# Types of Diabetes that the Dipeptidyl Peptidase-4 Inhibitor May Act Effectively and Safely

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**Abstract:** Dipeptidyl peptidase-4 (DPP-4) inhibitors prevent the inactivation of glucagon-like peptide-1 (GLP-1). This protein, released from the gut following ingestion of a meal, stimulates insulin secretion and inhibits glucagon secretion. Compared with other anti-diabetic drugs, the pharmacological characteristics of DDP-4 inhibitor include improvement in postprandial hyperglycemia, low frequency of hypoglycemia, prevention of development of obesity, few adverse events. Taking account of pharmacological characteristic and our therapeutic experiences with DPP-4 inhibitor, we believe that DPP-4 inhibitor may be a useful and safe oral anti-diabetic drug for diabetes in the elderly people, diabetes complicated with obesity, chronic hepatitis/liver cirrhosis, and steroid-induced diabetes.

**Keywords:** chronic hepatitis, dipeptidyl peptidase-4, glucagon-like peptide-1, obesity, steroid-induced diabetes.

## INTRODUCTION

The dipeptidyl peptidase-4 (DPP-4) inhibitor, which mainly prevents the inactivation of the glucagon-like peptide-1 (GLP-1), increases the endogenous GLP-1 concentrations [1, 2]. GLP-1 is released from the intestine following meal ingestion and GLP-1 stimulates insulin secretion and inhibits glucagon secretion, which reduces plasma glucose levels [1, 3]. Since GLP-1 is promptly inactivated by the enzyme, DPP-4, the half-life of GLP-1 is less than two minutes [1, 2]. Increased insulin secretion and decreased glucagon secretion due to DDP-4 inhibition reduce hepatic glucose production [4-6]. DPP-4 inhibitor has beneficial effects on pancreatic β-cell structure and function [7]. Clinical trials using DPP-4 inhibitors show high tolerability and safety [2]. Several studies with a number of different DPP-4 inhibitors show that the number of adverse events is not increased in DPP-4 inhibitors-group compared to the placebo-groups [2]. Hypoglycemia is very rare (less than 3%) during treatment with DPP-4 inhibitors as monotherapy or in combination with metformin or thiazolidinediones [2, 8-14]. Low frequency of hypoglycemia may be explained by GLP-1-mediated glucose-dependent insulin secretion. Furthermore, many studies demonstrated that DPP-4 inhibitor do not increase body weight compared to thiazolidinediones, sulfonylurea and insulin [2, 10-16].

The pharmacological characteristics of DDP-4 inhibitors include 1) improvement in postprandial hyperglycemia, 2) low frequency of hypoglycemia, 3) prevention of development of obesity, 4) few adverse events. Here, we will introduce types of diabetes that DPP-4 inhibitor, sitagliptin, may act effectively and safely, by showing case reports.

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## MATERIALS, METHODS, AND RESULTS

### Study Subject 1

In May, 2010, a 74-year-old female patient was diagnosed as diabetes for the first time and referred to our department. Her fasting plasma glucose level was 113 mg/dl and hemoglobin A1c level was 8.2%. Her body height, body weight and body mass index were 152.7 cm, 54.6 kg and 23.4 kg/m$^2$, respectively.

Before the use of sitagliptin, her postprandial blood glucose levels showed more than 150 mg/dl (Fig. **1**). At 3 days after the start of sitagliptin, postprandial blood glucose levels and the area under the curve (AUC) of blood glucose levels were significantly decreased (Fig. **1**). Interestingly, sitagliptin reduced serum insulin levels at 14:00, 18:00, and 20:00, and the AUC of serum insulin levels (Fig. **2**).

### Study Subject 2

A 46-year-old obese diabetic man with mental retardation who cannot control appetite has been treated as type 2 diabetes mellitus for previous 5 years. Metformin (1500 mg/day), pioglitazone (15 mg/day), miglitol (150 mg/day), and mitiglinide (60 mg/day) were used to treat diabetes. Since he could not perform a dietary therapy due to mental retardation, he is constantly in and out of hospital. On April 19, 2010, his blood glucose level was 382 mg/dl, and his hemoglobin A1c was 10.7%. His body height, body weight and body mass index were 170 cm, 90 kg and 31 kg/m$^2$, respectively. He was again admitted to our hospital for treatment of diabetes.

