Secretory units of islets in transplantation index is a useful clinical marker to evaluate the efficacy of sitagliptin in treatment of type 2 diabetes mellitus

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ABSTRACT
We carried out a retrospective analysis of 40 Japanese patients with type 2 diabetes mellitus who received sitagliptin. Glycated hemoglobin (HbA1c) and fasting plasma glucose were significantly decreased from 7.53 ± 0.65% and 155.2 ± 29.4 mg/dL at baseline to 6.80 ± 0.60% (P < 0.01) and 131.2 ± 22.3 mg/dL (P < 0.01) at week 20, respectively. β-Cell function was evaluated by the secretory units of islets in transplantation (SUIT) index, which was significantly increased from 28.5 ± 14.0 at baseline to 38.6 ± 17.0 at week 20 (P < 0.01). Multivariate analysis was carried out between ΔHbA1c, and several parameters (age, the duration of diabetes, body mass index, triglyceride [TG], C-peptide [CPR], ΔCPR, HbA1c [baseline] and ΔSUIT), which showed HbA1c (baseline; β = 0.580, P < 0.001) and ΔSUIT (β = 0.308, P < 0.05) as significant independent determinants of ΔHbA1c. These two variables explained 53% of the variance in HbA1c response. These results suggest that SUIT index can be a clinical marker for the efficacy of sitagliptin in treatment of diabetes mellitus. (J Diabetes Investig, doi: 10.1111/j.2040-1124.2011.00109.x, 2011)

KEY WORDS: DPP-4 inhibitor, Secretory units of islets in transplantation, Diabetes

INTRODUCTION
Sitagliptin belongs to a novel class of oral antihyperglycemic agents (OHA)³. It exerts its effects through the inhibition of DPP4 activity, which increases levels of the two plasma incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)²–⁵. These two incretin hormones play an important role in maintaining glucose homeostasis by stimulating insulin secretion from pancreatic β-cells, and sitagliptin can produce a twofold to threefold increase in their elevation⁶–⁸. GLP-1 also inhibits glucagon secretion, reducing food intake, and delaying gastric emptying. In addition, because it has been reported that active GLP-1 levels in both healthy subjects and patients with type 2 diabetes mellitus are remarkably low⁹, and the several mechanisms by which sitagliptin lowers blood glucose are unique among the available OHA, multiple aspects of the clinical profiles of the patients must be analyzed to understand the action of sitagliptin.

Secretory units of islets in transplantation (SUIT) is an index calculated from the fasting plasma glucose (FPG, mg/dL) and fasting C-peptide (F-CPR, ng/mL) levels using the formula: 1485 × F-CPR/(FPG – 61.8)¹⁰¹¹. SUIT has been shown to measure β-cell function in type 2 diabetes mellitus quite well, and is a useful tool in the management of diabetes patients¹². We carried out a retrospective analysis of clinical data extracted from the records of 40 adult Japanese patients with type 2 diabetes mellitus who received sitagliptin 50 mg/day from December 2009 to November 2010. We found in the present study that SUIT can be a clinical marker that correlates with the efficacy of sitagliptin.

MATERIALS AND METHODS
Patients
We carried out a retrospective analysis of 40 Japanese patients (29 male and 11 female) with type 2 diabetes mellitus who were given sitagliptin 50 mg for treatment. The study protocol was approved by local institutional review boards. We selected type 2 diabetes mellitus patients who were at least 18 years-of-age, had been treated for at least 4 months before the start of sitagliptin and had completed >20 weeks of treatment. We excluded patients with a history of type 1 diabetes, liver disease, major gastrointestinal surgery or renal dysfunction (Cr > 1.5 mg/dL). Their age was 65.1 ± 12.6 years, body mass index (BMI) 25.2 ± 3.1 kg/m² and the duration of diabetes was 10.6 ± 7.1 years (Table 1a). Among the 40 patients, nine patients were drug-naïve and the other 31 patients had received one to three other oral antihyperglycemic agents (sulfonylurea 27 patients, metformin 14 patients, thiazolidine 8 patients, α-glucosidase inhibitor 3 patients). During the study period, other oral antihyperglycemic agents were not changed.

Statistical Analysis
All data analyses were carried out using PASW statistics 18 for Windows (SPSS Inc., Chicago, IL, USA). A P-value of <0.05 was
Table 1 | (a) Summary of patients’ characteristics. (b) Summary of parameters at baseline and week 20

(a)

| Sex (n) | Male | 29 | Female | 11 |
|---------|------|----|--------|----|
| Age (years) | 65.1 ± 12.6 | | | |
| BMI (kg/m²) | 25.2 ± 3.1 | | | |
| Duration of diabetes (years) | 10.6 ± 7.1 | | | |
| Triglyceride (mg/dL) | 105.1 ± 38.8 | | | |

(b)

| Parameter | Baseline | Week 20 | Difference | Significance |
|-----------|----------|---------|------------|-------------|
| HbA₁c (%) | 7.53 ± 0.65 | 6.80 ± 0.60 | 0.73 ± 0.58 | P < 0.01 |
| FPG (mg/dL) | 155.2 ± 29.4 | 131.2 ± 22.3 | 24.0 ± 25.9 | P < 0.01 |
| CPR (ng/mL) | 1.76 ± 0.96 | 1.77 ± 1.05 | −0.3 ± 2.2 | NS |
| SUIT | 285 ± 140 | 386 ± 17.0 | 101 ± 10.1 | P < 0.01 |

