decrease in liver dysfunction, especially ALT. The improvement rate in the group with basal ALT > 20 IU/L was 38.66 ± 17.85%.The maximum improvement rate of liver enzymes was larger in Group A. The maximum BMI change during the study between the two groups was not statistically significant (Fig. 3).

The lower baseline 1, 5-AG in Group A was not affected by the use of insulin/SU, biguanide, and DPP-4 inhibitor (Fig. 4a–c). The maximum rate of percent change in AST and ALT was significantly different between Group A and Group B in users of insulin/SU agents, but not in non-users (Fig. 5a–b). These differences were not confirmed with or without the use of biguanide or DPP-4 inhibitors. Baseline BMI and maximum BMI change showed no relation to whether or not insulin/SU agents were used (Fig. 5c).

We constructed Receiver Operating Characteristic(ROC) curves of these indices to determine the optimal predictor (Fig. 6a). The area under the ROC curve of the baseline 1,5-AG shows higher accuracy than the baseline GA, BMI, and ALT. The area under the ROC curve was 0.765 (95% confidence interval: 0.851 to 0.679). The maximal sensitivity and specificity (88% and 62%, respectively) were obtained at a

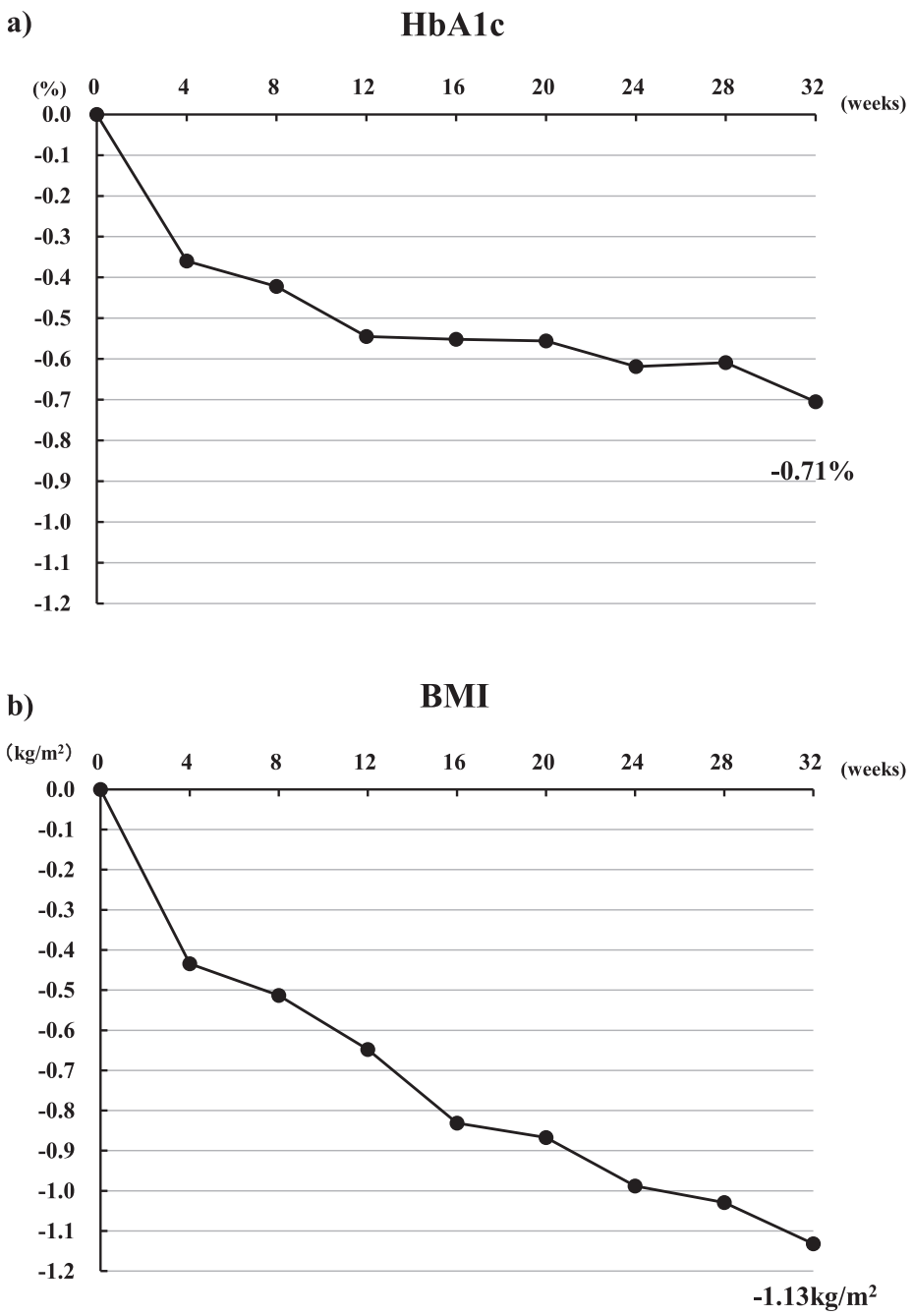

Fig. 2. The changes in the HbA1c level (a) and BMI (b) after using SGLT2 inhibitor for 32 weeks (n = 169).

