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C-peptide immunoreactivity index is associated with improvement of HbA1c: 2-Year follow-up of sitagliptin use in patients with type 2 diabetes

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ABSTRACT

Aims: This retrospective study aimed to determine the hypoglycaemic effect of 2 years of sitagliptin administration in terms of changes in HbA1c and C-peptide immunoreactivity (CPR) index (plasma CPR [ng/mL]/glucose [mg/dL] × 100).

Methods: The inclusion criteria for DPP-4 inhibitor-naive outpatients with type 2 diabetes ($n = 285$) were: continuation of sitagliptin for ≥700 days from initial administration and measurement of HbA1c, serum CPR, and plasma glucose levels at 0, 3, 6, 12, 18, and 24 months after sitagliptin initiation. Logistic regression analyses determined the factors contributing to the response to sitagliptin, based on responder (ΔHbA1c ≤−0.4% [≤−4 mmol/mol]) and non-responder (ΔHbA1c >−0.4% [>−4 mmol/mol]) groups.

Results: The HbA1c level decreased and CPR index increased from baseline to 3, 6, 12, 18, and 24 months after the start of sitagliptin administration (HbA1c: 7.4 ± 0.8% [57 ± 9 mmol/mol], 7.3 ± 0.9% [57 ± 9 mmol/mol], 7.4 ± 0.9% [58 ± 10 mmol/mol], 7.1 ± 0.8% [55 ± 9 mmol/mol], and 7.3 ± 0.9% [57 ± 10 mmol/mol], respectively, all $P < 0.001$ vs. baseline [8.0 ± 1.0%, 64 ± 11 mmol/mol] and CPR index: 1.69 ± 0.96, 1.71 ± 1.10, 1.62 ± 0.96, 1.64 ± 0.92, and 1.66 ± 0.96, respectively, all $P < 0.05$ vs. baseline [1.47 ± 0.81]). Higher baseline HbA1c level, shorter diabetes duration, and greater CPR index increase after sitagliptin administration were associated with the response to sitagliptin.

Conclusions: Our results suggest that sitagliptin improves glycaemic control via an improved intrinsic insulin response.

1. Introduction

Type 2 diabetes mellitus is a progressive disease characterized by an annual decline in insulin secretion [1]. Insulin secretion capacity is genetically lower in East Asian patients than in Caucasian patients [2,3]. This difference in insulin secretion capacity may explain the differences in diabetes treatment guidelines between Japan and Western countries.

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Dipeptidyl peptidase-4 (DPP-4) inhibitors have been widely used in clinical practice in Japan for the past 4 years, because of their efficacy, low risk of hypoglycaemia, and neutral effect on body weight [4]. DPP-4 inhibitors are considered effective for the treatment of type 2 diabetes in Asian patients, including Japanese patients, who often have insufficient insulin secretion [2,3], in contrast to Caucasian patients who usually have insulin resistance. DDP-4 inhibitors prevent degradation of the incretin hormones glucagon-like peptide-1 and gastric inhibitory polypeptide [5]. The mechanism of the hypoglycaemic effect of DPP-4 involves enhancement of the actions of incretins, which promotes insulin secretion and suppresses glucagon secretion, depending on the blood glucose level [6].

Serum C-peptide, which is split from and co-secreted with insulin, is known as an insulin secretion marker because C-peptide, unlike insulin, is not metabolized by the liver. In clinical practice, Pratley et al. reported that 12 weeks of DPP-4 (vildagliptin) treatment significantly decreased HbA1c ($-0.6 \pm 0.2\%$, $P = 0.0012$) and increased mean prandial C-peptide (0.10 ± 0.03 nmol/L, $P = 0.0031$) levels, compared to placebo [7]. Similarly, Charbonnel et al. reported that 24 weeks of DPP-4 (sitagliptin) treatment in addition to metformin therapy led to a significant reduction in HbA1c ($P < 0.001$) and increase in fasting C-peptide ($P < 0.010$) from baseline, compared with metformin alone [8]. Furthermore, in a report on liraglutide, a glucagon-like peptide-1 receptor agonist, serum C-peptide immunoreactivity (CPR) level 6 min after glucagon administration was strongly and significantly correlated with insulin secretion ($r = 0.92$, $P < 0.001$), and a higher CPR level 6 min after glucagon administration predicted a greater hypoglycaemic effect [9]. However, previous studies have demonstrated a short-term effect only, and, to our knowledge, there has been no report on the long-term efficacy of DPP-4 inhibitors for decreased insulin secretion and elevated HbA1c. Therefore, we hypothesized that the degree of HbA1c improvement is associated with the degree of increase in the CPR index. We investigated the changes in HbA1c and CPR index following 2 years of administration of sitagliptin, which is a DPP-4 inhibitor, by classifying the subjects as responders and non-responders based on the decrease in HbA1c.

