

Effect of the Addition of Sitagliptin and Miglitol on Insulin-Treated Type 2 Diabetes

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ABSTRACT

Introduction: To examine the efficacy of sitagliptin and miglitol when added to ongoing insulin treatment in a patient with type 2 diabetes who had undergone partial gastrectomy.

Methods: Continuous glucose monitoring (CGM) was performed and either sitagliptin or miglitol, or both, were added to fixed-dose insulin therapy. Blood was drawn at 0, 30, 60, and 120 min after breakfast, and C-peptide,

glucagon, glucagon-like peptide (GLP)-1, and glucose-dependent insulinotropic peptide (GIP) were measured.

Results: CGM showed that compared to insulin alone, the addition of either sitagliptin or miglitol, or both, to insulin achieved better glucose control. Compared to insulin alone, early postprandial increments in plasma C-peptide levels and suppressed glucagon levels were observed when sitagliptin was added. Glucagon suppression was even more prominent when both sitagliptin and miglitol were added. Compared to insulin alone, GLP-1 levels were higher during the early postprandial stage when sitagliptin or miglitol was added and even higher when both were added. GIP levels decreased when sitagliptin or miglitol, or both, were added to insulin therapy.

Conclusion: The authors showed that the addition of sitagliptin or miglitol, or both, was effective in this insulin-treated patient with diabetes who had undergone gastrectomy.

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INTRODUCTION

Insulin injections are widely used as the most dependable treatment for diabetes. The effectiveness of insulin injections has been established in various clinical studies. However, an increase in insulin dosage to achieve better glycemic control is associated with an increased risk of hypoglycemia and weight gain [1]. Many patients with diabetes are being treated with insulin alone, but only a few patients are able to achieve optimal glycemic control with this treatment strategy. For these patients, combination therapy with insulin injection and oral medication is worth considering. Incretins [2–4], glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4). DPP-4 inhibitors, such as sitagliptin [5], increase active GLP-1 and GIP levels by inhibiting DPP-4 enzymatic activity, and improve hyperglycemia in a glucose-dependent manner by increasing serum insulin and decreasing serum glucagon levels in patients with diabetes [6–10]. The safety and tolerability of sitagliptin has been demonstrated, with a low risk of hypoglycemia or weight gain [11]. Considering the different mechanisms and complementary effects of sitagliptin and insulin, a combination of these agents is a rational treatment option for insulin-treated patients [12]. Alpha-glucosidase inhibitors (alpha-GIs), such as miglitol, delay the absorption of digested carbohydrates from the small intestine and, thus, lower both postprandial glucose and insulin levels [13]. Alpha-GIs are considered to be effective for stabilizing glycemic levels in patients who have undergone gastric or esophageal surgery because alpha-GIs prevent reactive hypoglycemia due to late dumping syndrome

[14]. Therefore, the present study examined the efficacy of sitagliptin and miglitol when added to an ongoing insulin treatment in a patient with type 2 diabetes who had undergone partial gastrectomy. Efficacy was estimated with the use of a continuous glucose monitoring system (CGMS) [15–17], and by measuring hormones related to incretin and glucose metabolism.

METHODS

Subject

The patient was a 67-year-old Japanese man with a 15-year history of type 2 diabetes. At the age of 55 years, the patient was diagnosed as having gastric cancer and underwent a distal partial gastrectomy with reconstruction via the Billroth I operation. The patient was being medicated with insulin lispro, which was injected at a dose of 10, 12, and 12 units just before breakfast, lunch, and dinner, respectively. The patient was also injecting 12 units of insulin glargine before going to bed. The patient had no diabetic complications, such as neuropathy, retinopathy, or nephropathy. The patient had concomitant hypertension, dyslipidemia, and nontuberculous mycobacterial infection, but all these comorbid diseases were well controlled with oral medication. The patient was admitted to the authors' hospital because of deteriorating diabetic control. The patient's height was 163.1 cm, and at the time of admission, body weight was 66.9 kg (body mass index 25.2 kg/m²). Hemoglobin A1c and glycoalbumin levels were 9.1% and 24.0%, respectively. The urinary C-peptide level was 81.0 µg/day. The patient provided written informed consent for participation in the study.

CGMS

The patient was admitted to the diabetes ward of the authors' hospital and was equipped with a CGMS device (CGMS[®]-GOLD[™]; Medtronic MiniMed, Northridge, California, USA). The patient was monitored from 1 day before the study to the end of the 9-day study period. The CGMS soft sensor was changed at the appropriate times according to the manufacturer's instructions. Glucose levels measured using a self-monitoring blood glucose device (Nipro Stat Strip XP[®]; Nipro, Osaka, Japan) were checked at least four times per day for calibration of the CGMS. The recorded data were analyzed using CGMS Solutions[®] software (Medtronic MiniMed, Northridge, California, USA).

Breakfast

Breakfast with a similar number of calories each day was served throughout the study period. The total number of calories of a typical meal was 428 kcal, containing 73 g of carbohydrates, 14.2 g of protein, and 7.4 g of fat. The meal was ingested within 10–15 min.

