Efficacy and Safety of Switching from Basal Insulin to Sitagliptin in Japanese Type 2 Diabetes Patients

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Key words
- sitagliptin
- basal insulin
- insulin secretion capacity

Abstract

Basal-supported oral therapy (BOT) is often used to treat poorly controlled type 2 diabetes. However, patients sometimes experience nocturnal and early morning hypoglycemia. Thus, maintaining targeted glycemic control by BOT is limited in some patients. We assessed the efficacy and safety of replacing basal insulin by sitagliptin therapy in Japanese type 2 diabetes patients on BOT. Forty-nine subjects were sequentially recruited for the 52-week, prospective, single arm study. Patients on BOT therapy were switched from basal insulin to sitagliptin. The primary endpoint was change in HbA1c in 52 weeks. The secondary endpoints were dropout rate, changes in body weight, frequency of hypoglycemia, and relationship between change in HbA1c and insulin secretion capacity evaluated by glucagon loading test. The average dose of basal insulin was 15.0±8.4 units. Sixteen subjects (31.3%) were dropped because replacement by sitagliptin was less effective for glycemic control. In these subjects, diabetes duration was longer, FPG and HbA1c at baseline were higher, and insulin secretion capacity was lower. Change in HbA1c in 52 weeks was −4 mmol/mol (95% CI −5 to −4 mmol/mol) ($p<0.05$). Change in body weight was −0.71 kg (95% CI −1.42 to −0.004 kg) ($p<0.05$). Frequency of hypoglycemia was decreased from 1.21±1.05 to 0.06±0.24 times/month. HbA1c level was improved if C-peptide index (CPI) was over 1.19. In conclusion, basal insulin in BOT can be replaced by sitagliptin with a decrease in HbA1c level and frequency of hypoglycemia in cases where insulin secretion capacity was sufficiently preserved.

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Introduction

Basal insulin preparation is recommended by the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus algorithm when lifestyle interventions and oral glucose-lowering agents no longer achieve the glycemic goal of hemoglobin A1c (HbA1c) level less than 53 mmol/mol [1,2]. Recently, 2 long-acting insulin analogues, insulin glargine and insulin detemir, are available that attain glycemic targets more effectively and safely [3,4]. There are no significant differences reported in glycemic control and overall hypoglycemia between the 2 analogues [5]. The combination of basal insulin and oral hypoglycemic agents (OHAs), known as basal-supported oral therapy (BOT), is often used to treat poorly controlled type 2 diabetes [6,7]. Better glycemic control, fewer hypoglycemic episodes, and less weight gain are obtained by BOT than by biphasic insulin [8]. In addition, BOT is relatively cost effective with the same glycemic control level as biphasic insulin regimen [9]. BOT is also helpful in Japanese type 2 diabetes patients. In the ALOHA (Add-on to Lantus® to OHA) study, in which 5223 Japanese type 2 diabetes patents participated, mean HbA1c was reduced from 75±13 to 60±13 mmol/mol in 24 weeks [10]. Although BOT is well-tolerated and effective for glycemic control, patients sometimes experience nocturnal and early morning hypoglycemia. In the ALOHA study, 0.97% of the patients experienced frequent hypoglycemia. In the 4 T-study, 1.3% of BOT-treated patients experienced hypoglycemia with loss of consciousness [8]. Another problem of BOT is that postprandial glucose is high, although morning fasting blood glucose level is within normal range. An increase in dosage of basal insulin or sulfonyl ureas (SUs); which are most commonly administrated in BOT-treated Japanese patients, is not always effective, and can result in increased hypoglycemia. In Japanese interview forms, frequency of hypoglyc-

emia induced by SUs is reported to be 1.3–2.8%. Thus, maintaining targeted glycemic control by BOT is limited in some patients.

Dipeptidyl peptidase-4 (DDP-4) inhibitor is a newly developed OHA that prevents degradation of the incretin hormones, glucagon-like peptide-1, and gastric inhibitory polypeptide [11]. This compound stimulates glucose-dependent insulin secretion and suppresses glucagon release, and can improve both fasting and postprandial glucose levels. Four different DPP-4 inhibitors are available in Japan: sitagliptin, vildagliptin, alogliptin, and linagliptin. Of these, sitagliptin is most widely used, partly because it was the first approved DPP-4 inhibitor and the safety and efficacy are acceptable in Japanese clinical practice. Generally, sitagliptin is more effective for glycemic control in Japanese patients compared to Caucasian patients [12,13]. Sitaglipitn is usually combined with low dosage of SUs in Japan, less than or equal to 2 mg/day of glimepiride and 40 mg/day of gliclazide, which is enough for glycemic control when combined with sitagliptin [14]. Patients also show improved glycemic control even if insulin secretion capacity is insufficient for oral therapy [14,15]. The main pathophysiology of Japanese type 2 diabetes is impairment of insulin secretion [16,17]. Insulin secretion capacity in Japanese populations is only about half of that in Caucasians [18]. Both decreased basal and early phase insulin secretion contribute more to Japanese type 2 diabetes [16], and insulin therapy is usually required in those with C-peptide index (CPI) lower than 0.8 [19]. However**,** basal insulin therapy is not always ideal in some patients because postprandial glucose is still high and preprandial glucose is low, which results in large fluctuation**s** in blood glucose. On the other hand, DPP-4 inhibitor might nevertheless ameliorate decreased early phase insulin secretion. This encouraged us to consider whether basal insulin can be replaced with sitagliptin in type 2 diabetes patients treated with SUs and basal insulin in at least some BOT cases.