1,5-AG cutoff level of 7.65 μg/mL. In the low 1,5-AG group, the improvement rate of HbA1c and GA was significantly larger (Fig. 6b).

Next, the medical records were analyzed only for patients with HbA1c 7.0–8.4% (52–68 mmol/mol) (n = 98). The significant difference in the baseline GA between Group A and Group B disappeared (Fig. 7a), but Group A had a lower baseline 1,5-AG than Group B (Fig. 7b). The percent change in ALT and the change in the BMI level did not differ in either group (Fig. 7c–d).

Discussion

SGLT2 inhibitors reduce the workload of glucose metabolism by promoting the excretion of glucose in the urine, restoring the incretin-responsive insulin secretion [6],[7], and improve insulin sensitivity [8,9]. In patients with poorly controlled T2DM, these mechanisms attenuate the glucose load.

In this study, we show that SGLT2 inhibitors are effective in decreasing HbA1c levels after 32 weeks of treatment. The decreased

Table 2
The clinical characteristics of patients classified as group A (drug effective: n = 99) and group B (drug ineffective: n = 70).

	Group A	Group B	P value
Number	99	70	
Male (%)	56.7	50	0.403
Age (years)	56.3 ± 14.1	57.9 ± 13.1	0.447
BMI (kg/m^2)	28.77 ± 4.98	29.42 ± 4.85	0.396
eGFR (mL/min/1.73 m^2)	83.23 ± 28.38	73.16 ± 21.01	0.009
HbA1c (%)	8.38 ± 1.01	7.27 ± 0.65	< 0.0001
GA (%)	21.67 ± 5.67	17.90 ± 3.62	< 0.0001
1,5-AG (mg/ml)	5.02 ± 3.88	11.43 ± 7.00	< 0.0001
AST (IU/L)	33.4 ± 20.9	33.5 ± 22.9	0.986
ALT (IU/L)	42.7 ± 32.5	38.4 ± 26.7	0.354
γGTP (IU/L)	62.3 ± 72.4	45.4 ± 37.0	0.058
TG (mg/dl)	200.5 ± 141.7	145.4 ± 68.1	0.002
HDL-C (mg/dl)	47.80 ± 14.91	50.23 ± 14.07	0.28
LDL-C (mg/dl)	104.14 ± 31.92	105.79 ± 36.62	0.752
Use of statin (%)	40.4	51.4	0.159
Use of insulin or/and Sulfonylurea (%)	63.6	52.9	0.165

HbA1c levels were associated with improvement in the liver function. Consistent with previous studies [10–12], SGLT2 inhibitors decreased the HbA1c levels regardless of the baseline BMI. Moreover, we propose the novel use of 1,5-AG in predicting the hypoglycemic effect of SGLT2 inhibitors. 1,5-AG leaks into the urine with the excessive excretion of glucose and its blood concentration decreases. The serum 1,5-AG concentrations have been reported to reflect the postprandial glucose values [13–15] and also the hyperglycemic terms for 1–2 weeks in person with diabetes [16]. 1,5-AG was reported to be a useful biomarker to monitor hyperglycemic excursions and this level was strongly associated with important retinopathy and nephropathy outcomes of person with diabetes, even after adjusting for HbA1c [17]. 1,5-AG was also independently associated with cardiovascular outcomes and mortality, even after adjusting for baseline fasting glucose or HbA1c [18]. On the other hand, HbA1c includes the overall chronic exposure to hyperglycemia during the previous 2–3 months and reflects both the pre and postprandial glucose concentrations. However, 1,5-AG tends to decrease as HbA1c deteriorates. From 7.0% (52 mmol/mol) to 8.4% (68 mmol/mol) HbA1c, HbA1c contributes half of the postprandial plasma glucose level and fasting plasma glucose levels, and

