ORIGINAL ARTICLE

Effects of sodium-glucose cotransporter 2 inhibitors on hypoglycaemia in brittle diabetic patients with decreased endogenous insulin secretion

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Summary

Aims: The effects of sodium-glucose cotransporter 2 inhibitors (SGLT2Is) on fasting blood glucose concentration (FBG) in patients with unstable FBG despite undergoing intensive insulin therapy (IIT) remain unclear. This study aimed to identify the effects of SGLT2Is on unstable FBGs.

Materials and methods: Thirty brittle diabetic patients with unstable FBGs despite undergoing IIT were included in the study. SGLT2Is were added and used in combination. We evaluated the data of the subjects in Evaluation 1 (immediately before using SGLT2Is) and evaluations 2, 3 and 4 (4, 24 and 48 weeks after starting concomitant therapy, respectively). FBGs were measured every day for a period of 28 days immediately before conducting Evaluations 1, 2, 3 and 4. The mean value of the 28 sets of FBG data (FBG mean) and their standard deviation (SD) values were established as each evaluation's FBGs. The changes in the mean values of the 30 subjects as well as their SD before and after concomitant therapy were evaluated.

Results: The concomitant use of SGLT2Is helped reduce not only FBG mean but also SD. FBG max dropped, and the frequency of occurrence of hyperglycaemic FBG (>11.1 mmol/L) decreased. However, FBG min did not drop, and the frequency of occurrence of hypoglycaemic FBG (<3.9 mmol/L) increased. The frequency of occurrence of subjective hypoglycaemia decreased. The decrease in the SD of FBG was related to the decrease in subjective hypoglycaemia.

Conclusion: Concomitant use of SGLT2Is in patients with brittle diabetes appears to be useful in terms of improvement of FBG and fewer occurrences of hypoglycaemic events.

KEYWORDS
brittle diabetes, fasting blood glucose concentration, hypoglycaemia, intensive insulin therapy, SGLT2 inhibitors

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1 | INTRODUCTION

In addition to the importance of preventing hyperglycaemia, preventing hypoglycaemia has been of importance in recent years.[1,2] With the establishment of basal-bolus intensive insulin therapy (IIT), which uses ultra-rapid-acting insulin alongside long-acting insulin, we no longer find cases where blood glucose cannot be lowered.[3] Because of this, however, the incidence of hypoglycaemia has increased, suggesting that this form of therapy may worsen the patients' prognosis.[4] Preventing hypoglycaemia has thus become an important therapeutic challenge.

Patients whose endogenous insulin secretion has decreased markedly, in particular, have unstable blood glucose levels, even in a fasting state. This may be attributable to a marked hyperglycaemia in early morning (the dawn phenomenon) or to a serious hypoglycaemia leading to the development of hyperglycaemia as a backlash (the Somogyi phenomenon).[5-7] If the dose of insulin is increased, serious hypoglycaemia is frequently induced; if it is decreased, serious hyperglycaemia is induced. Physicians therefore have a hard time controlling the symptoms in patients who have "brittle diabetes."[8] We attempted to treat patients with brittle diabetes by switching to even more stable long-acting insulin,[9] or using concomitant glucagon-like polypeptide-1 receptor agonists.[10] We observed therapeutic effects in some cases. However, we were still left with a considerable number of refractory cases.

As we have seen, a major problem observed in these brittle diabetic patients is the instability of their blood glucose levels. They may experience continued hyperglycaemia and then suddenly become hypoglycaemic, making it difficult for their physicians to discover and set the amount of insulin to administer. If this hypoglycaemia—particularly cases of serious hypoglycaemia—could be kept under control, it would be considerably easier to manage the patients' blood glucose levels. Although there are numerous drugs that lower the blood glucose levels, there are none that can reduce incidents of hypoglycaemia. Moreover, unlike non-diabetic patients and diabetic patients with favourable blood glucose control, patients with brittle diabetes sometimes experience hypoglycaemic symptoms, even with blood glucose levels exceeding 3.9 mmol/L (70 mg/dL), making us reluctant to adopt more aggressive hypoglycaemic treatment.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT2Is), which have been released in recent years, lower the blood glucose levels in a non-insulin-dependent fashion by increasing the excretion of glucose into the urine.[11,12] Because of this, decreased glycaemic actions can be expected, even in patients whose endogenous insulin secretion has markedly decreased.[13-15] However, very few studies have thus far been conducted on this subject. Even fewer studies have been made on SGLT2Is' influence on hypoglycaemia.