We show here that sitagliptin can be switched from basal insulin in patients with C-peptide index (CPI) and/or secretory unit of islet in transplantation (SUIT) equal to or larger than 1.19 and/or 36.4, respectively, with beneficial effects on glycemic control.

Materials and Methods

Study design and participants

This was a prospective, 52-week, single center, and single arm intervention study to evaluate the effects on glycemic control of replacement of basal insulin to sitagliptin in type 2 diabetes patients inadequately controlled with BOT. Outpatients of Takashima General Hospital were recruited consecutively for a sample size of 45 subjects. Inclusion criteria were: type 2 diabetes treated with basal insulin (insulin glargine or detemir) and SUs (glimepiride or gliclazide) ± metformin ± thiazolidinedione ± α-glucosidase inhibitors for more than 1 year; aged ≥ 20 years; HbA1c level ≥ 52 mmol/mol; no improvement in HbA1c ≥ 5 mmol/mol within 3 months in BOT; and a fasting C-peptide reactin (CPR) of > 0.5 ng/ml. Exclusion criteria were: type 1 diabetes; secondary diabetes; alcoholism; severe depression, or severe psychological condition; malignancy; and abnormal hemoglobinemia. The study protocol was approved by the Institutional Review Board of Takashima General Hospital, and registered at the University hospital Medical Information Network in Japan (UMIN000005499). Written informed consent was obtained from all subjects.

Procedures and intervention

The duration of the study was 52 weeks. Subjects were screened for eligibility and gave basic demographic information, medical history, and frequency of hypoglycemia. Within a month before changing therapy from basal insulin to sitagliptin, glucagon loading test was performed without any OHAs or basal insulin for more than 24 h to evaluate insulin secretion capacity. When basal insulin was replaced by sitagliptin, the dosage of glimepiride or gliclazide was decreased to equal to or less than 2.0 mg/day or 40 mg/day, respectively, to prevent increased hypoglycemia if the subjects had been treated with more than 2.0 mg/day glimepiride or 40 mg/day gliclazide. If the subjects had been treated with equal to or less than 2.0 mg/day of glimepride or 40 mg/day of gliclazide, that dosage of SUs was maintained. Metformin (Met) and thiazolidinedione (TZD) were continued without any changes during the study. α-Glucosidase inhibitors were discontinued. The dosage of SUs was changed depending on the frequency of hypoglycemic episodes and glycemic control level. Sitagliptin was started at 50 mg/day, the usual initial dosage in Japan, which was increased to 100 mg/day if the HbA1c level did not reach 52 mmol/mol, since titration to 100 mg/day is acceptable.

Measurements

The primary endpoint was the change in HbA1c in 52 weeks. The secondary endpoints were dropout rate due to lesser efficacy of replacement by sitagliptin of basal insulin on glycemic control, change in body weight in 52 weeks, change in body mass index (BMI) in 52 weeks, change in frequency of hypoglycemia in 52 weeks, adverse events, and the correlation between change in HbA1c at the 8th week and insulin secretion capacity or CPI or SUIT at baseline. HbA1c are expressed in mmol/mol according to the recommendation of IFCC. CPI was calculated by the formula: [100 × fasting CPR (ng/ml)]/[18 × FPG (mM)] [19]. SUIT index was calculated by the formula: [250 × fasting CPR (nM)]/[(FPG − 3.43) (mM)] [20]. Blood glucose and C-peptide level were measured before (0 min) and 6 min after intravenous administration of 1 mg glucagon.

Statistical analysis

Sample size was estimated to be 34 to detect a 4 mmol/mol change in HbA1c in 52 weeks with a power of 95%, alpha 0.05 2-tailed, beta 0.20, standardized effect size 0.7. To take the dropout rate of 30% into account, the aim was to include 45 subjects. IBM SPSS Statistics was used for analysis. Dependent samples Student's *t*-test was used to compare the means of HbA1c level, insulin secretion capacity, BMI, body weight, age, and diabetes duration of the subjects between baseline and 52th week. Person's product-moment correlation test was used to evaluate the relationship between change in HbA1c and insulin secretion capacity or CPI or SUIT. To evaluate cutoff values of diabetes duration, FPG, HbA1c, 0-min CPR, 6-min CPR, delta-CPR, CPI, SUIT, and receiver operating characteristics curve (ROC) analysis were used. Independent sample Student's *t*-test was used to compare the mean of change in HbA1c in 52 weeks between subjects treated with sitagliptin + glimepiride and sitagliptin + gliclazide. Dunnett analysis was used to compare change in HbA1c in 52 weeks among subjects treated with sitagliptin + SUs and sitagliptin + SUs + MET and sitagliptin + SUs + TZD. A p-value of < 0.05 was considered as statistically significant.