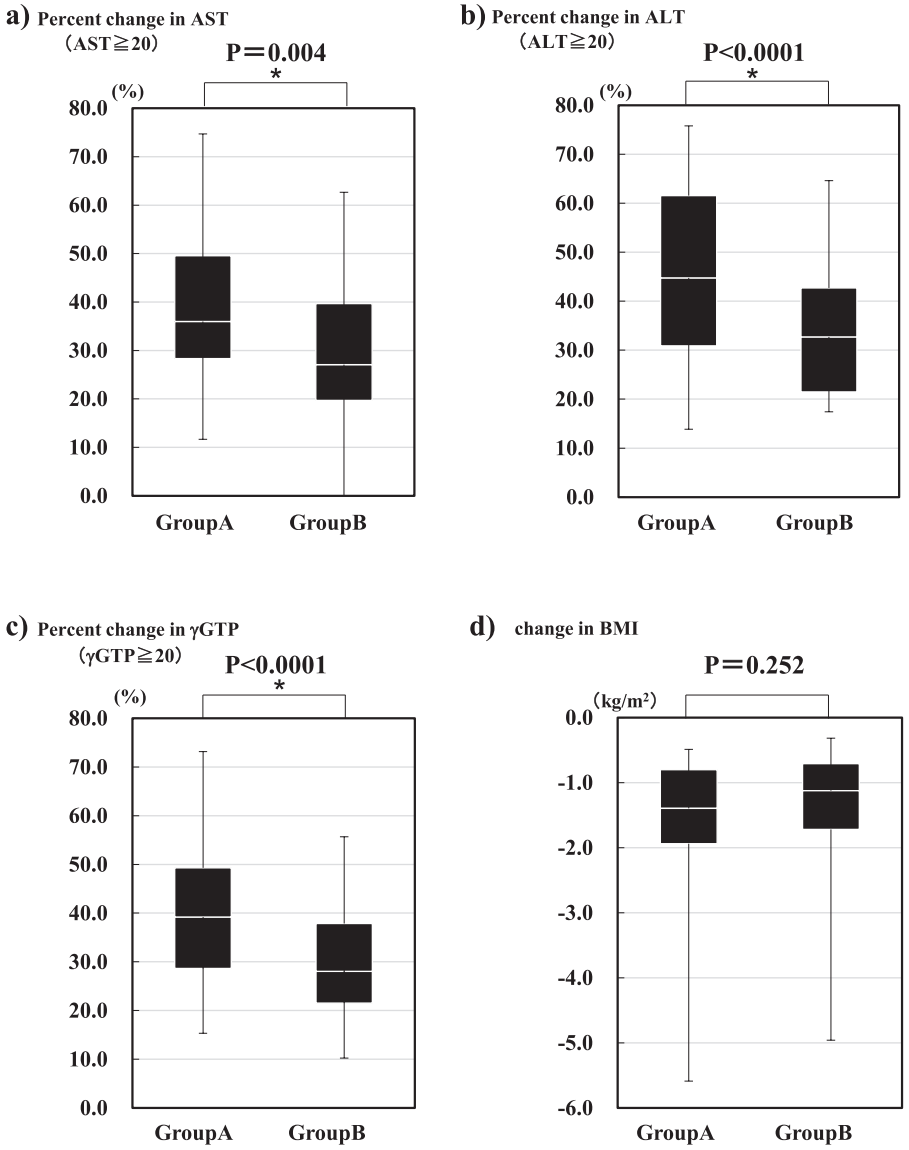

Fig. 3. The percent changes in the AST level (a), ALT level (b), γGTP level (c) in Group A and Group B. The change in BMI (d) between group A and group B. The data used in Fig. 3a–c were limited to patients with AST, ALT, and γGTP levels above 20 IU/ml upon SGLT2 inhibitor administration (Group A: n = 62; Group B: n = 53).