We therefore included, as our study subjects, diabetic patients whose endogenous insulin secretion has become depleted and who had unstable fasting blood glucose (FBG) and poor blood glucose control even after undergoing IIT, and tested the effects of SGLT2I add-on therapy on hypoglycaemia.

2 | MATERIALS AND METHODS

2.1 | Study subjects

As our study subjects, we selected diabetic patients showing a marked reduction in the endogenous insulin secretion, with unstable FBG and poor glycaemic control [HbA1c >53.0 mmol/mol (>7.0% of NGSP)],[13] despite having undergone IIT.

Reduced endogenous insulin secretion was defined as meeting two or more of the following requirements: homeostatic model assessment (HOMA)-β of <30%,[16,17] C-peptide index (CPI) of <0.7,[18,19] and the difference in glucagon loading test between the C-peptide immunoreactivity (CPR) values at 0 min and 6 min (ΔCPR) of <0.1 (ng/mL) [CPR 6 min after intravenous injection of glucagon (CPR-6 min), increment of CPR (ΔCPR)].[14,20,21] However, all the subjects in our study showed fasting immunoreactive insulin (IRI) and fasting CPR below measurement sensitivity in a test performed on initiation of insulin. Their ΔCPR-6 min was also below 0.1 ng/mL in a glucagon loading test. In other words, endogenous insulin secretion had decreased significantly in all our study subjects: their insulin secretion was practically zero.
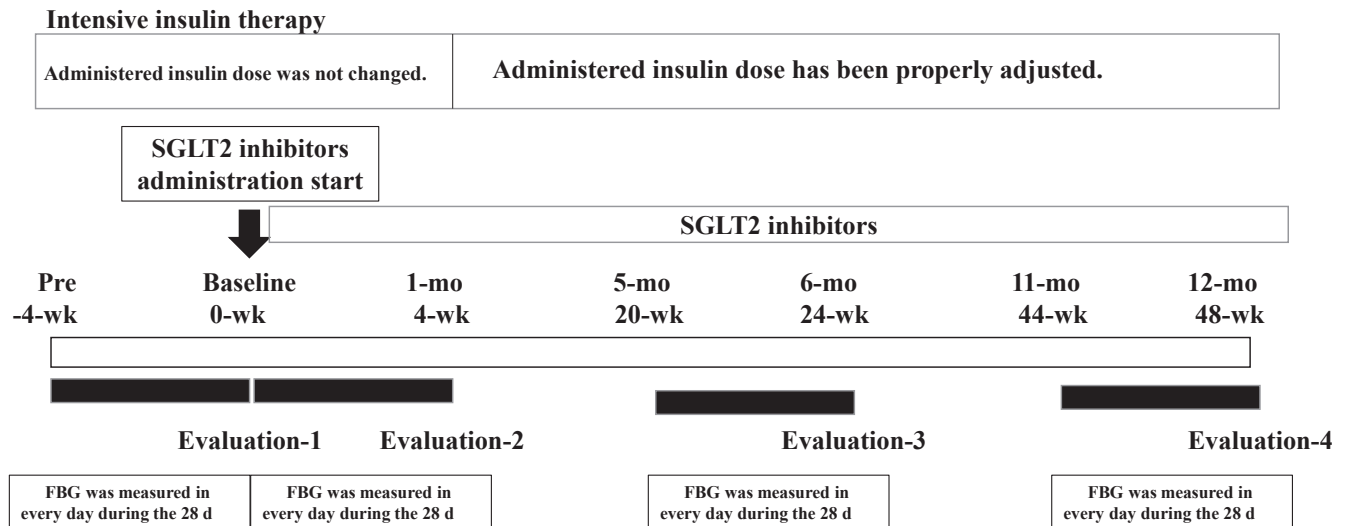
The subjects included 21 patients with type 1 diabetes who were positive for GAD antibodies (including those who had been positive in the past). There were also seven subjects with hyperthyroidism and three with hypothyroidism, but their symptoms were all being controlled to euthyroid status. In consideration of the characteristics of SGLT2Is, patients with an eGFR of <60 mL/min/1.73 m^2 were excluded from the study.[22]