Results

Participants

Forty-nine patients were eligible and were consecutively enrolled in the study (Table 1). Average age of subjects was 70.0±10.2 years; ratio of male was 60.8%; duration of diabetes was 14.3±8.2 years; average body weight was 62.3±10.4 kg; average BMI was 24.3±3.8 kg/m^2; and HbA1c was 64±9 mmol/mol. All subjects were treated with SUs; 17 subjects (34.7%) were treated with glimepiride (average dose 1.67±1.47 mg) and 32 (65.3%) were treated with gliclazide (average dose 33.8±12.0 mg). Average dosage of basal insulin analogues was 15.0±8.4 units. Glucagon loading test showed that 0-min CPR, 6-min CPR, CPI, and SUIT were 1.65±1.02 ng/ml, 3.37±1.98 ng/ml, 1.19±0.64, and 36.5±22.1, respectively. Sixteen subjects (32.6%) were dropped due to an increase in HbA1c in 8th week; 6 (29.4%) and 11 (34.4%) were dropped in glimepiride- and gliclazide-treated subjects, respectively (Table 2). No subjects were dropped for other reasons. Thirty-three subjects completed the study.

HbA1c findings and dosage of SUs and sitagliptin

Therapy adherence was confirmed by certified diabetes educators (nurses) in the study. Adherence of BOT therapy and the switching therapy were almost 100% for both therapies (data not shown).

HbA1c level in 52 weeks in final subjects was significantly decreased from 61±8 to 57±8 mmol/mol ($p<0.01$) (Table 2). Change in HbA1c in 52 weeks was −4 mmol/mol (95% CI; −5 to −4 mmol/mol) ($p<0.05$). HbA1c levels in 52 weeks in glimepiride-treated subjects (n=12) were significantly decreased from 63±9 mmol/mol to 55±9 mmol/mol ($p<0.01$). Change in HbA1c in 52 weeks was −8 mmol/mol (95% CI; −11 to −5 mmol/mol) ($p<0.05$). HbA1c levels in 52 weeks in gliclazide-treated subjects (n=21) were significantly decreased from 54±6 to 58±7 mmol/mol ($p<0.05$). Change in HbA1c in 52 weeks was −2 mmol/mol (95% CI; −4 to −0 mmol/mol) ($p<0.05$). There was a significant difference in change in HbA1c in 52 weeks between glimepiride-treated and gliclazide-treated subjects ($p<0.01$). The original dosages of glimepiride and gliclazide before the study were 1.58±0.93 mg/day and 38.2±14.0 mg/day, respectively; the initial dosages at the beginning of the study were significantly decreased to 0.96±0.40 mg/day and 24.8±8.7 mg/day, respectively ($p<0.05$); and the final dosages were significantly increased to 1.42±0.57 mg/day and 31.4±12.0 mg/day, respectively, compared to the initial dosages ($p<0.05$), and were almost equal to the original dosages (Table 2). Final dosage of sitagliptin was 74.2±25.4 mg/day in all subjects; 70.8±25.7 mg/day

Subjects (n)	49	**Basal insulin**	15.0±8.4 Units
Age (years)	70.0±10.2	**Medications**	SU 100% Glimepiride 34.7% 1.67±1.47 mg Gliclazide 65.3% 33.8±12.0 mg
Male	60.8%		
Diabetes duration (years)	14.3±8.2		Metformin 22.4% 636±131 mg
Complications	Nephropathy 61.2%		Thiazolidinedione 16.3% 10.3±3.9 mg
	Retinopathy 69.4%		α-Glucosidase inhibitors 8.1%
	Neuropathy 42.8%	**Glucagon test** 0-min CPR (ng/ml)	1.65±1.02
	Cardiovascular diseases 34.7%	6-min CPR (ng/ml)	3.37±1.98
Weight (kg)	62.3±10.4	Delta CPR (ng/ml)	1.72±1.23
BMI (kg/m^2)	24.3±3.8	**CPI**	1.19±0.64
HbA1c (mmol/mol)	64±8	**SUIT**	36.5±22.1

Table 1 Demographic and clinical features of subjects participating in the study.

Table 2 Changes in HbA1c, and dosages of SUs and sitagliptin in final subjects.

Subjects (n)	Dropout rate (%) (n)	HbA1c level baseline (mmol/mol)	HbA1c level 52nd week (%)	Change in HbA1c (mmol/mol) (95% CI)	Original dosage of SUs (mg)	Initial dosage of SUs (mg)	Final dosage of SUs (mg)	Final dosage of sitagliptin (mg)
Final 33	32.6% 16	61±7	57±7**	−4* (−5 to −4)	–	–	–	74.2±25.4
Glimepiride 12	29.4% 5	63±9	55±9**	−8* (−11 to −5)	1.58±0.93	0.96±0.40*	1.42±0.57*	70.8±25.7
Gliclazide 21	34.4% 11	60±6	58±7*	−2* (−4 to −0)	38.2±14.0	24.8±8.7*	31.4±12.0*	77.3±25.5
SUs 23	30.3% 10	60±7	56±7*	−4* (−6 to −2)	–	–	–	67.4±24.3
SUs+Met 7	36.4% 4	64±9	58±8	−6* (−10 to −2)	–	–	–	87.5±23.1
SUs+TZD 3	62.5% 5	65±6	63±5	−2* (−5 to −0)	–	–	–	100±0.0

*$p<0.05$, **$p<0.01$

in glimepiride-treated subjects; and 77.3±25.5 mg/day in gliclazide-treated subjects with no significant difference between the 2 groups.