The patient could not keep to a dietary therapy (1600 kcal/day), and was a frequent repeat offender consuming additional calories daily. When discovered we stopped mitiglinide and started intensive insulin therapy (Fig. **3**). 30 days post admission we discontinued miglitol and insulin and initiated treatment with sitagliptin. Since his blood glucose levels were significantly ameliorated (Fig. **3**), he left

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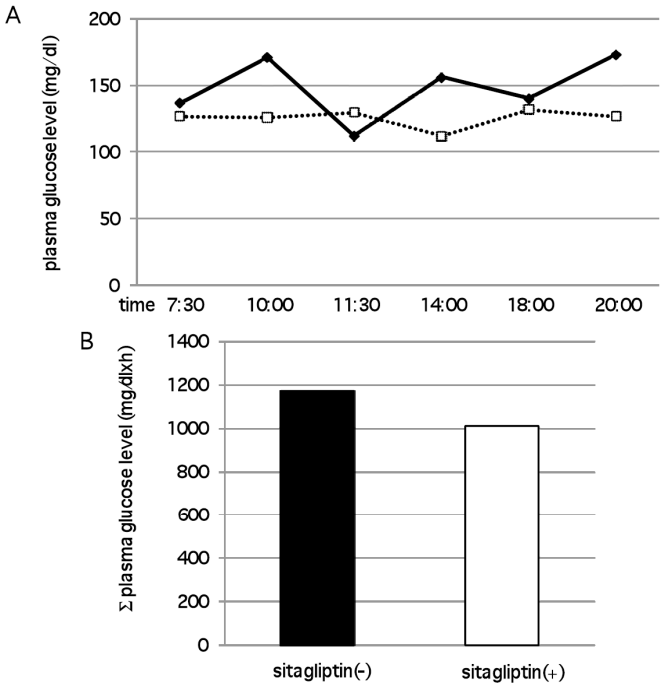


**Fig. (1).** (**A**) Changes of plasma glucose levels. Closed and opened boxes indicate values before and after the use of sitagliptin (50 mg/day). 7:30, 10:00, 11:30, 14:00, 18:00, and 20:00 mean before breakfast, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, and 2 hours after dinner, respectively. (**B**) The area under the curve of plasma glucose levels of before (closed bar) and after (opened bar) the use of sitagliptin (50 mg/day).

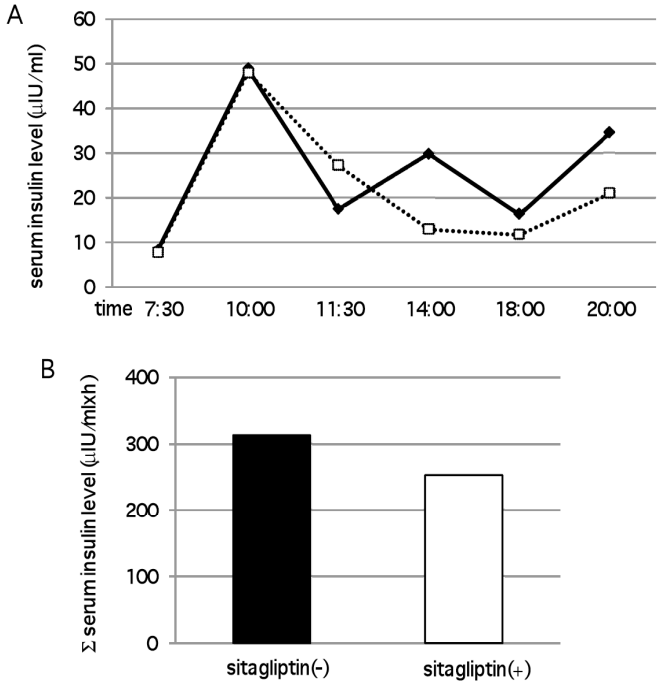


**Fig. (2).** (**A**) Changes of serum insulin levels. Closed and opened boxes indicate values before and after the use of sitagliptin (50 mg/day). 7:30, 10:00, 11:30, 14:00, 18:00, and 20:00 mean before breakfast, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, and 2 hours after dinner, respectively. (**B**) The area under the curve of serum insulin levels of before (closed bar) and after (opened bar) the use of sitagliptin (50 mg/day).