We decided not to change the amount of insulin until the end of the first 4 weeks after starting combination therapy in consideration of the fact that (a) it was completely unknown by how much the dose of insulin should be reduced if SGLT2Is were added and used in combination, (b) the blood glucose level changes sharply as a result of slight changes in insulin dose, and (c) at this point, hyperglycaemia had occurred frequently in subjects with poor blood glucose control, making us reluctant to reduce the dose of insulin. Subsequently, the dose of insulin was adjusted based on the judgement of the primary physician while taking fluctuations in blood glucose levels into consideration.

Forty individuals were nominated as possible study subjects. However, two withdrew their informed consent, six had insufficient data [had missing values for self-monitoring of blood glucose (SMBG)], and two discontinued medication (one did so because of frequent occurrence of serious hypoglycaemia, and one temporarily withdrew the drug because of cystitis). In the end, thirty individuals were recruited as analysis subjects.

2.2 | Study protocol

Figure 1 shows an overview of the study protocol. The study subjects' clinical data were evaluated immediately before administering SGLT2Is (baseline, Evaluation 1) and 4 (Evaluation 2), 24 (Evaluation 3) and 48 weeks after administration (Evaluation 4). We compared the

Intensive insulin therapy

Administered insulin dose was not changed.	Administered insulin dose has been properly adjusted.

SGLT2 inhibitors administration start

SGLT2 inhibitors

Pre	Baseline	1-mo	5-mo	6-mo	11-mo	12-mo
-4-wk	0-wk	4-wk	20-wk	24-wk	44-wk	48-wk

Evaluation-1	Evaluation-2	Evaluation-3	Evaluation-4
FBG was measured in every day during the 28 d	FBG was measured in every day during the 28 d	FBG was measured in every day during the 28 d	FBG was measured in every day during the 28 d

The mean and SD of these 28 FBG values were assumed to be FBG value and SD values (scattering condition of FBG) of the case.

FIGURE 1 Overview of the study protocol. The evaluation made when the administered insulin dose was unchanged and concomitant sodium-glucose cotransporter 2 (SGLT2) inhibitors were added was considered as Evaluation 1. Evaluations made 4, 24 and 48 weeks after the start of this concomitant therapy were considered as evaluations 2, 3 and 4, respectively. We measured the blood glucose levels before breakfast during the 28 days immediately before each evaluation and set their mean value and SD levels as the individual patient's fasting blood glucose levels (FBG) and SD level before and after the change in treatment. We evaluated the changes in these FBG and SD values of the 30 target patients. We also measured the blood glucose levels before and after three meals in an optional day within 1 week immediately before each evaluation and evaluated the changes in various blood glucose levels before and after the change in therapy

data for Evaluation 1 and those for Evaluation 4, for which the duration of administration of the drug had been the longest, and evaluated the effects of concomitant SGLT2Is as add-on therapy to IIT.

The subjects were asked to record any detectable hypoglycaemic events (subjective hypoglycaemia). Even if the SMBG's numerical values were low, if the hypoglycaemia was asymptomatic, it was not counted as subjective hypoglycaemia. On the other hand, incidents of subjective hypoglycaemia that had occurred not only during fasting but also during randomly selected time zones were also counted. Because the FBG of the study subjects showed wide daily changes, we felt that numerical figures measured once during the day of the evaluation were too accidental and lacked reliability, so we measured fasting glucose every day, via SMBG, starting on 28 days before each evaluation. We designated the average of the 28 numerical values as the subject's "FBG mean" and established the standard deviation as the subject's "SD." Of the 28 FBG values, the lowest was designated as the individual's FBG min, and the highest, FBG max. Moreover, of the 28 FBG values, we evaluated the number of times that hyperglycaemic events [glucose >11.1 mmol/L (200 mg/dL)] and hypoglycaemic events [glucose <3.9 mmol/L (70 mg/dL)] had occurred. We divided the dose of insulin at each evaluation into bolus insulin, basal insulin and total insulin and evaluated them.[9,10] We focused on the 30 subjects' Evaluation 1 and Evaluation 4 measurement values and compared the FBG mean and SD, FBG min, FBG max, the number of occurrences of hyperglycaemic events, the number of occurrences of hypoglycaemic events, and insulin dose. We then investigated the changes in these values.

