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

Akira Kubota[1]*, Ikuro Matsuba[2], Tatsuhiko Saito[3], Koichiro Nabe[1], Yutaka Seino[4]

ABSTRACT

We carried out a retrospective analysis of 40 Japanese patients with type 2 diabetes mellitus who received sitagliptin. Glycated hemoglobin (HbA_{1c}) 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 ΔHbA_{1c} and several parameters (age, the duration of diabetes, body mass index, triglyceride [TG], C-peptide [CPR], ΔCPR, HbA_{1c} [baseline] and ΔSUIT), which showed HbA_{1c} (baseline; $\beta = 0.580$, $P < 0.001$) and ΔSUIT ($\beta = 0.308$, $P < 0.05$) as significant independent determinants of ΔHbA_{1c}. These two variables explained 53% of the variance in HbA_{1c} response. These results suggest that SUIT index can be a clinical marker for the efficacy of sitagliptin in treatment of diabetes mellitus. (J Diabetes Invest, 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)[1]. 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 elevation[6–8]. 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 low[9], 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: $1485 \times \text{F-CPR}/(\text{FPG} - 61.8)$[10,11]. 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 patients[10]. 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.

[1]Kubota Clinic of Internal Medicine and [2]Matsuba Clinic, Kanagawa, [3]Kobari General Hospital, Chiba, and [4]Department of Medicine, Kansai Electric Power Hospital, Osaka, Japan

*Corresponding author. Akira Kubota Tel.: +81-44-932-0161 Fax: +81-44-932-0253
E-mail address: kubota@sj8.so-net.ne.jp

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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 on stable treatment 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/m^2 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/m^2)	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 between baseline and week 20	Significance
HbA_{1c} (%)	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	28.5 ± 14.0	38.6 ± 17.0	10.4 ± 10.1	$P < 0.01$

Data are mean ± SD values. $P < 0.01$ vs baseline. BMI, body mass index; CPR, C-peptide; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; SUIT, secretory units of islets in transplantation.

considered statistically significant. Data were expressed as mean ± SD values. For HbA_{1c}, 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. SUIT 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 HbA_{1c} are expressed using National Glycohemoglobin Standardization Program values. ΔHbA_{1c}, ΔSUIT and ΔCPR represent the difference between the baseline value and the week 20 value of HbA_{1c}, SUIT and CPR, respectively.

RESULTS

The glycemic characteristics of baseline and week 20 are listed in Table 1b. Mean HbA_{1c} was 7.53 ± 0.65% and FPG was 155.2 ± 29.4 mg/dL. At week 20, sitagliptin produced significant reductions from baseline in HbA_{1c} 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 HbA_{1c} was 0.73 ± 0.58%, and the degree of HbA_{1c} 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 HbA_{1c} decline (ΔHbA_{1c}) and several parameters: sex, age, the duration of diabetes, BMI, triglyceride (baseline), C-peptide (baseline), degree of C-peptide increment (ΔCPR), HbA_{1c} (baseline), SUIT (baseline) and degree of SUIT increment (ΔSUIT; Table 2a). A significant correlation was found between ΔHbA_{1c} and HbA_{1c} (baseline; $r = 0.572$, $P < 0.01$) and between ΔHbA_{1c} and ΔSUIT ($r = 0.454$, $P < 0.01$) (Table 2a, Figure 1). ΔHbA_{1c} had no significant correlation with age, duration of diabetes, triglyceride, CPR (baseline), ΔCPR, SUIT (baseline) or BMI (Table 2a). Subsequent multivariate analysis showed HbA_{1c} (baseline; $\beta = 0.580$, $P < 0.001$) and ΔSUIT ($\beta = 0.308$, $P < 0.05$) as significant independent determinants of ΔHbA_{1c}. These two variables explained 53% of the variance in HbA_{1c} response (Table 2b). We also carried out univariate correlation analyses of different variables with ΔSUIT (Table 2c). ΔSUIT had no significant correlation with

Table 2 | (a) Univariate correlation of degree of glycated hemoglobin decline to the parameters. (b) Independent determinants of ΔHbA_{1c}. (c) Univariate correlation of degree of secretory units of islets in transplantation increment to the parameters

(a)