Table 2 | (a) Univariate correlation of degree of glycated hemoglobin decline to the parameters. (b) Independent determinants of ΔHbA₁c. (c) Univariate correlation of degree of secretory units of islets in transplantation increment to the parameters

(a)

| ΔHbA₁c (0–20 weeks, %) | r | P |
|------------------------|---|---|
| Sex | −0.151 | NS |
| Age (years) | −0.061 | NS |
| Duration of diabetes (years) | 0.131 | NS |
| BMI (kg/m²) | 0.117 | NS |
| HbA₁c (baseline) | 0.572 | <0.01 |
| SUIT (baseline) | −0.193 | NS |
| CPR (baseline) | 0.005 | NS |
| ΔCPR (0–20 weeks; ng/mL) | 0.033 | NS |
| ΔTG (0–20 weeks; mg/dL) | −0.208 | NS |
| ΔSUIT (0–20 weeks) | 0.454 | <0.01 |

(b)

| β | P | R | R² |
|---|---|---|---|
| HbA₁c (baseline) | 0.580 | <0.001 | 0.631 | 0.531 |
| ΔSUIT (0–20 weeks) | 0.308 | <0.05 | |

(c)

| ΔSUIT (0–20 weeks) | r | P |
|---------------------|---|---|
| Sex | 0.85 | NS |
| Age (years) | 0.007 | NS |
| Duration of diabetes (years) | −0.062 | NS |
| SUIT (baseline) | −0.085 | NS |
| CPR (baseline) | 0.184 | NS |
| ΔCPR (0–20 weeks; ng/mL) | 0.133 | NS |
| ΔTG (0–20 weeks; mg/dL) | 0.064 | NS |

Considered statistically significant. Data were expressed as mean ± SD values. For HbA₁c, FPG and SUIT values, paired t-test was applied. A multiple regression analysis was carried out to obtain the correlation coefficient (r) and regression coefficient (β) of independent variables that predict the dependent variables. HbA₁c was calculated from fasting plasma glucose (FPG, mg/dL) and C-peptide (F-CPR, ng/mL) levels using the formula: 1485 × F-CPR/(FPG – 61.8). The values of HbA₁c are considered statistically significant. Data were expressed as mean ± SD values. For HbA₁c, FPG and SUIT values, paired t-test was applied. A multiple regression analysis was carried out to obtain the correlation coefficient (r) and regression coefficient (β) of independent variables that predict the dependent variables. HbA₁c was calculated from fasting plasma glucose (FPG, mg/dL) and C-peptide (F-CPR, ng/mL) levels using the formula: 1485 × F-CPR/(FPG – 61.8). The values of HbA₁c are expressed using National Glycohemoglobin Standardization Program values. ΔHbA₁c, ΔSUIT and ΔCPR represent the difference between the baseline value and the week 20 value of HbA₁c, SUIT and CPR, respectively.

RESULTS

The glycemic characteristics of baseline and week 20 are listed in Table 1b. Mean HbA₁c was 7.53 ± 0.65% and FPG was 155.2 ± 29.4 mg/dL. At week 20, sitagliptin produced significant reductions from baseline in HbA₁c to 6.80 ± 0.60% (P < 0.01) and in FPG to 131.2 ± 22.3 mg/dL (P < 0.01). The mean change from baseline HbA₁c was 0.73 ± 0.58%, and the degree of HbA₁c decline ranged from −0.7 to 2.6%. The changes from baseline FPG were 24.0 ± 25.9 mg/dL. The baseline SUIT index was 28.5 ± 14.0. Sitagliptin produced a significant increase in SUIT index up to 38.6 ± 17.0 at week 20 (P < 0.01). The increment of SUIT was 10.4 ± 10.1 on average and in each case showed a distribution ranging from −11.3 to 38.4. To elucidate the factors correlating with the efficacy of sitagliptin, we carried out a univariate analysis between the degree of HbA₁c decline (ΔHbA₁c) and several parameters: sex, age, the duration of diabetes, BMI, triglyceride (baseline), C-peptide (baseline), degree of C-peptide increment (ΔCPR), BMI (baseline), SUIT (baseline) and degree of SUIT increment (ΔSUIT) (Table 2a). A significant correlation was found between ΔHbA₁c and HbA₁c (baseline; r = 0.572, P < 0.01) and between ΔHbA₁c and ΔSUIT (r = 0.454, P < 0.01) (Table 2a, Figure 1). ΔHbA₁c had no significant correlation with age, duration of diabetes, triglyceride, CPR (baseline), ΔCPR, SUIT (baseline) or BMI (Table 2a). Subsequent multivariate analysis showed HbA₁c (baseline; β = 0.580, P < 0.001) and ΔSUIT (β = 0.308, P < 0.05) as significant independent determinants of ΔHbA₁c. These two variables explained 53% of the variance in HbA₁c response (Table 2b). We also carried out univariate correlation analyses of different variables with ΔSUIT (Table 2c). ΔSUIT had no significant correlation with...
HbA1c more in case the HbA1c at the baseline is
In the present study, sitagliptin produced a significant reduction
DISCUSSION
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line),
sex, age, duration of diabetes, BMI, SUIT (baseline), CPR (baseline), ΔCPR or TG (baseline; Table 2c).

In conclusion, the present results suggest that the SUIT index
might be a useful clinical marker of the efficacy of DPP4 inhibitors in the treatment of type 2 diabetes mellitus.

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Figure 1 | Correlation of degree of secretory units of islets in transplantation increment (ΔSUIT) and degree of glycated hemoglobin decline (ΔHbA1c).
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