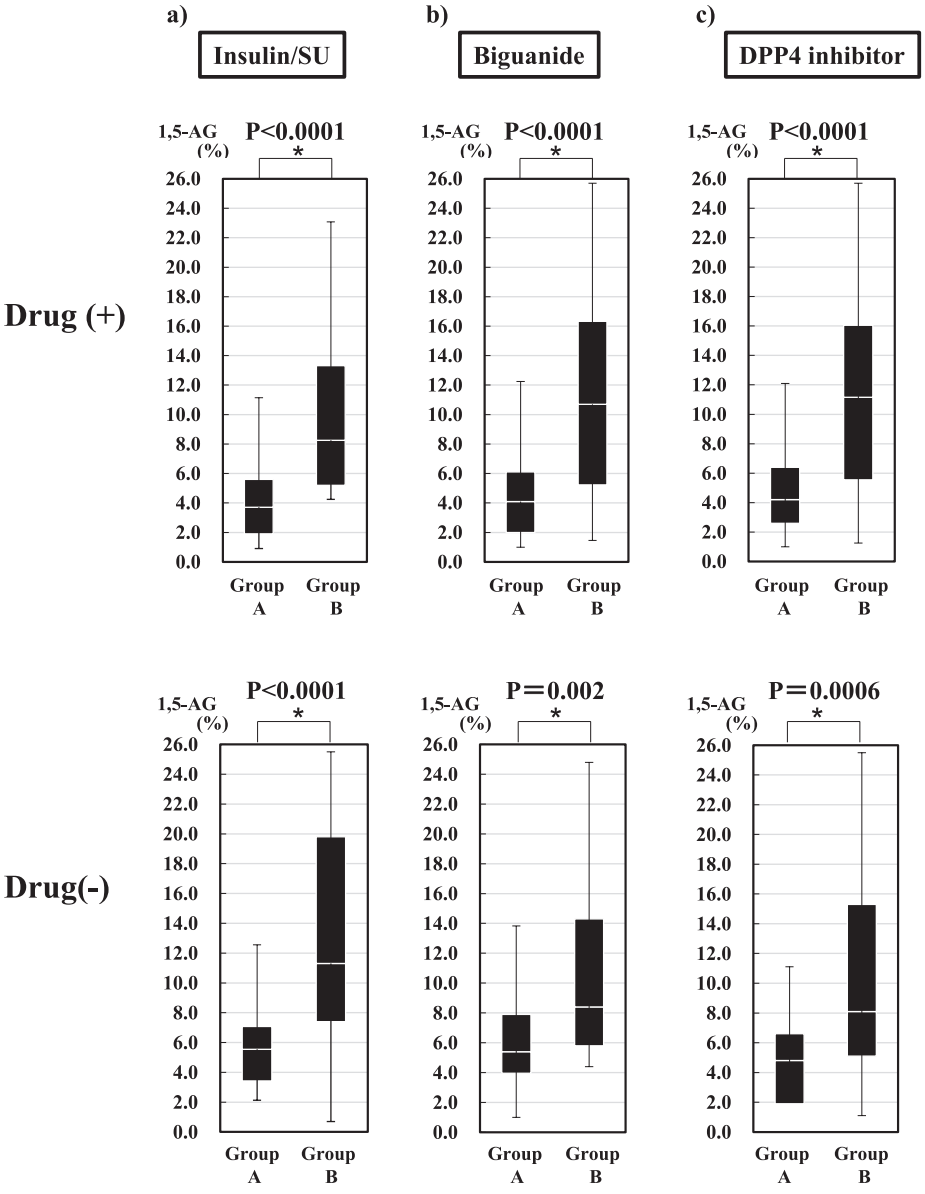

Fig. 4. (a) Box plots of 1,5-AG values in group A and group B classified by the presence (upper panel: Group A n = 63, Group B n = 37) or absence (lower panel: Group A n = 36, Group B n = 33) of insulin/SU administration. (b) Box plots of 1,5-AG values in group A and group B classified by the presence (upper panel: Group A n = 73, Group B n = 49) or absence (lower panel: Group A n = 26, Group B n = 21) of biguanide administration. (c) Box plots of 1,5-AG values in group A and group B classified by the presence (upper panel: Group A n = 58, Group B n = 47) or absence (lower panel: Group A n = 41, Group B n = 23) of DPP-4 inhibitors administration.

postprandial glucose (PPG) also plays an important role [19]. For this reason, both groups were analyzed with HbA1c limited to within 7.0%−8.4% (52–68 mmol/mol). Despite the loss of significant differences in the GA values between the two groups, 1,5-AG remained an important predictor of decreased HbA1c levels and indicated that BMI may not be a predictor of the usefulness of SGLT2 inhibitors.

Our study revealed that 1,5-AG can predict the glycemic-improving effects of SGLT2 inhibitor regardless of the patient's eGFR, body weight and anti-diabetic medication. 1,5-AG remained the most beneficial factor after the multivariate analysis. 1,5-AG has detective ability more useful for patients than HbA1c value or eGFR value, which was previously reported [12].

In patients with 1,5-AG > 7.7 μg/mL, the negative predictive value of SGLT2 inhibitor use was 0.831. This result indicates that the administration of SGLT2 inhibitors cannot improve HbA1c in high 1,5-AG patients. SGLT2 inhibitors were identified as more effective in person with diabetes with elevated HbA1c due to the high circadian glycemic variability. The risk of drug-induced hypoglycemia can be reduced by predicting the effect and adjusting the concomitant medications based on this indicator. This study could provide a great source of judgment.

SGLT2 inhibitor does not act directly in insulin secretion. On the other hand, patients with higher basal insulin levels were considered to have excellent blood glucose ameliorating effects due to SGLT2 inhibitors [20]. Although our study did not measure blood insulin or blood C-peptide concentrations, the larger insulin/SU use ratio in the effective group suggested that SGLT2 inhibitors may be able to exert their effects more effectively if insulin concentration is sufficient.

