

An Effective Insulin Therapy in Combination With Sodium-Glucose Cotransporter 2 Inhibitors

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To the Editor

Recently, Suzuki et al. reported the comparison of combined tofogliflozin (sodium-glucose cotransporter 2 inhibitor, SGLT2i) and insulin glargine, tofogliflozin added to insulin, and insulin dose-increase therapy in uncontrolled type 2 diabetes. [1]. In the tofogliflozin + insulin group, approximately 90% of patients were treated by mixed insulin or bolus + basal insulin. In the glargine + tofogliflozin group, only basal insulin was used. After 24 weeks, HbA1c significantly decreased in the groups using tofogliflozin than in insulin alone group, suggesting that the addition of SGLT2i to insulin is superior to insulin alone with regard to glycemic control. Reduction of HbA1c was non-significantly greater in the tofogliflozin + insulin group (-1.04%) than in the glargine + tofogliflozin group (-0.76%). However, reduction of daily insulin dose was significantly greater in the glargine + tofogliflozin group (-12.67 U) than in the tofogliflozin + insulin group (-2.56 U). Furthermore, body weight reduction was greater in the glargine + tofogliflozin group (-3.4 kg) than in the tofogliflozin + insulin group (-2.9 kg). In the report which studied effects of dapagliflozin on 24-h glycemic control in type 2 diabetic patients by using continuous glucose monitoring (CGM), the improvement of 24-h mean glucose was greater in the metformin group (-36.2 mg/dL) than in the insulin group (-11.9 mg/dL) [2]. The improvement in time in hyperglycemic range was also more pronounced in the metformin group (-15.3%) than in the insulin group (-8.9%). These recent studies let us think about an effective insulin therapy in combination with SGLT2i.

The meta-analyses showed that the addition of SGLT2i to insulin therapy significantly reduced fasting plasma glucose, HbA1c, total daily insulin dose and body weight in both type 1 and type 2 diabetes [3, 4].

SGLT2i caused a decrease in the renal threshold for glucose excretion (RT_G), and an increase in urinary glucose excretion and a reduction in plasma glucose levels in both health individuals and diabetic patients [5, 6]. Therefore, if plasma glucose levels were above RT_G , SGLT2i was effective to decrease plasma glucose (Fig. 1a). However, if plasma glucose levels were below RT_G , SGLT2i did not work to decrease plasma glucose (ineffective range of SGLT2i) (Fig. 1b).

Studies which showed effects of the addition of SGLT2i to insulin therapy on insulin dose were shown in Table 1 [7-11]. Insulin reduced plasma glucose in a relatively dose-dependent manner in type 1 diabetic patients whose intrinsic insulin was depleted. However, SGLT2i reduced plasma glucose independently of insulin. Dose-dependent effects of SGLT2i on reduction of both bolus insulin and basal insulin were not observed in patients with type 1 diabetes [7, 8]. In type 1 diabetic patients treated with insulin and SGLT2i, glycemic control may be determined by administered insulin dose and RT_G reduced by SGLT2i. Interestingly, the reduction in basal insulin dose was small in type 1 diabetic group showing a large reduction in bolus insulin dose [7, 8]. There was a tendency to show a negative correlation between changes in bolus insulin dose and basal insulin dose (Fig. 2), indicating that if bolus insulin dose was increased, basal insulin can be reduced and *vice versa*. When we treat type 1 diabetic patients, we should titrate bolus and basal insulin dose not to make plasma glucose below RT_G (ineffective range of SGLT2i).

If patients who had the profile shown in Figure 3a took SGLT2i and showed a reduction in plasma glucose shown in Figure 3b, they can reduce both basal and bolus insulin doses like patients in the study by Matsumura et al [9]. If they show a reduction in plasma glucose as shown in Figure 3c, they can reduce only bolus insulin dose like patients in our previous study [10]. In type 2 diabetic patients whose intrinsic insulin was preserved, treated with insulin and SGLT2i, glycemic control may be determined by the following factors, 1) an improvement of insulin resistance due to body weight loss by SGLT2i; 2) an improvement of glucotoxicity by insulin and/or SGLT2i; 3) administered insulin dose; 4) RT_G reduced by SGLT2i. If we can decrease plasma glucose to target plasma glucose levels by using basal insulin and SGLT2i and other oral anti-diabetic drugs (OADs) which can reduce postprandial glucose such as dipeptidyl-peptidase 4 inhibitors and alpha glucosidase inhibitor, we can stop using bolus insulin like Figure 3d. Furthermore, SGLT2i was reported to reduce insulin dose in patients