We also asked the subjects to measure their blood glucose before taking each of their daily three meals and 90 minutes after taking the three meals, on any day within 1 week prior to Evaluation 1 and Evaluation 4, and had them record the values.[10]

This study complied with the Helsinki Declaration and was conducted with the approval of the Medical Ethics Committee of Tohoku University. All participants provided their full informed consent.

2.3 | Statistical methods

We used Shapiro-Wilk's W test to confirm that all the numerical values showed normal distributions. The values are shown as "mean ± SD." Student's t test was also used to compare and study the values between Evaluation 1 and Evaluation 4. The χ^2 test was also employed to compare and study the number of occurrences of hyperglycaemic events, hypoglycaemic events and subjective hypoglycaemia.

Any correlation between the changes in the number of occurrences of subjective hypoglycaemia and various factors was studied using Spearman's rank-order correlation. $P < 0.05$ was regarded as statistically significant.

3 | RESULTS

All the subjects were brittle diabetic patients who had a marked reduction in endogenous insulin secretion and who had undergone

IIT. The concomitant drugs used were α-glucosidase inhibitors in 5 subjects, biguanide in 2, pioglitazone in 1, GLP-1 receptor agonist in 2, renin-angiotensin system inhibitors in 23 and statins in 13. The complications observed were simple diabetic retinopathy in 7 subjects, proliferative retinopathy after photocoagulation in 2, microalbuminuric nephropathy in 6 and macroalbuminuric nephropathy in 1. The types of SGLT2Is used were ipragliflozin (n = 11), empagliflozin (n = 6), dapagliflozin (n = 6), canagliflozin (n = 4), luseogliflozin (n = 2) and tofogliflozin (n = 1).

Table 1 shows the values of each factor at various evaluations and the results of a comparison between Evaluation 1 and Evaluation 4.

The subjects' body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), serum triglycerides (TGs),

alanine transaminase (ALT), aspartate aminotransferase (AST) and eGFR all dropped slightly but significantly. The levels of serum total cholesterol and serum high-density lipoprotein cholesterol also rose slightly but significantly. However, these were variations within the normal ranges, so their therapeutic significances were unclear.[22] The changes in eGFR, however, suggest that hyperfiltration had been corrected. However, it was unclear whether this was the effect of SGLT2I (tubuloglomerular feedback) or a result attributable to decreased glycaemia.[23]

Both HbA1c and FBG mean dropped significantly, and the standard deviation (SD) of FBG fell as well. This shows that not only the 28 FBG values had become lower, but also their dispersion had narrowed. The fact that HbA1c had decreased suggests that blood

TABLE 1 The values of each factor at various Evaluations, and the results of a comparison between Evaluation 1 and Evaluation 4