Recent large clinical randomized trials have suggested that SGLT2 inhibitor treatment significantly reduces the risk of cardiovascular outcomes, such as major adverse cardiovascular events (MACE) or some of its components [21]. Postprandial hyperglycemia is an independent risk factor for cardiovascular events [22–24]. Although the

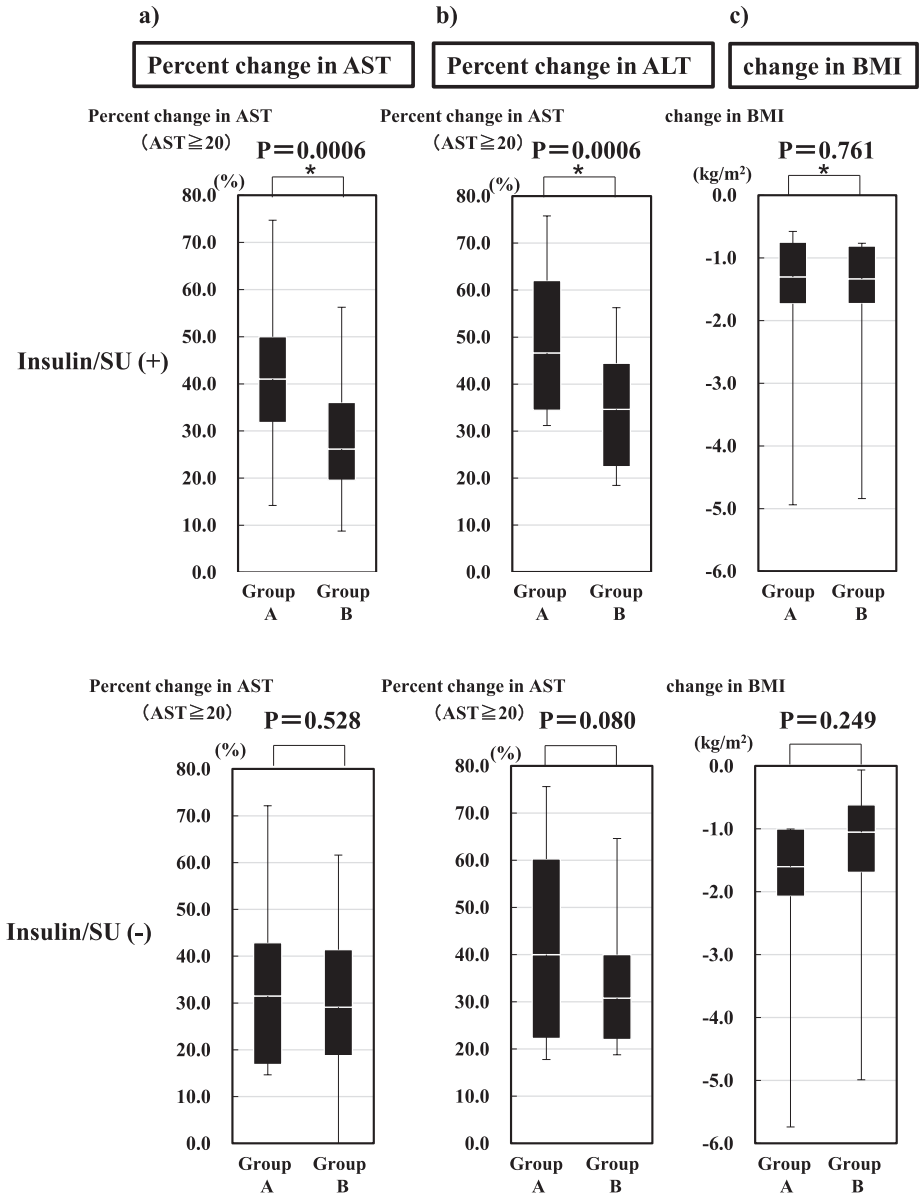

Fig. 5. Box plots of the percent changes in the AST level (a) and the ALT level (b) for group A and group B classified by the presence (upper panel: Group A n = 35, Group B n = 24) or absence (lower panel: Group A n = 27, Group B n = 29) of insulin/SU administration. Box plots of the change in BMI (c) for group A and group B classified by the presence (upper panel: Group A n = 63, Group B n = 37) or absence (lower panel: Group A n = 36, Group B n = 33) of insulin/SU administration. The data used in Fig. 5a–c are identical to the data used in Fig. 3a, b and d.

multifaceted effects of SGLT2 inhibitors have been reported, 1,5-AG was not measured in these studies. This usefulness could be affected by the reduction in the coefficient of variation of glucose caused by SGLT2 inhibitors. The use of SGLT2 inhibitors may have a more versatile effect in T2DM patients with low 1,5-AG.

The present study has several limitations. First, we analyzed only outpatients who had been treated with SGLT2 inhibitors for at least 12 months at our hospital.It was up to the attending physician to decide which patients were prescribed the SGLT2 inhibitor. Thus, our study has an inherent patient selection bias, such as age, disease duration, and follow-up duration. Second, about 96% of the patients were undergoing combination therapy with SGLT2 inhibitors and oral hypoglycemic agent and/or insulin. Therefore, we could not exclude the synergistic effects of concomitant use of these anti-diabetic medication.