Of 33 subjects who completed the study, 22 subjects were treated with sitagliptin and SUs, 6 subjects were treated with sitagliptin and SUs and MET, and 3 subjects were treated with sitagliptin and SUs and TZD; changes in HbA1c in 52 weeks were −4 mmol/mol (95% CI; −6 to −2 mmol/mol) ($p<0.05$), −6 mmol/mol (95% CI; −10 to −2 mmol/mol) ($p<0.05$), and −3 mmol/mol (95% CI; −0.5 to −0 mmol/mol) ($p<0.05$), respectively (**Table 2**). However, there was no significant difference among the 3 groups.

Change in body weight, BMI, and frequency of hypoglycemia

Body weight in final subjects at baseline was 64.2±9.5 kg, and was decreased to 63.5±8.7 kg at 52nd week. Change in body weight in 52 weeks was −0.71 kg (95% CI; −1.42 to −0.004 kg) ($p<0.05$) (**Table 3**). BMI at baseline was 24.8±3.6 kg/m^2, and decreased to 24.5±3.4 kg/m^2 at 52nd week. Change in BMI in 52 weeks was −0.27 kg/m^2 (95% CI; −0.54 to 0.004 kg/m^2) ($p>0.05$). Frequency of hypoglycemia at baseline was 1.21±1.05 times/month, and was significantly decreased to 0.06±0.24 times/month at 52nd week ($p<0.001$). Change in frequency in hypoglycemia in 52 weeks was −1.21 times/months (95% CI; −1.5 to −0.80 times/month) ($p<0.05$) (**Table 3**). During the study, no severe hypoglycemia was noted. During the study, no other adverse events were observed after replacement of basal insulin with sitagliptin.

Differences in HbA1c findings in 8-week in the final and dropped subjects

Sixteen of 49 subjects recruited dropped out after 8 weeks due to increased HbA1c level. The remaining 33 subjects completed the study. HbA1c level at baseline (0-week) in final subjects was 61±8 mmol/mol, and was significantly decreased to

Table 3 Changes in weight, BMI, and frequency in hypoglycemia.

	Weight (kg)	BMI (kg/m^2)	Hypoglycemia (times/month)
0-week	64.2±9.5	24.8±3.6	1.21±1.05
52nd week	63.5±8.7	24.5±3.4	0.06±0.24***
Change (95% CI)	−0.71* (−1.42 to −0.004)	−0.27 (−0.54 to 0.004)	−1.21* (−1.5 to −0.80)

*$p<0.05$, ***$p<0.001$

	Diabetes Duration (Years)	FPG (mM)	HbA1c (mmol/mol)	0-min CPR (ng/ml)	6-min CPR (ng/ml)	Delta CPR (ng/ml)	CPI	SUIT
Cut-off value	16.5	8.2	6.1	1.25	2.80	1.60	1.34	37.5
AUC	0.468	0.507	0.252	0.530	0.570	0.541	0.509	0.482
Specificity	0.600	0.600	0.800	0.800	0.800	0.800	0.600	0.600
Sensitivity	0.545	0.568	0.159	0.432	0.455	0.364	0.545	0.432