2. Materials and methods

2.1. Patients

The subjects included 285 outpatients with type 2 diabetes who were naïve to DPP-4 inhibitors and in whom sitagliptin was initiated between December 1, 2009 and December 31, 2011. Subjects were included when they satisfied the following criteria: continuation of sitagliptin for ≥700 days from the start of administration, regardless of changes in concomitant agents, and measurement of HbA1c, serum CPR, and plasma glucose levels at 0, 3, 6, 12, 18, and 24 months after the start of sitagliptin administration. Subjects were excluded from the study if they had poor drug compliance, based on information in their medical records.

The subjects were classified into a responder group, which was defined as an HbA1c improvement ≥0.4% [≥4 mmol/mol] during 24 months, and a non-responder group, which was defined as an HbA1c improvement <0.4% [<4 mmol/mol] during 24 months. The study was approved by the ethical committee of Keio University School of Medicine and performed in accordance with the Declaration of Helsinki.

2.2. Data collection

Basic demographic data were collected for all patients from their medical records, including sex, age, height, weight, duration of diabetes, baseline HbA1c, estimated glomerular filtration rate (eGFR), lipid levels, and complications such as hypertension (blood pressure ≥140/90 mmHg and/or on antihypertensive drugs), dyslipidaemia (total cholesterol ≥220 mg/dL and/or HDL cholesterol <40 mg/dL and/or triglycerides ≥150 mg/dL and/or taking a hypolipidaemic agent), or retinopathy (modified Davis classification: no diabetic retinopathy [NDR], simple diabetic retinopathy [SDR], preproliferative diabetic retinopathy [PPDR], or proliferative diabetic retinopathy [PDR]) [10]. Fasting was not required for sample collection. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m^2).

All measurements were performed by the Department of Laboratory Medicine of Keio University School of Medicine using routine automated laboratory methods, as previously described [11]. HbA1c level was expressed in accordance with the National Glycohaemoglobin Standardization Program (NGSP) guidelines (%) as recommended by the Japanese Diabetes Society [12], in addition to International Federation of Clinical Chemistry (IFCC) (mmol/mol) calculated by the following equation: HbA1C-IFCC = 10.93 × HbA1C-NGSP − 23.52 [13].

Plasma glucose was measured using the glucose oxidase method, and CPR was measured using EIA. CPR index was calculated as follows: serum CPR (ng/mL)/plasma glucose (mg/dL) × 100. eGFR was calculated using the formula established by the working group of the Japanese Chronic Kidney Disease Initiative [14]: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ (×0.739 for women).

ΔHbA1c, Δbody weight (BW), and ΔCPR index were defined as HbA1c, BW, and CPR index at 24 months – HbA1c, BW, and CPR index at baseline, respectively.

The baseline date for HbA1c measurement was defined as the blood collection date 14 days before sitagliptin initiation. The HbA1c measurement date (month 24) was defined as the first blood collection date ≥700 days after the date of sitagliptin initiation.

2.3. Statistical methods

Descriptive statistics were calculated for the baseline characteristics. Normally distributed data were compared between the two groups using Student's *t*-test or Fisher's exact test. Mann–Whitney *U*-test was used to compare the data that were not normally distributed.

Changes from the baseline HbA1c level and CPR index were analysed using repeated-measures ANOVA; then, post hoc pairwise group comparisons were conducted using Bonferroni tests. The association between two variables was estimated using Pearson's correlation coefficient.

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