Sample Collection and Analysis

On the first day of the study, after an overnight fast for 14 h, an intravenous line was inserted into one forearm vein and flushed with sterile 0.9% NaCl solution for repeated blood sampling. Blood was drawn at 0, 30, 60, and 120 min after breakfast for the measurement of serum C-peptide, plasma glucagon, active GLP-1, and total GIP levels. Blood samples were immediately cooled and centrifuged at 4 °C, and plasma was stored at –20 °C until analysis. Blood samples for the determination of glucagon, active GLP-1, and total GIP levels were collected into BD[™] P800

tubes (Becton, Dickinson and Co., Franklin Lakes, New Jersey, USA) containing spray-dried potassium EDTA anticoagulant and a proprietary cocktail of protease, esterase, and DPP-4 inhibitors (Becton, Dickinson and Co.). Plasma samples for active GLP-1 measurements were subjected to solid-phase extraction to remove interference that affects immunoassays [18], and samples were analyzed using an enzyme-linked immunosorbent assay (ELISA) kit (Millipore Corp., Billerica, Massachusetts, USA). Plasma concentrations of amidated GLP-1 (7–36) and (7–37) were measured using an antibody that is highly specific for the N-terminus of GLP-1 and does not react with GLP-1 (9–36), GLP-2, or glucagon. The detection limit of the ELISA was 0.83 pmol/L, with an intra-assay coefficient of variation (CV) of 4.06–14.90% and an interassay CV of 11.1–13.2%. The total GIP level was measured using a human GIP ELISA kit (Millipore Corp.). This kit has 100% cross-reactivity to human GIP (1–42) amide and GIP (3–42) amide, with a detection limit of 0.50 pmol/L, an intra-assay CV of 1.00–3.94%, and an interassay CV of 4.99–10.10%. Both active GLP-1 and total GIP levels were measured at Mitsubishi Chemical Medience Corp. (Tokyo, Japan). The serum C-peptide level was measured using an electrochemiluminescence immunoassay. Blood samples for glucagon detection were analyzed using a double-antibody radioimmunoassay at SRL, Inc. (Tokyo, Japan). The area under the curve (AUC) values for these hormones after meal ingestion were calculated using the trapezoidal rule.

Medications

Throughout the study period, insulin dosages were not changed. On the first and second days of the study (days 1 and 2), the patient used insulin alone. From days 3 to 6, sitagliptin

(50 mg, one tablet per day) was also taken, before breakfast, in addition to the insulin injections. On day 7, miglitol (50 mg, three tablets per day) was taken before meals, in addition to the insulin injections and sitagliptin. From day 8 to the end of the study, sitagliptin was discontinued, and the patient received only insulin injections and miglitol. Blood sampling was performed on days 2, 6, 7, and 9. The sampling methods and timing were identical for each blood sampling period.

RESULTS

Throughout the study period, continuous glucose monitoring (CGM) was completed without any problems and the patient

experienced no gastrointestinal symptoms associated with the study medications.

Figure 1 shows the escalations and fluctuations in glucose levels measured by CGM during treatment with insulin alone (days 1 and 2), insulin plus sitagliptin (days 3–6), insulin plus sitagliptin and miglitol (day 7), and insulin plus miglitol (days 8 and 9). The mean and SD values of CGM measurements for days 1, 2, 3, 4, 6, 7, 8, and 9 were 185 ± 58 , 210 ± 75 , 154 ± 44 , 157 ± 53 , 158 ± 36 , 144 ± 31 , 137 ± 30 , and 132 ± 31 mg/dL, respectively, reflecting the attenuation of glucose fluctuations when sitagliptin, miglitol, or both, were added to insulin therapy.

Time-dependent changes in C-peptide, glucagon, active GLP-1 and total GIP levels,