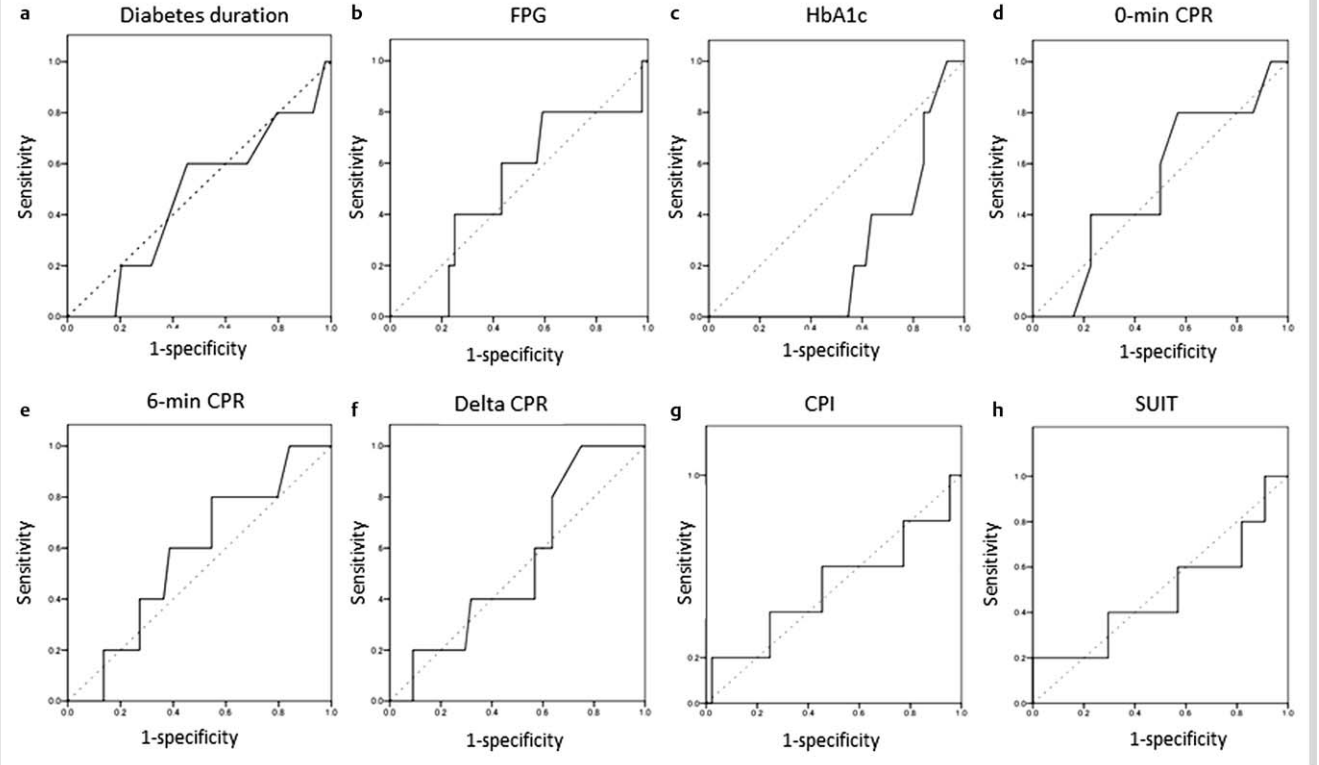

Fig. 1 Cutoff values and receiver-operator characteristic curves of **a** diabetes duration, **b** fasting plasma glucose, **c** HbA1c, **d** 0-min CPR, **e** 6-min CPR, **f** delta CPR, **g** CPI, and **h** SUIT at baseline. CPR: C-peptide reaction; CPI: C-peptide index; SUIT: the secretory unit of islet in transplantation.

Table 4 Changes in HbA1c and background of final and dropped subjects.

	Final subjects 33	Dropped subjects 16		Final subjects 33	Dropped subjects 16
0 Wk HbA1c (mmol/mol)	61 ± 7	69 ± 10	**Original dosage of SUs (mg)**	Glimepiride 1.58 ± 0.93 Gliclazide 36.2 ± 10.2	Glimepiride 2.70 ± 2.05 Gliclazide 38.2 ± 14.1
8 Wk HbA1c (mmol/mol)	58 ± 7***	73 ± 10**	**Basal insulin (Units)**	14.8 ± 9.3	15.2 ± 6.4
Delta HbA1c (mmol/mol) (95% CI)	−4* (−5 to −2)	7* (0.3 to 11)	**FPG (mM)**	7.4 ± 1.5	8.9 ± 2.9*
Age (years)	69.8 ± 10.7	70.5 ± 9.3	**HbA1c (mmol/mol)**	61 ± 7	69 ± 10**
Male (%)	66.7	56.3	**Glucagon test** 0-min CPR (ng/ml)	1.95 ± 1.25	1.37 ± 0.64*
Diabetes duration (years)	12.1 ± 6.6	18.7 ± 9.5*	6-min CPR (ng/ml)	3.81 ± 2.13	2.42 ± 1.21*
Weight (kg)	64.2 ± 9.5	58.4 ± 11.5	Delta CPR (ng/ml)	1.98 ± 1.35	1.16 ± 0.69*
BMI (kg/m^2)	24.8 ± 3.6	23.4 ± 4.0	**CPI**	1.35 ± 0.68	0.92 ± 0.51*
			SUIT	42.7 ± 23.0	23.1 ± 10.6**

*p < 0.05, **p < 0.01, ***p < 0.001

58 ± 7 mmol/mol at 8th week (p < 0.001) (**Table 4**). Change in HbA1c was −4 mmol/mol (95% CI; −5 to −2 mmol/mol) (p < 0.05). On the other hand, HbA1c level at baseline (0-week) in dropped subjects was significantly higher than that in final subjects (p < 0.05), and was significantly increased from 69 ± 9 to 73 ± 11 mmol/mol in 8 weeks (p < 0.01). Change in HbA1c was +7 mmol/mol (95% CI; 0.3 to 11 mmol/mol) (p < 0.05).

Differences in clinical factors in final and dropped subjects

There were no differences in age, sex, dosage of SUs, or dosage of basal insulin in final and dropped subjects (**Table 4**). Body weight and BMI also were not significantly different (p = 0.065 and p = 0.2432, respectively). On the other hand, diabetes duration in dropped subjects was longer than that in final subjects (12.1 ± 6.6 vs. 18.7 ± 9.5 years, p < 0.05). FPG and HbA1c also were higher in dropped subjects than in final subjects (FPG; 7.4 ± 1.5 vs. 8.9 ± 2.9 mM, p < 0.05) (HbA1c; 61 ± 7 vs. 69 ± 9 mmol/mol, p < 0.01).