Third, changes in diet are presently the only mechanism of action considered to explain the loss of efficacy of SGLT2 inhibitors on body weight. Nutritional guidance counsels and provides support to patients with T2DM as needed. And interviews during the study did not reveal any significant changes in diet therapy, but it is possible that we could not fully grasp complete picture of the diet therapy. Fourth, in several patients after 32 weeks treatment of SGLT2 inhibitors the maximal HbA1c reduction was attenuated. Extensive clinical cohort studies with longer observation periods may be needed to define reliable predictors of the effectiveness of SGLT2 inhibitors for continuous lowering of the

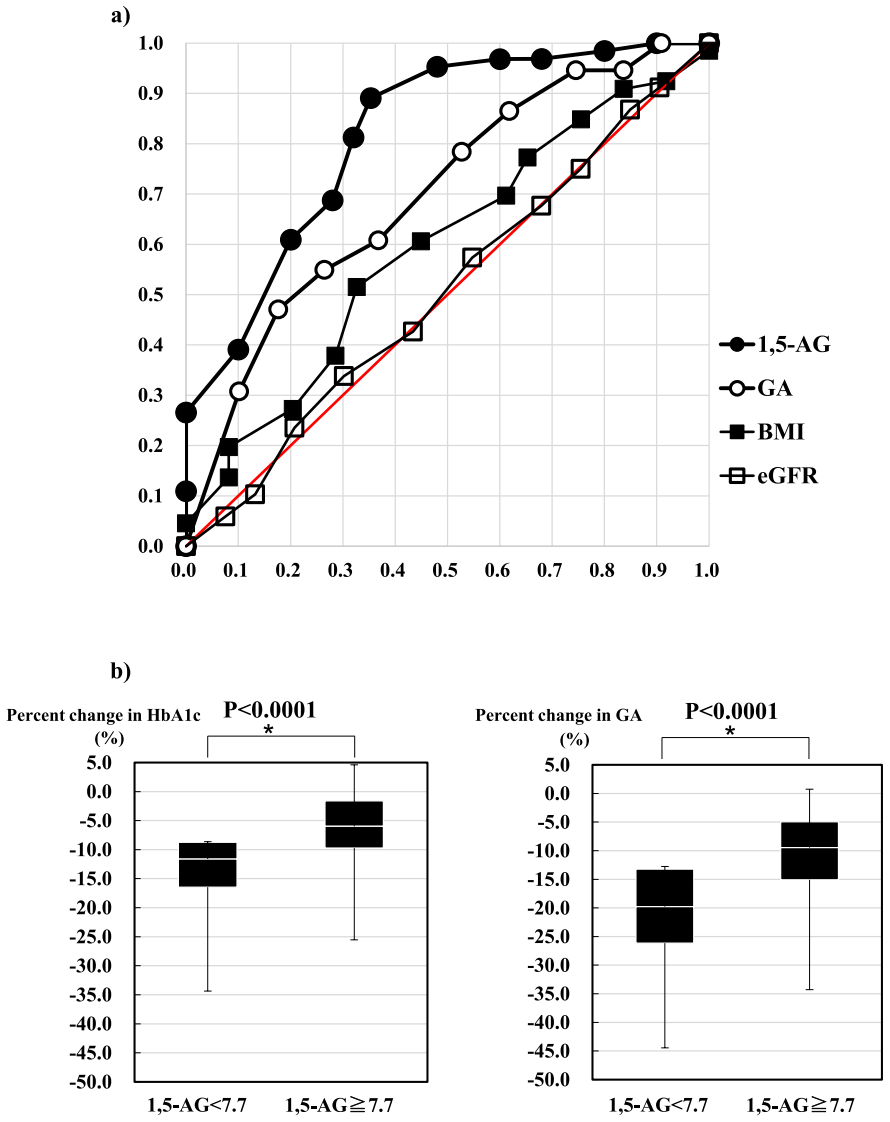

Fig. 6. (a) ROC curves for 1,5-AG(closed circle), GA(open circle), BMI (black square), and eGFR(white square) were constructed as indicators of the efficacy of the SGLT2 inhibitors. (b) Box plots of the percent change in HbA1c and GA when classified at 1,5-AG < 7.7 μg/mL (n = 109) or 1,5-AG > =7.7 μg/mL(n = 59).

HbA1c levels.

Our study results suggested that patients with greater circadian variability in blood glucose levels are more likely to benefit from SGLT2 inhibitors. But, it is unclear what molecular mechanisms and functional changes contribute to our new findings because we did not quantify changes in systemic transcription factor expression or urinary glucose excretion. We anticipate that future elucidation of these will complement our research.

