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Impact of baseline body mass index status on glucose lowering and weight change during sitagliptin treatment for type 2 diabetics

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ABSTRACT

Aims: This study was designed to evaluate the efficacy of sitagliptin in Taiwanese diabetic subjects with different baseline BMI status.

Methods: This was a single-center, hospital-based, retrospective chart review in subjects ($n = 1874$) with type 2 diabetes who received sitagliptin. Subjects were classified into subgroups depending upon their baseline BMI by Taiwan national weight classification: normal (BMI < 24 kg/m^2) ($n = 504$), overweight (BMI: 24–27 kg/m^2) ($n = 615$), and obese (BMI ⩾ 27 kg/m^2) ($n = 755$). Changes in HbA1c and weight were evaluated over a 12month treatment period.

Results: For all three groups, the HbA1c levels declined over the first three months by about 8%, and subsequently plateaued for the next nine months. Obese subjects were slower in reducing HbA1c compared with normal and overweight subjects ($P < 0.05$), but at nine months the reduction was similar across groups. Mean body weight increased over the first nine months of sitagliptin therapy in subjects with normal BMI (57.12–58.30 kg), but there was no change in mean body weight in the overweight group. After three months the obese groups had significantly greater loss in body weight compared with the normal group.

Conclusions: Baseline BMI status may influence the reduction of HbA1c levels within the first six months of sitagliptin therapy and affect weight change after three months. Being obese was associated with an initial lag in HbA1c reduction and greater weight loss compared with normal and overweight subjects.

1. Introduction

Type 2 diabetes is one of the most common chronic diseases and is increasing in prevalence worldwide [1]. Obesity is a well-known risk factor for type 2 diabetes [1,2], and exacerbates the metabolic abnormalities of type 2 diabetes [3]. Abdominal adiposity is associated with inflammation, abnormal hormone secretion, and a number of metabolic disturbances that contribute to the development of type 2 diabetes, as well as cardiovascular risk, cancer, and liver disease [1]. Patients with type 2 diabetes are at risk for weight gain due to a number of factors including dysregulated entero-endocrine axis, sedentary lifestyle, diabetes medications, and high-caloric diet [2]. The management of type 2

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diabetes aims to reduce disease-related complications and improve long-term outcomes. Reaching glycemic control is a key component of this strategy by maintaining the glycosylated hemoglobin level to less than 7% without predisposing patients to hypoglycemia [4].

Currently, there are five major classes of anti-diabetic drugs approved for treating type 2 diabetes. They are biguanides (such as metformin), sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and incretin-based therapies, such as dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide (GLP-1) receptor agonists. Sitagliptin is a DPP-4 inhibitor that acts by increasing the levels of the endogenous GLP-1 and glucose-dependent insulinotropic peptide [5]. The increase in the amounts of these factors causes glucose-dependent insulin secretion and simultaneously reduces glucagon secretion [5]. Some type 2 diabetes therapies lead to unwanted weight gain. Sulfonylureas, thiazolidinediones, and insulin all increase weight by about 2 kg for every 1% decrease in HbA1c [6]. In contrast, sitagliptin is reported as weight neutral and metformin is associated with a slight weight loss [6].

The efficacy and tolerability of sitagliptin has been evaluated in a number of clinical studies, primarily in non-Asian patients [7–14]. One study that pooled data across clinical trials and analyzed >10,000 subjects found that sitagliptin was well tolerated for at least two years of treatment [13]. It is of clinical and scientific interest to understand the efficacy and tolerability of sitagliptin in a broader patient population and in a real-world clinical setting. Differences in genetics, cultural factors, and life-styles in different ethnic populations may potentially influence treatment outcomes. Compared with Caucasians, South-Asians have a relatively higher incidence of insulin resistance, central obesity, type 2 diabetes, and cardiovascular disease [15–17].

Sitagliptin is currently available and has reimbursement status from the Bureau of National Health Insurance in Taiwan. The purpose of this study was to assess the efficacy of sitagliptin, as measured by HbA1c levels, in type 2 diabetes patients being treated at Kaohsiung Chang Gung Memorial Hospital, one of the medical centers in southern Taiwan. We also evaluated the effect of sitagliptin on weight change and investigated whether glycemic control or weight loss were impacted by different BMI status at the start of treatment.

2. Methods

This single-center, hospital-based, retrospective chart review was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital and performed in accordance with the Declaration of Helsinki. No investigational medication was given during the study. No identifiable or protected health information was extracted during the course of the study; hence, the study did not require informed consent.

2.1. Study population

Included subjects were outpatients with diagnosed type 2 diabetes (ICD-9 code = 250.0; 250.1; 250.2; 250.3; 250.4; 250.5; 250.6) who were regularly examined and treated at the hospital and who were receiving sitagliptin as adjunctive therapy for $\geqslant$24 weeks during the study period. Eligible subjects had to have been on a stable does of all antidiabetic regimens (i.e., no change in therapy or dose for $\geqslant$3 months) prior to adding sitagliptin. Only subjects whose charts included the minimum core data for the outcomes of interest were included. Patients were divided into subgroups depending upon their baseline BMI according Taiwan's Health Promotion Administration's classification of obesity. The subgroups were normal (body mass index [BMI] < 24 kg/m^2), overweight (24–27 kg/m^2), and obese (BMI $\geqslant$ 27 kg/m^2).

Subjects with type 1 diabetes who regularly received insulin, or whose diabetes was due to medical intervention, or other diseases/conditions, such as surgery, pharmaceutical products, infections, malnutrition etc., were excluded. Subjects who participated in a clinical trial or another clinical study during the index period were also excluded.

2.2. Demographic and baseline patient characteristic variables

Demographic categorical variables were age and gender. Clinical categorical variables included duration of diabetes and sitagliptin dose; and levels of fasting plasma glucose (FPG), high-density lipoprotein (HDL) low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG); and comorbidities, such as hypertension or hyperlipidemia, or the presence of both hypertension and hyperlipidemia

2.3. Outcome measures

The primary outcome measures of interest were the association of weight and glycosylated hemoglobin A1C (HbA1c) levels with BMI.

2.4. Statistical analysis

Age, HbA1c and body weight were expressed as mean ± standard deviation (SD); other continuous variables were presented as median (interquartile range, P_{25}–P_{75}). Count and percentage were presented for categorical variables. Analysis of variance (ANOVA) for age difference, Kruskal–Wallis (K–W) test for differences in duration of type 2 diabetes, dose of sitagliptin, FPG, blood lipids, and Chi-square for gender, as well as comorbidity were performed. When 20% of cells had expected values of <5, Fisher's exact test was used instead. When ANOVA indicated significant findings, post-hoc analyses using Bonferroni's method and Dunnett's T3 test were performed for variables with equal SDs and with unequal SDs, respectively. When the K–W test indicated as significant difference, a Mann–Whitney *U* test was performed. Differences in changes in body weight and HbA1c level from baseline were first adjusted for age, diabetes duration, and comorbidities using linear regression analysis, and subsequently the differences were evaluated by K–W test. Generalized estimation equation (GEE) was performed to test the group and time effect on HbA1c level and body weight; the interaction between group and time was also examined. All tests were 2-sided and $P < 0.05$ was considered statistically significant.