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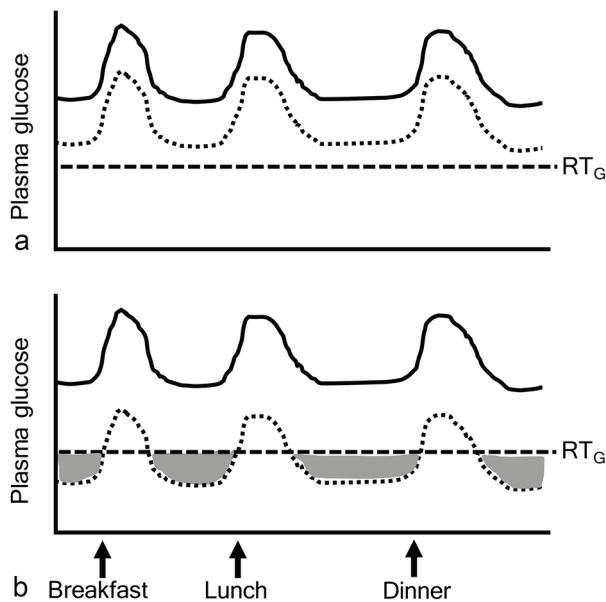


Figure 1. Ineffective range of SGLT2 inhibitors. The gray area indicates “ineffective range of SGLT2i” which shows that plasma glucose levels are below the renal threshold for glucose excretion (RT_G). Solid and dotted lines indicate plasma glucose levels before and after the addition of SGLT2 inhibitors, respectively.

treated by using basal insulin and OADs [11]. As seen in the study by Suzuki et al [1], a larger reduction of insulin dose produced a greater decrease in body weight.

Basal insulin therapy was less likely to induce hypoglycemia as compared with bolus-basal insulin therapy, suggesting that basal insulin therapy was less likely to produce “ineffective range of SGLT2i” as compared with bolus-basal insulin therapy. The addition of SGLT2i to basal insulin therapy

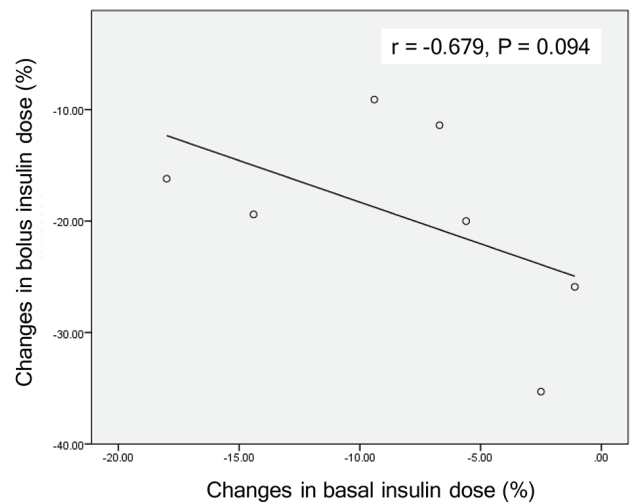


Figure 2. A correlation between changes in bolus insulin dose and changes in basal insulin dose by the addition of SGLT2 inhibitors in patients with type 1 diabetes. Correlation was analyzed by Spearman’s correlation.

showed a greater reduction in HbA1c (-1.03%), insulin dose (-1.58 U/day) and body weight (-1.64 kg) as compared with the addition of SGLT2i to bolus-basal insulin therapy (-0.39%, -1.33 U/day and -1.18 kg) [12], supporting our suggestion.

In conclusion, when we use insulin in addition to SGLT2i in both type 1 and type 2 diabetes, we should titrate insulin dose not to make “ineffective range of SGLT2i”.

Conflict of Interests

The authors declare that they have no conflict of interest con-

Table 1. Insulin Therapy in Combination With SGLT2 Inhibitors in Type 1 and Type 2 Diabetes