The baseline 1,5-AG is a valuable predictor for the treatment effect of SGLT2 inhibitors. However, 1,5-AG levels are affected by nation-specific dietary habits, and the 1,5-AG level has been reported to be absolutely different between Asians and Caucasians [25]. Such factors will inevitably lead to heterogeneity. Our study has derived optimal cut-off levels for 1,5-AG in the Japanese population, but it may be necessary to decide each appropriate cut-off levels by taking into account ethnic differences in the future.

Ethics policy

This study was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the ethics committee of the Osaki Citizen Hospital (H29-36) and registered with the University Hospital Information Network (UMIN000032848).

CRediT authorship contribution statement

Masahiro Usui: Conceptualization, Methodology, Validation, Formal analysis, Writing - original draft, Writing - review & editing, Supervision, Project administration. **Mamiko Tanaka:** Data curation, Investigation. **Hironori Takahashi:** Investigation, Visualization.

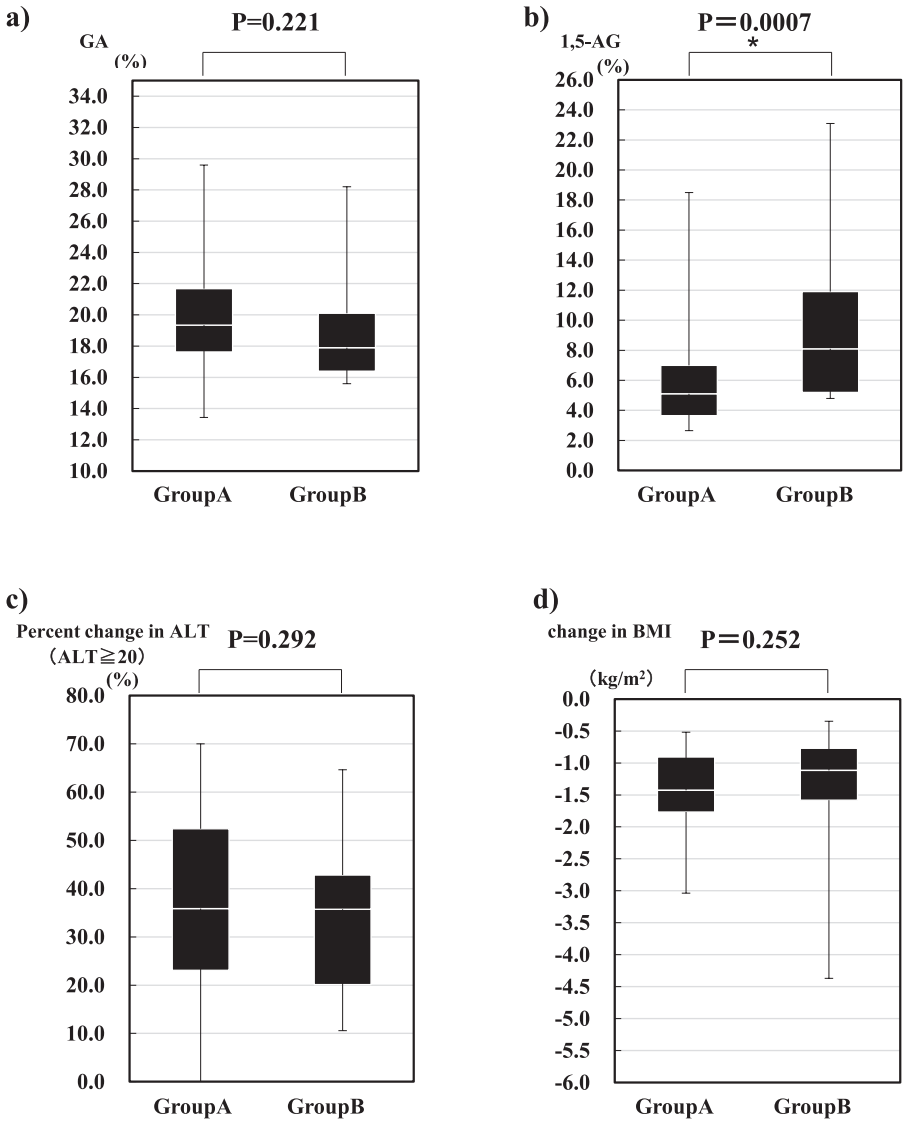

Fig. 7. This analysis was restricted to patients with the HbA1c value of 7.0–8.4% (52–68 mmol/mol) at the start of SGLT2 inhibitor treatment.(n = 97). Box plots of the GA (a) and 1,5-AG(b) in Group A (n = 56) and Group B (n = 41). Box plots of the percent change in ALT level (c) in Group A and Group B. Box plots of change in BMI (d) in Group A and Group B. The data used in Fig. 7c were limited to patients with an ALT level above 20 IU/ml upon at the administration of SGLT2 inhibitor under these HbA1c conditions.(Group A n = 41, Group B n = 30).