Insulin secretion capacity was significantly higher in final subjects than that in dropped subjects (**Table 4**) (p < 0.05). In final subjects, CPR level at 0-min, 6-min, and delta CPR (6-min CPR to 0-min CPR) were 1.95 ± 1.25 ng/ml, 3.81 ± 2.13 ng/ml, and 1.98 ± 1.35 ng/ml, respectively. In dropped subjects, CPR level at 0-min, 6-min, and delta CPR were 1.37 ± 0.64 ng/ml, 2.42 ± 1.21 ng/ml, and 1.16 ± 0.69 ng/ml, respectively. CPI and SUIT index also were significantly higher in final subjects than those in dropped subjects. CPI at baseline in final subjects was 1.35 ± 0.68, while that in dropped subjects was 0.92 ± 0.51 (p < 0.05). SUIT at baseline was 42.7 ± 23.0 in final subjects, and 23.1 ± 10.6 in dropped subjects (p < 0.01). We examined cutoff values of diabetes duration, FPG, HbA1c, 0-min CPR, 6-min CPR, delta-CPR, CPI, and SUIT by analyzing ROC curves; they were 16.5 years, 8.2 mM, 62 mmol/mol, 1.25 ng/ml, 2.80 ng/ml, 1.60 ng/ml, 1.34, and 37.5, respectively (**Fig. 1**).This indicates that with longer diabetes duration, insulin secretion capacity becomes lower and the consequent poorer glycemic control makes switching BOT-treated patients from basal insulin to sitagliptin unsafe.

Correlation between efficacy of sitagliptin on glycemic control and insulin secretion capacity, CPI, and SUIT

We examined whether or not insulin secretion capacity, CPI, or SUIT at baseline predicted the efficacy of replacing basal insulin with sitagliptin on glycemic control (**Fig. 2**). There was a correlation between change in HbA1c at 8th week and 0-min CPR (r = −0.281), 6-min CPR (r = −0.326), and delta CPR (r = −0.290), assessed by glucagon loading test at baseline (**Fig. 2a, b, c**) (p < 0.05). In addition, CPI (r = −0.360) or SUIT (r = −0.306) at baseline was correlated with change in HbA1c at 8th week (**Fig. 2d, e**) (p < 0.05). The value of 0-min CPR, 6-min CPR, delta CPR, CPI, and SUIT at which the HbA1c level was not increased by replacement of basal insulin by sitagliptin were calculated to be 1.64 ng/ml, 3.36 ng/ml, 1.71 ng/ml, 1.19, and 36.4, respectively, by Pearson's product-moment correlation test (**Table 5**). The value of 0-min CPR, 6-min CPR, delta CPR, CPI, and SUIT at which the HbA1c level was decreased by 0.5% in 8 weeks were calculated to be 1.86 ng/ml, 3.83 ng/ml, 1.98 ng/ml, 1.36, and 41.3, respectively. Other clinical characteristics of the patients such as disease duration and body weight were not significantly correlated with efficacy of replacing basal insulin with sitagliptin on glycemic control (data not shown).

Discussion

We show here that basal insulin can be switched to sitagliptin with good effects in type 2 diabetes patients treated with BOT. With this treatment, the HbA1c level decreased from 61 ± 7 to 57 ± 7 mmol/mol in 52-week (p < 0.01). The change in HbA1c in 52 weeks was −4 mmol/mol (95% CI; −5 to −4 mmol/mol) (p < 0.05). The efficacy of switching to sitagliptin from basal insulin was correlated with insulin secretion capacity, CPI, and SUIT; CPI being most correlated marker in the present study. The average CPI in final subjects was 1.35 ± 0.68 ng/ml, while that of dropped subjects was 0.92 ± 0.51 ng/ml. Pearson's product-moment correlation test revealed that HbA1c was improved by switching from basal insulin to sitagliptin if CPI was equal to or higher than 1.19 (**Fig. 2d** and **Table 5**). Similarly, basal insulin could be switched to sitagliptin if SUIT was equal to or larger than 36.4 (**Fig. 2e** and **Table 5**). In the dropped subjects, diabetes duration was longer, FPG and HbA1c were worse, 0-min CPR, 6-min CPR, delta-CPR, CPI, and SUIT were lower compared to those in final subjects (**Table 4**). Cutoff values were 16.5 years, 8.2 mM, 62 mmol/mol, 1.25 ng/ml, 2.80 ng/ml, 1.60 ng/ml, 1.34, and 37.5, respectively (**Fig. 1**). This suggests that the efficacy of switching from basal insulin to sitagliptin, when