Evaluations	1 (baseline)	2 (4-wk)	3 (24-wk)	4 (48-wk)	P
Age (years)	40.7 ± 10.7				
Gender (M/F)	12/18				
Duration (years)	12.0 ± 5.3				
BMI (kg/m^2)	22.4 ± 2.0	22.3 ± 2.0	22.1 ± 1.9	22.1 ± 1.7	<0.0001
HbA1c (mmol/mol)	66.3 ± 4.5	64.9 ± 4.7	56.8 ± 3.3	54.7 ± 2.7	<0.0001
SBP (mmHg)	120.9 ± 7.8	118.2 ± 9.2	115.1 ± 8.0	114.9 ± 7.6	<0.0001
DBP (mmHg)	66.3 ± 6.5	65.5 ± 6.1	64.3 ± 6.4	64.0 ± 5.6	0.000177
TG (mmol/L)	0.9 ± 0.5	0.9 ± 0.5	0.8 ± 0.4	0.8 ± 0.4	0.002465
TC (mmol/L)	5.0 ± 0.5	5.1 ± 0.6	5.0 ± 0.6	5.1 ± 0.6	<0.0001
HDL-C (mmol/L)	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.1	<0.0001
ALT (IU/L)	23.9 ± 7.1	24.3 ± 7.9	22.7 ± 6.9	21.1 ± 6.0	0.000750
AST (IU/L)	24.5 ± 8.1	25.1 ± 7.2	22.9 ± 7.6	22.5 ± 7.1	0.006362
eGFR (mL/min/1.73 m^2)	97.9 ± 14.8	90.8 ± 13.0	91.2 ± 11.8	93.6 ± 11.5	<0.0001
FBG mean (mmol/L)	10.3 ± 1.1	6.9 ± 1.0	5.7 ± 0.4	5.4 ± 0.3	<0.0001
FBG SD	5.1 ± 0.8	4.5 ± 0.7	3.1 ± 0.5	2.6 ± 0.4	<0.0001
FBG min (mmol/L)	2.4 ± 0.4	2.2 ± 0.3	2.4 ± 0.3	2.5 ± 0.4	0.094721
FBG max (mmol/L)	19.0 ± 1.4	17.5 ± 1.8	14.0 ± 1.5	12.5 ± 1.4	<0.0001
FBG <3.9[a] (counts/28)	5.4 ± 1.7	10.9 ± 2.2	10.2 ± 2.0	10.3 ± 2.5	<0.0001
FBG >11.1[b] (counts/28)	13.0 ± 2.8	5.8 ± 1.7	2.9 ± 1.1	1.9 ± 0.9	<0.0001
Hypoglycemia (counts/28 d)	16.7 ± 3.8	18.5 ± 3.8	5.0 ± 1.5	2.6 ± 1.2	<0.0001
Bolus Insulin (U/d)	35.2 ± 9.3	35.2 ± 9.3	33.7 ± 9.2	32.6 ± 8.8	0.263616
Base Insulin (U/d)	21.8 ± 5.8	21.8 ± 5.8	18.6 ± 5.4	17.1 ± 5.1	0.001565
Total-Insulin (U/d)	57.0 ± 14.6	57.0 ± 14.6	52.4 ± 13.9	49.7 ± 13.1	0.045077

p: baseline vs after 48-wk treatment.

ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG max, maximum value in the FBG; FBG mean, mean of the FBGs; FBG min, minimum value in the FBG; FBG, fasting blood glucose concentration; HDL-C, serum high density lipoprotein cholesterol concentration; Insulin, insulin dose; SBP, systolic blood pressure; SD, standard deviation; TC, serum total cholesterol concentration; TG, serum triglyceride concentration.

[a]Frequency of occurrence of FBG value <3.9 mmol/L.

[b]Frequency of occurrence of FBG value more than 11.1 mmol/L, hypoglycemia: subjective hypoglycemia.

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glucose levels had dropped not only during fasting but also during a variety of other time zones (Figure 2 and Table S1).

Although FBG min remained unchanged, FBG max decreased significantly (Table 1). This shows that because of the combined use of SGLT2Is, although the blood glucose levels in the low range did not drop any further, the levels in the higher part of the range had dropped. The number of occurrences of hyperglycaemia events decreased significantly, and that of hypoglycaemia events increased significantly. In contrast, the number of occurrences of subjective hypoglycaemia significantly decreased (Table 1). This reveals that although the occurrence of FBG corresponding to hyperglycaemic value had decreased and that of FBG corresponding to hypoglycaemic value had increased, the frequency of hypoglycaemia that the subjects were aware of had decreased. Autonomic responses such as finger tremor and palpitation and cold sweat decreased. Neuroglycopenic hypoglycaemia symptoms such as unconsciousness and confusion did not occur additionally either. This was not that the subjects comes not to notice hypoglycemia easily. They were able to notice hypoglycemia. Subjective hypoglycemia had not occurred really though the blood glucose value was low.

Although bolus insulin was not changed, basal insulin was significantly decreased and total insulin was decreased. It is possible that SGLT2Is are more effective against preprandial glucose than against postprandial glucose.