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References

[1] Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes 2005;54:3427–34.
[2] DeFronzo RA, Hompesch M, Kasichayanula S, Liu X, Hong Y, Pfister M, et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diab Care 2013;36:3169–76.
[3] Takahara M, Shiraiwa T, Matsuoka TA, Katakami N, Shimomura I. Ameliorated pancreatic beta cell dysfunction in type 2 diabetic patients treated with a sodium-glucose cotransporter 2 inhibitor ipragliflozin. Endocr J 2015;62:77–86.
[4] Al Jobori H, Daniele G, Adams J, Cersosimo E, Solis-Herrera C, Triplitt C, et al. Empagliflozin treatment is associated with improved beta-cell function in Type 2 diabetes mellitus. J Clin Endocrinol Metab 2018;103:1402–7.
[5] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–92.
[6] Ahn CH, Oh TJ, Kwak SH, Cho YM. Sodium-glucose cotransporter-2 inhibition improves incretin sensitivity of pancreatic beta-cells in people with type 2 diabetes. Diab Obes Metab 2018;20:370–7.
[7] Kim Y, Babu AR. Clinical potential of sodium-glucose cotransporter 2 inhibitors in the management of type 2 diabetes. Diab Metab Syndr Obes. 2012;5:313–27.
[8] Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124:499–508.
[9] Merovci A, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124:509–14.
[10] Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diab Care 2014;37:1815–23.
[11] Sakai S, Kaku K, Seino Y, Inagaki N, Haneda M, Sasaki T, et al. Efficacy and safety of the SGLT2 inhibitor luseogliflozin in japanese patients with type 2 diabetes mellitus stratified according to baseline body mass index: pooled analysis of data from 52-week phase III trials. Clin Ther 2016;38:843–62. e9.
[12] Yagi S, Aihara KI, Kondo T, Kurahashi K, Yoshida S, Endo I, et al. Predictors for the treatment effect of sodium glucose co-transporter 2 inhibitors in patients with type 2 diabetes mellitus. Adv Ther 2018;35:124–34.
[13] Stettler C, Stahl M, Allemann S, Diem P, Schmidlin K, Zwahlen M, et al. Association of 1,5-anhydroglucitol and 2-h postprandial blood glucose in type 2 diabetic patients. Diab Care 2008;31:1534–5.
[14] Won JC, Park CY, Park HS, Kim JH, Choi ES, Rhee EJ, et al. 1,5-Anhydroglucitol reflects postprandial hyperglycemia and a decreased insulinogenic index, even in

subjects with prediabetes and well-controlled type 2 diabetes. Diab Res Clin Pract 2009;84:51–7.
[15] Goto M, Yamamoto-Honda R, Shimbo T, Goto A, Terauchi Y, Kanazawa Y, et al. Correlation between baseline serum 1,5-anhydroglucitol levels and 2-hour post-challenge glucose levels during oral glucose tolerance tests. Endocr J 2011;58:13–7.
[16] McGill JB, Cole TG, Nowatzke W, Houghton S, Ammirati EB, Gautille T, et al. Circulating 1,5-anhydroglucitol levels in adult patients with diabetes reflect longitudinal changes of glycemia: a U.S. trial of the GlycoMark assay. Diab Care 2004;27:1859–65.
[17] Selvin E, Rawlings AM, Grams M, Klein R, Steffes M, Coresh J. Association of 1,5-anhydroglucitol with diabetes and microvascular conditions. Clin Chem 2014;60:1409–18.
[18] Selvin E, Rawlings A, Lutsey P, Maruthur N, Pankow JS, Steffes M, et al. Association of 1,5-anhydroglucitol with cardiovascular disease and mortality. Diabetes 2016;65:201–8.
[19] Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diab Care 2003;26:881–5.
[20] Tobe K, Suganami H, Kaku K. Sodium-glucose cotransporter 2 inhibitor, tofogliflozin, shows better improvements of blood glucose and insulin secretion in patients with high insulin levels at baseline. J Diab Invest 2018;9:862–9.
[21] Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31–9.
[22] Cavalot F, Pagliarino A, Valle M, Di Martino L, Bonomo K, Massucco P, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. Diab Care 2011;34:2237–43.
[23] Hiki M, Shimada K, Kiyanagi T, Fukao K, Hirose K, Ohsaka H, et al. Single administration of alpha-glucosidase inhibitors on endothelial function and incretin secretion in diabetic patients with coronary artery disease - Juntendo University trial: effects of miglitol on endothelial vascular reactivity in type 2 diabetic patients with coronary heart disease (J-MACH). Circ J 2010;74:1471–8.
[24] Nakagami T, Group DS. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. Diabetologia 2004;47:385–94.
[25] Herman WH, Dungan KM, Wolffenbuttel BH, Buse JB, Fahrbach JL, Jiang H, et al. Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes. J Clin Endocrinol Metab 2009;94:1689–94.