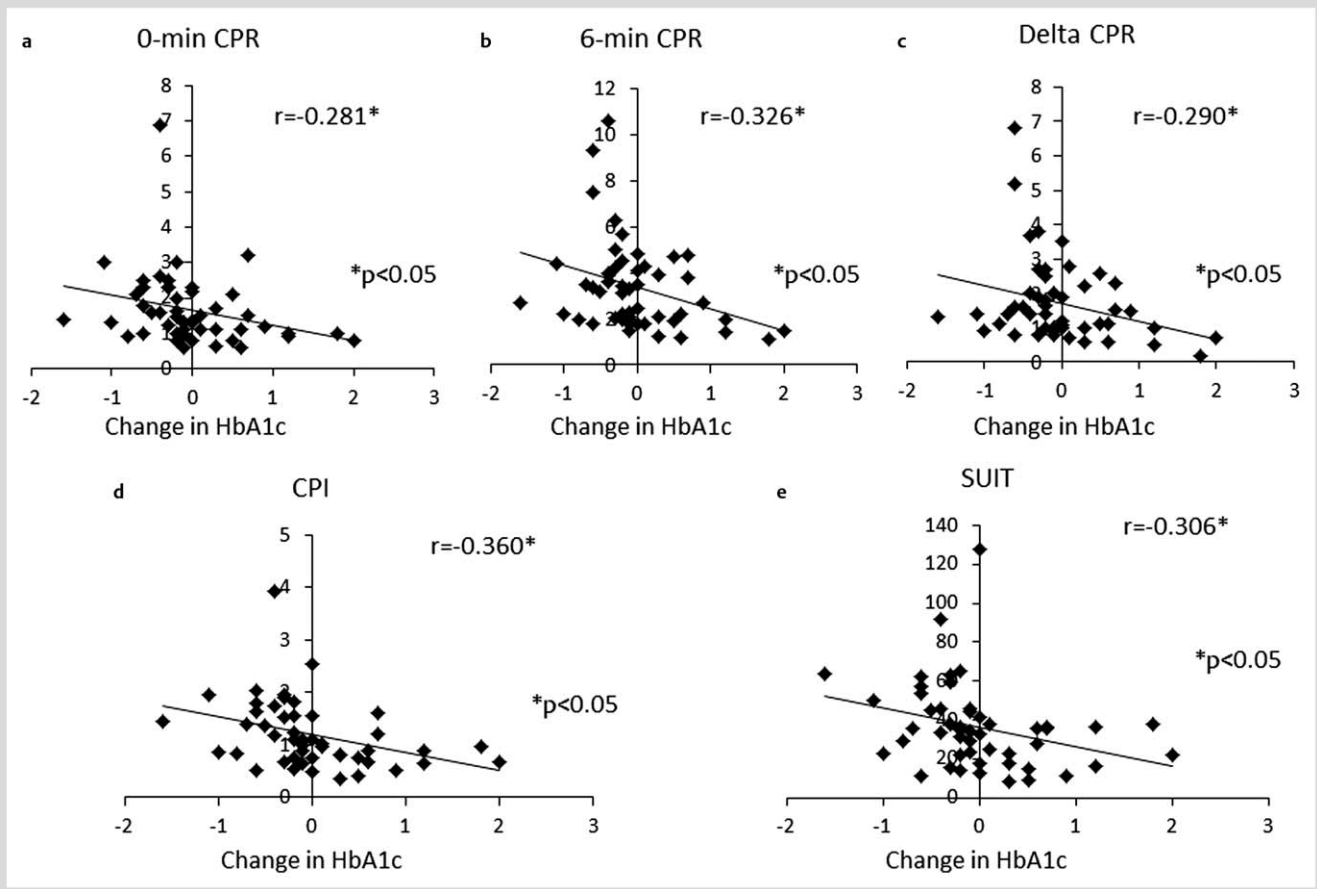

Fig. 2 Relationship between changes in HbA1c in 8 weeks and results of glucagon loading test, CPI, and SUIT at baseline. Changes in HbA1c in 8 weeks and 0-min CPR **a**, 6-min CPR **b**, delta CPR **c**, CPI **d**, and SUIT index **e** at baseline. CPR: C-peptide reaction; CPI: C-peptide index; SUIT: the secretory unit of islet in transplantation. *p<0.05.

Table 5 Correlation between change in HbA1c and insulin secretion capacity.

Change in HbA1c (mmol)	0-Minute CPR (ng/ml)	6-Minute CPR (ng/ml)	Delta CPR (ng/ml)	CPI	SUIT
0.0	1.64	3.36	1.71	1.19	36.4
−5	1.86	3.83	1.98	1.36	41.3

combined with SUs, is dependent on basal glycemic control and the insulin secretion capacity. Baseline HbA1c of dropped subjects was higher than that of the final subjects. A higher dosage of basal insulin was required to reach target HbA1c level in dropped subjects compared to that in final subjects because of lower insulin secretion capacity. Thus, if baseline HbA1c level were reduced by increasing the dosage of basal insulin, it would be difficult to replace basal insulin with sitagliptin.