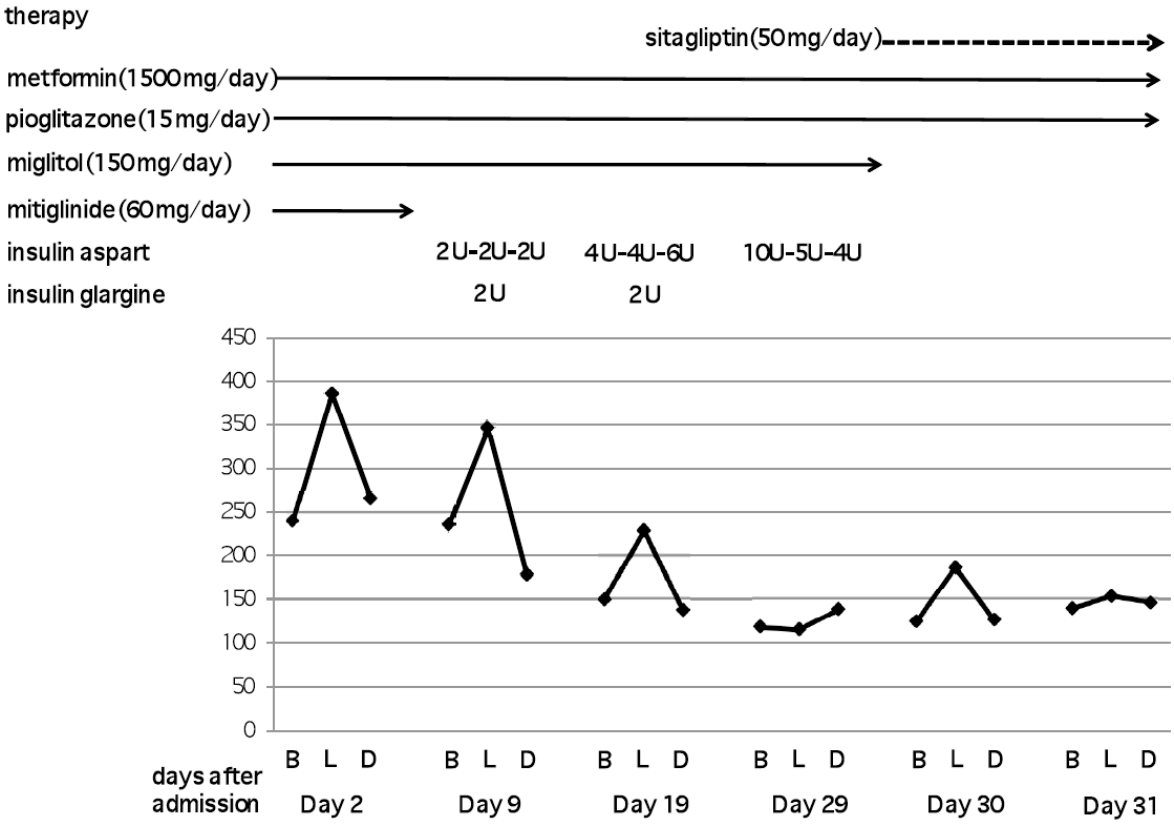


**Fig. (3).** Changes of blood glucose levels. B, L, and D mean before breakfast (7:30), before lunch (11:30), and before dinner (18:00), respectively.

the hospital on May 20, 2010 (Day 32). After discharge, hemoglobin A1c level was reduced (9.1% on June 1, 2010), and his body weight has been decreasing (Fig. **4**).