Authors	Study design	SGLT2 inhibitors	Changes in bolus insulin dose	Changes in basal insulin dose
Type 1 diabetic patients				
Henry et al [7]	RCT (n = 70, 2 weeks)	Dapagliflozin 1 mg	-19.4%	-14.4%
		Dapagliflozin 2.5 mg	-25.9%	-1.1%
		Dapagliflozin 5 mg	-16.2%	-18.0%
		Dapagliflozin 10 mg	-35.3%	-2.5%
Pieber et al. [8]	RCT (n = 75, 4 weeks)	Empagliflozin 2.5 mg	-0.04 U/kg/day (-11.4%)	-0.02 U/kg/day (-6.7%)
		Empagliflozin 10 mg	-0.07 U/kg/day (-20.0%)	-0.02 U/kg/day (-5.6%)
		Empagliflozin 25 mg	-0.03 U/kg/day (-9.1%)	-0.03 U/kg/day (-9.4%)
Type 2 diabetic patients receiving insulin therapy				
Matsumura et al [9]	One-arm (n = 15, 1 week)	Canagliflozin 100 mg	-112 U/week (-42.1%)	-52 U/week (-40.6%)
Hakoshima et al [10]	Retrospective observational study (n = 12, 10.2 days)	Dapagliflozin 5 mg (n = 6)	0	-4.6 U/day (-66%)
		Ruseogliflozin 2.5 mg (n = 6)		
Rosenstock et al [11]	RCT (78 weeks)	Empagliflozin 10 mg (n = 169)	UD	-1.2 U/day
		Empagliflozin 25 mg (n = 155)	UD	-0.5 U/day

RCT, randomized, double-blind, placebo-controlled study; UD, undetermined.

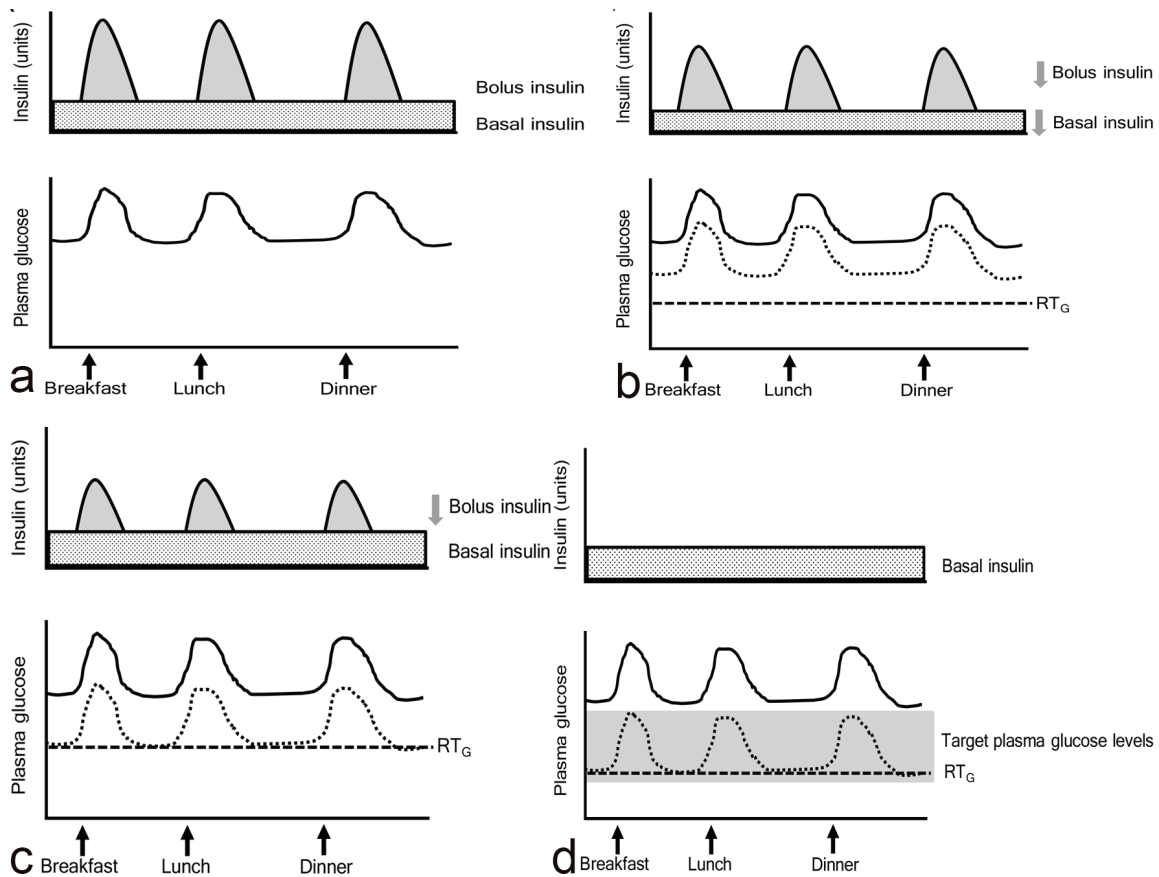


Figure 3. The association among bolus and basal insulin dose, plasma glucose and the renal threshold for glucose excretion (RT_G) in patients treated with insulin and SGLT2 inhibitors. Solid and dotted lines indicate plasma glucose levels before and after the addition of SGLT2 inhibitors, respectively.

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