To further test this possibility, we evaluated the blood glucose levels that the subjects measured before and after taking each of their daily three meals, on any chosen day within 1 week immediately prior to Evaluation 1 and Evaluation 4 (Figure 2). Because the subjects of our study had brittle diabetes, their daily blood glucose levels varied erratically, so the measured values did not necessarily represent their actual blood glucose levels. Therefore, although it was unclear whether analysing them was meaningful, and if so, to what degree, we proceeded with our analysis, assuming that it would provide some useful evidence. The results showed that blood glucose levels before and after three meals had dropped significantly after 48 weeks of SGLT2I add-on therapy. The combined therapy with SGLT2Is led to a wider range of blood glucose elevation after breakfast, but that after lunch and dinner remained unchanged (Figure 2 and Table S1). These findings suggest that with SGLT2I add-on therapy, (a) preprandial blood glucose drops and (b) postprandial blood glucose elevation is not suppressed, but (c) the postprandial blood glucose level appears to fall in proportion to the drop in preprandial blood glucose. Concerning the post-treatment rise in blood glucose after breakfast, there is a possibility that because the FBG level was markedly low, some patients had received some sort of intervention (eg, ingestion of complementary diet, increased amount of breakfast, reduced dose of insulin).

We found it extremely interesting that although the number of occurrences of FBGs that correspond to hypoglycaemic events had increased, the occurrence of subjective hypoglycaemia that the subjects were aware of had decreased. We therefore investigated the factors that might be correlated with these changes in the number of occurrences of subjective hypoglycaemia. The results are shown in Table 2. The changes in the number of occurrences of subjective hypoglycaemia correlated positively with the degree of change in SD (ΔSD of FBG). The smaller the SD, the fewer the occurrences of subjective hypoglycaemia (Figure S2A), and it correlated negatively with the rate of change of basal insulin (per cent change of basal
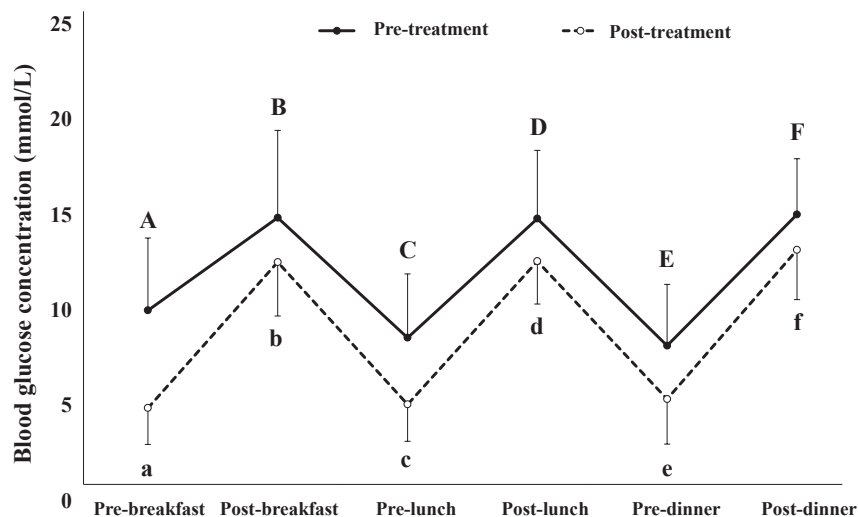

FIGURE 2 Results of the patients' blood glucose levels before taking each of their daily three meals and 90 minutes after taking the three meals, on any day within 1 week prior to Evaluation 1 (pretreatment) and Evaluation 4 (48 weeks after treatment). Table S1 shows the numerical values at each of these points. Blood glucose levels before and after taking three meals dropped significantly after treatment compared to before treatment (prebreakfast blood glucose: A → a; post-breakfast blood glucose: B → b; prelunch blood glucose: C → c; post-lunch blood glucose: D → d; predinner blood glucose: E → e; post-dinner blood glucose: F → f.) In contrast, the range of rise in blood glucose at breakfast (ΔBG) was broader after treatment (corresponding to the slope of "ab") as compared to before treatment (corresponding to the slope of "AB") (ΔBG at breakfast in Table S1). The ΔBG value at lunch and at dinner did not change before and after treatment (comparison between CD's slope and cd's slope and between EF's slope and ef's slope in the figure) (ΔBG at lunch and dinner in Table S1)