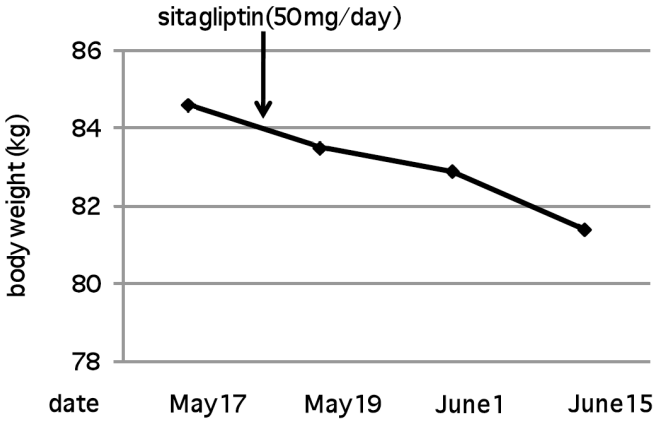


**Fig. (4).** Changes of body weight.

### Study Subject 3

In March, 2010, a 56-year-old woman has been found to show remarkable hyperglycemia (plasma glucose level, 712 mg/dl; hemoglobin A1c level, 11.4%). Her body height, body weight and body mass index were 150.4 cm, 42.9 kg and 19.0 kg/m$^2$, respectively. Elevated serum aspartate transaminase (AST, 75 IU/l, normal range; 10-35 IU/l) and alanine transaminase (ALT, 64 IU/l, normal range; 5-40 IU/l) levels were observed. The high titer of anti-hepatitis C virus (HCV) antibody (61.1) and high quantity of RNA for HCV genotype 1b (7.3). Serum total bilirubin level was within normal range (0.6 mg/dl, normal range; 0.3-1.2 mg/dl), and slight abnormal levels of serum albumin (3.5 g/dl, normal range; 3.9-5.0 g/dl), platelet (9.8 x $10^4$ /μl, normal range; 15.0-35.0 x $10^4$ /μl), and prothorombin time (13.3 seconds, normal range; 10.0-13.0 seconds) were observed. Based on these laboratory data and ultrasound of her liver, she has been diagnosed as having not liver cirrhosis but chronic active hepatitis.

When her blood glucose levels were decreased by the intensive insulin therapy, we started to use glimepiride (1 mg/day) and metformin (750 mg/day). This combination of sulfonylurea and biguanides was effective to reduce her plasma glucose levels (blood glucose levels, 120-187 mg/dl), however, this combination therapy deteriorated liver function (AST, from 60 to 135 IU/l; ALT, from 48 to 84 IU/l), and then, we changed from this combination therapy to the DPP-4 inhibitor, sitagliptin (50 mg/day). The hypoglycemic ability of sitagliptin was comparable to the ability of the combination of sulfonyurea and biguanides (blood glucose levels one week after the start of sitagliptin, 101-150 mg/dl), and sitagliptin ameliorated liver function (AST, from 135 to 54 IU/l; ALT, from 84 to 64 IU/l) [17].

### Study Subject 4

An 81-year-old female patient with polymyalgia rheumatica was treated with daily 20 mg prednisolone, and she developed steroid-induced diabetes. Her hemoglobin A1c level was 8.3%, and daily 30-40 unites of insulin were needed to treat hyperglycemia. Her fasting blood glucose levels were relatively low (blood glucose levels, 88-146 mg/dl), and postprandial glucose levels were remarkably elevated (blood glucose levels, 200-417 mg/dl). Since she refused to use insulin at home, we started to use metformin (250 mg/day), nateglinide (270 mg/day), and pioglitazone (15 mg/day). Since 6-8 unites of insulin were needed to reduce blood glucose levels below 200 mg/dl, we changed from nateglinide to sitagliptin (50 mg/dl). After the change of therapy, her postprandial glucose levels were significantly decreased (blood glucose levels, 99-168 mg/dl) and finally the addition of insulin was not required [18]. After discharge, hemoglobin A1c level has been decreasing (Fig. **5**).

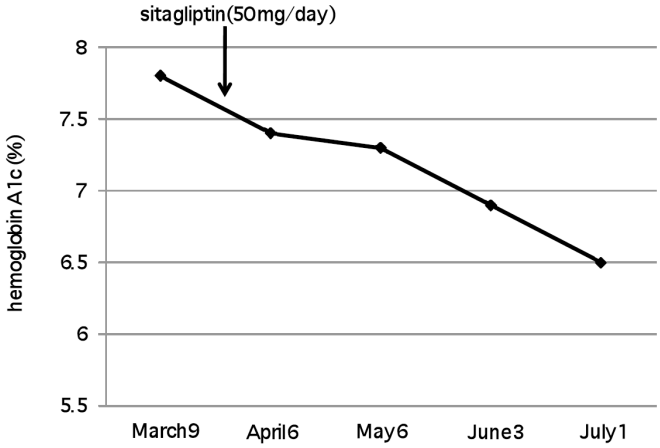


**Fig. (5).** Changes of hemoglobin A1c levels.

## DISCUSSION

Sitagliptin reduced postprandial blood glucose levels and the AUC of blood glucose levels, in spite of decreased AUC of serum insulin levels in study subject 1, suggesting that sitagliptin ameliorates insulin resistance. Hypoglycemia was not observed at every time point. This observation suggests that DPP-4 inhibitor improves insulin sensitivity even in the elderly people and is also safe and efficacious drug for diabetes in the elderly people. However, in general, elderly people have renal dysfunction due to declined glomerular filtration rate (GFR) with aging. Plasma levels of sitagliptin are increased by 2-fold in patients with moderate renal dysfunction (creatinin clearance 30-50 mL/min) and by 4-fold in patients with severe renal dysfunction (creatinin clearance < 30 mL/min) [19]. Increased circulating levels of sitagliptin induce severe hypoglycemia. Making dose adjustment is recommended for these patients.