Replacement of basal insulin by sitagliptin resulted in a reduction in body weight and hypoglycemia. Body weight was reduced by 0.71 kg (95% CI; −1.41 to −0.004 kg) ($p<0.05$). Frequency of hypoglycemia was decreased from 1.21±1.05 to 0.06±0.24 times/month ($p<0.001$). Since sitagliptin is known to be body weight neutral [21,22], discontinuation of basal insulin might contribute to body weight reduction. The combination of basal insulin and SUs often induces mild hypoglycemia by which patients feel a sense of hunger and eat between-meal snacks. This sometimes induces weight gain and poor glycemic control in BOT-treated patients. On the other hand, combination therapy with sitagliptin and low dosage SUs (less than or equal to 2 mg/day glimepiride or 40 mg/day gliclazide) was body weight neutral or led to a decrease in BMI [14]. In the current study, hypoglycemia seldom occurred, and BMI was significantly decreased by 0.38 kg/m^2 (95% CI −0.72 to −0.04 kg/m^2) [14]. Switching from basal insulin to sitagliptin also reduced the frequency of hypoglycemia. Although energy intake was not evaluated between baseline and 52-week in the present study, patients who had previously experienced frequent hypoglycemia reported to their physicians that the number of between-meal snacks in 52 weeks was fewer than at baseline. Thus, excess energy intake may be reduced after switching from basal insulin to sitagliptin to account for some of the body weight reduction and improvement in HbA1c. Another reason for improvement in the HbA1c level may be the reduced postprandial glucose level by the combination therapy with sitagliptin and SUs compared to that by BOT.

The combination therapy of glimepiride and sitagliptin was more effective for HbA1c reduction than that of gliclazide and sitagliptin. Recently, it was reported that cAMP sensor Epac2 is a direct target of several sulfonylureas [23]. Tolbutamide, glibenclimide, and glimepiride bound Epac2 and enhanced glucose-stimulated insulin secretion. However, gliclazide did not bind Epac2. Because Epac2 also mediates the potentiation of insulin secretion by cAMP increased by endogenous incretin, the combination therapy of glimepiride and sitagliptin enhances more insulin secretion through activation of Epac2. This might be a potential mechanism why the combination therapy of glimepir-

ide and sitagliptin was more effective for glycemic control than that of gliclazide and sitagliptin.

Generally, insulin secretion capacity of Japanese is as half as that of Caucasian [16–18]. Therefore, more than 60% of Japanese type 2 diabetes patients are treated with SUs [24]. DPP-4 inhibitor now is one of the most popular OADs, and more than 2 million patients were treated with DPP-4 inhibitors in Japan. Based on pathophysiology of Japanese patients and the mechanism of incretin effect, the combination therapy with SUs and DPP-4 inhibitors seems to be most effective for glycemic control compared to that with other OADs and DPP-4 inhibitors. On the other hand, the main pathophysiology of Caucasian type 2 diabetes is insulin resistance compared to that of Japanese type 2 diabetes [25,26]. Dosage of basal insulin in BOT in Caucasian patients is greater than that in Japanese patients. For example, in 4-T study, the mean dosage of basal insulin was 86 U (1.03 U/kg) [8], while 8.5 U (0.15 U/kg) in Japanese type 2 diabetes [10], and 15 U (0.24 U/kg) in our study. Therefore, it is not sure if basal insulin could be replaced with DPP-4 inhibitors even in subjects treated with high dosage of basal insulin. However, there is still a possibility that in Caucasian subjects whose BMI is less than 25 kg/m^2 and CPI is over 1.3, basal insulin could be replaced with DPP-4 inhibitors. Or, if the combination therapy with high dosage of MET and DPP-4 inhibitors is more effective for glycemic control compared to other combinations in Caucasian type 2 diabetes, basal insulin with MET could be replaced with DPP-4 inhibitors and metformin.

During the course of the disease, type 2 diabetes patients are treated with several OHAs [27,28]. However, if the HbA1c level does not reach less than 53 mmol/mol, insulin treatment is considered the next step [1,2]. BOT is often selected for outpatients because once daily injection is acceptable and the glycemic control is superior, with fewer hypoglycemic episodes and less weight gain compared to biphasic insulin [8]. In Japan, the commonly used SUs are combined with basal insulin in BOT [10]. One of the biggest problems of combination therapy with basal insulin and SUs is the high level of postprandial blood glucose while fasting blood glucose is within normal range. An increase in dosage of SUs or basal insulin does not resolve this problem, and sometimes leads to increased hypoglycemia. However, our results show that better glycemic control and lower frequency of hypoglycemia is obtained when switching from basal insulin to sitagliptin in subjects with sufficiently preserved insulin secretion capacity.

The advantages of discontinuation of basal insulin are 1) patients become free from daily injections; 2) they do not need to regularly perform self-monitoring of blood glucose (SMBG); and 3) oral therapy costs less than insulin therapy.

In summary, basal insulin in BOT can be switched to sitagliptin if CPI and/or SUIT are equal to or higher than 1.19 or 36.4, respectively. On the other hand, sitagliptin can be added to insulin therapy if insulin secretion capacity is not sufficient for switching to sitagliptin. However, the effectiveness of combination therapy with basal insulin and sitagliptin on glycemic control in type 2 patients with CPI and/or SUIT less than 1.19 or 36.4, respectively, is unknown. Further studies are required to determine the optimum insulin secretion capacities for switching BOT therapy to sitagliptin combined with SUs or combination therapy with sitagliptin and basal insulin or GLP-1 receptor analogues.

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Conflict of Interest

None of the authors have any conflicts of interest to declare.

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