insulin). The more the dose of basal insulin had been decreased, the more frequent the occurrences of subjective hypoglycaemia were. In other words, the less we had decreased the dose of basal insulin, the less the frequency of the subjective hypoglycaemia had been decreased (Figure S2B). Changes in the number of occurrences of subjective hypoglycaemia did not correlate with changes in BMI, HbA1c or FBG mean, or the amount of changes in basal insulin, or the per cent change in SD.

4 | DISCUSSION

If the mechanism of action of SGLT2Is is taken into consideration, it can be predicted that hyperglycaemic values would decrease, and the levels of HbA1c and FBG mean would drop. What is interesting, though, is that although the dispersion of FBG narrowed and the frequency of occurrence of hypoglycaemic events (FBG <3.92 mmol/L) increased, the frequency of occurrence of subjective hypoglycaemia had decreased. Needless to say, we cannot deny the possibility that the number of occurrences of hypoglycaemia had decreased since the dose of insulin, particularly the dose of basal insulin (FBG's responsible insulin), has been decreased. If that was the case, however, the occurrence of low blood glucose level (FBG <3.9 mmol/L) should decrease, and the incidence of subjective hypoglycaemia should decrease. The fact in our study is, however, that the number of occurrences of subjective hypoglycaemia decreased, even though blood glucose levels dropped (the occurrence of low blood glucose level increased). Although the dose of insulin, in particular the dose of basal insulin, was decreased, not only FBG mean but also FBG max and the number of occurrence

TABLE 2 Any correlation between the changes in the number of occurrences of subjective hypoglycemia and various factors

	Subjective hypoglycemia	
	r	*P*
ΔSD of FBG	0.4017	0.0278
% change in SD of FBG	0.3415	0.0647
ΔFBG mean	0.2984	0.1092
% change in FBG mean	0.2656	0.1560
Δdose of base insulin	-0.2119	0.2609
% change in base insulin	-0.5225	0.0031
Δdose of total insulin	-0.0356	0.8518
% change in total insulin	-0.2560	0.1721
Δdose of HbA1c	0.2475	0.1872
% change in HbA1c	0.2091	0.2674
ΔBMI	-0.0322	0.8657
% change in BMI	-0.0623	0.7435

FBG, fasting blood glucose concentration; SD, standard deviation.
% change: percent change, BMI: body mass index, hypoglycemia: symptomatic hypoglycemia.
Subjective hypoglycemia: the number of occurrences of subjective (symptomatic) hypoglycemia.

of hyperglycaemic events decreased, and HbA1c also decreased. For these reasons, treatment with SGLT2Is appears to exhibit significant anti-hyperglycaemic actions, especially during periods of high blood glucose levels. This drop in high blood glucose area appears to be the major reason for the drop in FBG mean, FBG max and HbA1c. In addition, since the number of occurrences of hypoglycaemic values increased, and the values of FBG min remained unchanged even though the dose of insulin had been reduced, it appears that SGLT2Is increase the occurrences of blood glucose levels below 3.9 mmol/L, but do not lower the blood glucose level in this low range any further. This conclusion is supported by the fact that even though SGLT2 inhibitors completely block glucose reabsorption in the S1 portion of the proximal tubules, glucose is reabsorbed by SGLT1 further downstream (the S3 portion); and if the blood glucose drops to a certain level, the amount of glucose that can be filtered out decreases. All glucose then would be reabsorbed by SGLT1, so urinary glucose is no longer excreted, and blood glucose level drops no further (threshold).