	ΔHbA_{1c} (0–20 weeks, %)	
	r	*P*
Sex	−0.151	NS
Age (years)	−0.061	NS
Duration of diabetes (years)	0.131	NS
BMI (kg/m^2)	0.117	NS
HbA_{1c} (baseline)	0.572	<0.01
SUIT (baseline)	−0.193	NS
CPR (baseline)	0.005	NS
ΔCPR (0–20 weeks; ng/mL)	0.033	NS
TG (0 weeks; mg/dL)	−0.208	NS
ΔSUIT (0–20 weeks)	0.454	<0.01

(b)

	β	*P*	*R*	R^2
HbA_{1c} (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
TG (0 weeks, mg/dL)	0.064	NS

BMI, body mass index; CPR, C-peptide; HbA_{1c}, glycated hemoglobin; SUIT, secretory units of islets in transplantation; TG, triglyceride.

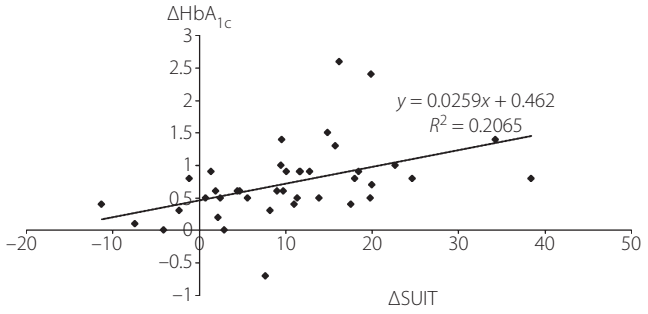

Figure 1 | Correlation of degree of secretory units of islets in transplantation increment (ΔSUIT) and degree of glycated hemoglobin decline (ΔHbA_{1c}).

sex, age, duration of diabetes, BMI, SUIT (baseline), CPR (baseline), ΔCPR or TG (baseline; Table 2c).

DISCUSSION

In the present study, sitagliptin produced a significant reduction in HbA_{1c} of an average of 0.73 ± 0.58% at week 20, which is comparable to previously reported data in Japanese type 2 diabetes mellitus[12]. The degree of response to sitagliptin in each case showed a distribution from −0.7 to 2.6% at week 20. Sitagliptin became available globally 3 years ago; it and other DPP4 inhibitors lower blood glucose by novel mechanisms. At present, the mechanism underlying the distinct action of sitagliptin is not well understood. In the present study, we found that sitagliptin caused a significant increase in SUIT, an index of β-cell function, with an average increment of 10.4 ± 10.1 at week 20. Improvement of β-cell function by sitagliptin treatment in type 2 diabetes mellitus estimated by homeostasis model assessment-β (HOMA-β) has been reported by many investigators[12–19]. HOMA-β by 50 mg sitagliptin was found to be improved in Japanese patients by 15.5%[10], which is comparable with the increment of SUIT found in the present study. Interestingly, the response of SUIT to sitagliptin showed a distribution from −11.3 to 38.4. Multivariate analysis in the present study showed HbA_{1c} (baseline; $\beta = 0.580$, $P < 0.001$) and ΔSUIT ($\beta = 0.308$, $P < 0.05$) as significant independent determinants of ΔHbA_{1c}. These two variables explained 53% of the variance in HbA_{1c} response. It was reported in several studies that sitagliptin decreases HbA_{1c} more in case the HbA_{1c} at the baseline is higher[20–22]. Therefore, it is suggested that the group of patients recruited in the present study was appropriate to evaluate the efficacy of sitagliptin, although the number of the patients was small. The degree of decline of HbA_{1c} had no significant correlation with sex, age, duration of diabetes, BMI, SUIT (baseline), CPR (baseline), the degree of increment of C-peptide, or triglyceride. These results suggest that the response of SUIT to sitagliptin can be a clinical marker that correlates with the efficacy of sitagliptin. As no significant correlation was found between ΔSUIT and several other variables, the difference in the response of SUIT to sitagliptin remains to be elucidated. However, there is one report in which treatment of type 2 diabetes mellitus patients with sitagliptin improved β-cell function estimated by C-peptide minimal model of meal test and a correlation was found between β-cell function parameters and the reductions in HbA_{1c}[22]. Considering that SUIT is an index that correlates well with the C-peptide levels stimulated by glucagon in type 2 diabetes mellitus[10], one possible explanation is that the increment of SUIT represents an improvement in the response of insulin secretion. At present, because the number of patients in the present study was small, further clinical analysis recruiting a large number of patients is required to clarify the mechanism of the response of SUIT.

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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