Sitagliptin improved glucose metabolism and decreased body weight in obese diabetic patient (study subject 2) who could not perform a dietary therapy due to mental retardation, suggesting the usefulness of DPP-4 inhibitors for diabetes complicated with obesity. Insulin resistance is commonly observed in obese people. Sitagliptin-mediated amelioration in insulin resistance found in study subjects 1 may support the effectiveness of DPP-4 inhibitors for the glycemic control in obese people. Several studies also demonstrated that DPP-4 inhibitor do not increase body weight compared to thiazolidinediones, sulfonylurea and insulin [2, 10-16].

Although a high prevalence of glucose intolerance in patients with chronic hepatitis has been reported [20], few studies have evaluated what is the most effective and safe therapy for diabetes mellitus in chronic hepatitis patients.

We experienced a diabetic 56-year-old female patient complicated with chronic hepatitis C (study subject 3), who could be effectively and safely treated by the DPP-4 inhibitor, sitagliptin [17].

The treatment of diabetes complicated with chronic hepatitis/liver cirrhosis is difficult, because most of the oral anti-diabetic drugs (sulfonyurea, biguanides, and thiazolidines) are metabolized in the liver and patients frequently show hypoglycemia. Relatively low fasting plasma glucose levels due to insufficient hepatic gluconeogenesis, and postprandial hyperglycemia due to insufficient hepatic glucose uptake are characteristics for diabetes complicated with chronic hepatitis/liver cirrhosis. Since DPP-4 inhibitor induces GLP-1-mediated meal ingestion (glucose)-dependent insulin secretion, DPP-4 inhibitor improves postprandial glucose levels but do not cause hypoglycemia. Further, since sitagliptin is minimally metabolized and over 80% of the compound is excreted unchanged in the urine, hepatic insufficiency do not seem to alter the pharmacokinetics of sitagliptin [21]. DPP-4 inhibitors may be effective and safe drug for diabetes complicated with chronic hepatitis/liver cirrhosis. Currently, another DPP-4 inhibitor, vildagliptin, is available for the treatment of type 2 diabetes. Based on observations using higher doses than ones proposed for clinical use, a caution for liver dysfunction was built in to the label [2]. Although moderate liver dysfunction has been reported to have no clinically meaningful effect on the pharmacokinetics of sitagliptin [22], liver function tests should be performed prior to initiation of use of DPP-4 inhibitors, and periodically thereafter.

The mechanisms for steroid-induced diabetes may include increased hepatic glucose output and insulin resistance. The characteristics for steroid-induced diabetes are normal fasting plasma glucose levels and postprandial hyperglycemia [23]. We experienced a patient with steroid-induced diabetes, whose blood glucose levels were ameliorated by the use of sitagliptin [18]. The DPP-4 inhibitor improves postprandial hyperglycemia and insulin resistance, and rarely induces hypoglycemia. Therefore, DPP-4 inhibitor may be a useful and safe oral anti-diabetic drug for steroid-induced diabetes.

The incidence of gastrointestinal-related adverse experiences during treatments with sitagliptin has been reported to be approximately 10% [24]. None of our patients studied complained of gastrointestinal-related adverse experiences. Further, none of our patients showed laboratory adverse experiences including liver dysfunction and renal dysfunction.

## CONCLUSION

The pharmacological characteristics of DDP-4 inhibitor includes improvement in postprandial hyperglycemia, low frequency of hypoglycemia, prevention of development of obesity, few adverse events. DPP-4 inhibitor may be an effective and safe oral anti-diabetic drug for diabetes in the elderly, diabetes complicated with obesity, chronic hepatitis/liver cirrhosis, and steroid-induced diabetes (Table **1**).

**Table 1. Types of Diabetes that DPP4 Inhibitor May Act Effectively and Safely**

| |
|---|
| 1) Elderly people |
| 2) Obesity |
| 3) Chronic hepatitis, liver cirrhosis |
| 4) Steroid induced diabetes |

## ACKNOWLEDGEMENT

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