Moreover, the fact that a reduction in the per cent change of basal insulin (not amount but rate of decrease) showed a negative correlation with a decrease in the frequency of occurrence of subjective hypoglycaemia (Figure S2B) indicates that the more the per cent decrease rate of administering basal insulin dose (ratio of the decreased insulin dose to the original insulin dose) is increased, the more the frequency of occurrence of subjective hypoglycaemia increases. This appears, at first glance, to be a contradictory finding, suggesting that "the more the amount of basal insulin is decreased, the more the incidence of subjective hypoglycaemia increases." This is likely to be the result of the primary physician decreasing the dose of insulin in greater amounts and to a greater extent in patients whose incidents of subjective hypoglycaemia have increased, that is, when the frequency of occurrence of subjective hypoglycaemia is higher.

There is a possibility that the signs of hypoglycaemia are not determined by blood glucose level alone. That is to say, whereas non-diabetic patients with a blood glucose level <3.9 mmol/L (70 mg/dL) rarely experience hypoglycaemic symptoms, diabetic patients with poor blood glucose control may experience hypoglycaemic symptoms, even at a blood glucose level of around 5.6 mmol/L (100 mg/dL). In our study too, many subjects experienced periods of low blood glucose early in the morning after taking SGLT2Is concomitantly, but had vanishingly few incidences of hypoglycaemia that they were able to detect by themselves. Figure S1 shows the results of continuous glucose monitoring in one such patient, immediately after Evaluation 4. This subject took SGLT2I in combination and experienced numerous occurrences of blood glucose levels (subcutaneous glucose concentrations, to be more exact) that corresponded to hypoglycaemic events; however, there were extremely few incidences of subjective hypoglycaemia.

Concomitant use of SGLT2 inhibitors in patients who are undergoing intensive insulin therapy and whose endogenous insulin secretion has been depleted causes a sharp drop in preprandial blood glucose levels, particularly FBG levels. As a result, many such

patients show low blood glucose measurements that might, up to now, indicate an increased risk of hypoglycaemia. However, the frequency of hypoglycaemic incidents that the subjects become aware of decreased rather than increased. The mechanism by which this occurs was not elucidated in this study. We propose a mechanism to explain this unexpected phenomenon (Appendix S1 and Figures S3-S6). Further investigations are therefore required.

In Japan, the use of SGLT2Is in type 1 diabetes is currently not approved or recommended, but is not contraindicated, either. At present, although a Phase 3 clinical trial is under way, we cannot at this point recommend the combined use of SGLT2Is in patients with type 1 diabetes whose insulin secretion has dropped markedly. What we did on this occasion was to perform combination therapy using SGLT2Is, as a last resort, and examined its effects, in patients with brittle diabetes whose treatment had reached a dead end: we were unable to control their blood glucose simply by adjusting the insulin dose, nor could we expect any positive effects from administering conventional oral drugs in combination. As a result, we were able to confirm the following unique effects: even though hyperglycaemia was suppressed, and low blood glucose levels increased, the occurrence of hypoglycaemia that the subjects were aware of decreased. Reduction in body weight, which was our initial concern, was mild, and there were no clinically problematic cases. It should be noted, however, that this study was conducted with an extremely small sample size of 30 patients, so we cannot confidently recommend the concomitant use of SGLT2Is in diabetic patients whose insulin secretion has markedly decreased. We must wait for the results of the Phase 3 clinical studies to be released.

5 | CONCLUSION

The concomitant use of SGLT2Is helped not only to reduce FBG value, but also to narrow its dispersion. Hyperglycaemic FBG value dropped, and the frequency of occurrence of hyperglycaemic FBG decreased. Hypoglycaemic FBG value did not drop any further, and the frequency of occurrence of hypoglycaemic values in FBG increased. However, the frequency of occurrence of subjective hypoglycaemia decreased.

The concomitant use of SGLT2Is in diabetic patients with decreased endogenous insulin secretion appears to be useful in terms of improvement of blood glucose, reduction of basal insulin dosage and fewer occurrences of hypoglycaemic symptoms.

AUTHOR CONTRIBUTIONS

SO wrote the manuscript and researched the data. KN and MO contributed to the discussion and researched the data. SI reviewed and edited the manuscript.

DATA ACCESSIBILITY

The acceptable types of data access statement are given below. Data underlying this article can be accessed on the repository website. If possible, use an identifier, such as a DataCite DOI. Supplementary data associated with this article can be found in the online version at web link to online article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.