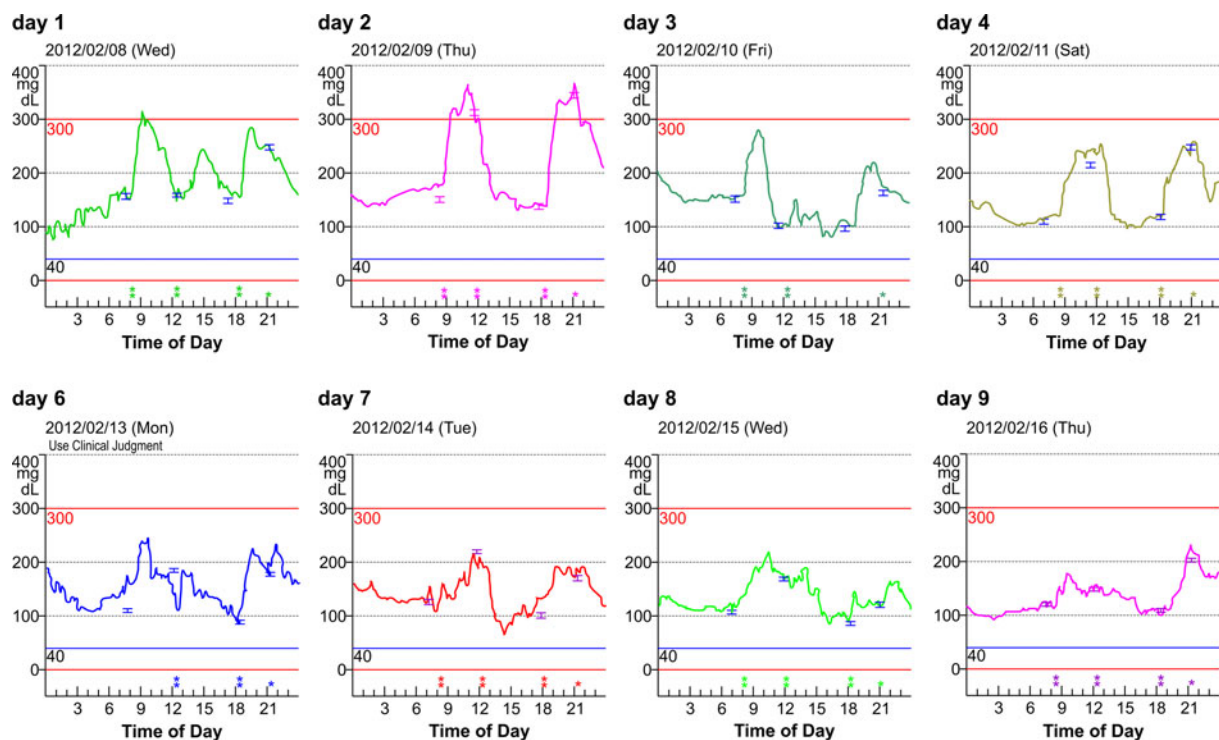


Fig. 1 CGM results during insulin therapy alone (days 1 and 2), insulin therapy plus sitagliptin (days 3, 4, and 6), insulin therapy plus sitagliptin and miglitol (day 7), and insulin therapy plus miglitol (days 8 and 9). The whole-day result of CGM on day 5 is not available, because the

CGMS soft sensor changed. *Double asterisk* indicates times of meals (this sign for dinner for day 3, and breakfast for day 6 are missing). *Single asterisk* indicates times of bedtime calibration. *CGM* continuous glucose monitoring, *CGMS* continuous glucose monitoring system

and the AUC values of these hormones up to 2 h after meal ingestion are summarized in Table 1 and Fig. 2. Compared to insulin alone, remarkable early postprandial increments in plasma C-peptide levels were observed when sitagliptin was added to insulin therapy, whereas no remarkable changes in postprandial increments in plasma C-peptide levels were observed when insulin was administered in combination with sitagliptin and miglitol or when insulin was administered with miglitol only (Fig. 2a). Compared to insulin alone, the addition of sitagliptin to insulin therapy suppressed glucagon levels for at least 2 h after meal ingestion. This tendency was even more prominent when miglitol was coadministered with sitagliptin and insulin; however, the administration of miglitol in combination with insulin had no observable effect on glucagon levels during the early postprandial phase (Fig. 2b). Compared with insulin alone, the addition of sitagliptin or miglitol to insulin therapy increased GLP-1 levels at least 30 min after meal ingestion. When both sitagliptin and miglitol were added to insulin therapy, remarkable incremental

increases in GLP-1 levels were observed. GLP-1 fluctuation in response to sitagliptin or miglitol alone was transient, as opposed to the sustained increase observed when both drugs were combined with insulin (Fig. 2c). In contrast to the GLP-1 results, GIP levels decreased when sitagliptin or miglitol was added to insulin therapy. This tendency was particularly prominent when both sitagliptin and miglitol were added to insulin therapy (Fig. 2d).

DISCUSSION

The results of the present study in a Japanese patient with type 2 diabetes show that the administration of sitagliptin in addition to insulin therapy has beneficial effects on stabilizing the fluctuating glucose levels. The administration of miglitol in addition to insulin therapy and the coadministration of sitagliptin and miglitol also had beneficial effects in lowering glycemic levels in this patient. These effects were demonstrated precisely by the mean \pm SD values and calculated AUC values of the glucose levels monitored by CGMS. The authors have previously shown that the

Table 1 AUC values during the 2-h meal test

	Insulin alone	Insulin + sitagliptin	Insulin + sitagliptin + miglitol	Insulin + miglitol
Glucose (CGM) AUC (mg/dL \times 2 h)	35,345	26,265	17,588	18,528
C-peptide AUC (nmol/L \times 2 h)	79.4	105.2	62.1	62.9
Glucagon AUC (ng/L \times 2 h)	7,725	6,210	5,235	7,335
Active GLP-1 AUC (pmol/L \times 2 h)	266.7	355.4	789.5	392.2
Total GIP AUC (pmol/L \times 2 h)	9,270	5,532	1,993	4,210

AUC area under the curve, CGM continuous glucose monitoring, GIP glucose-dependent insulinotropic peptide, GLP-1 glucagon-like peptide 1

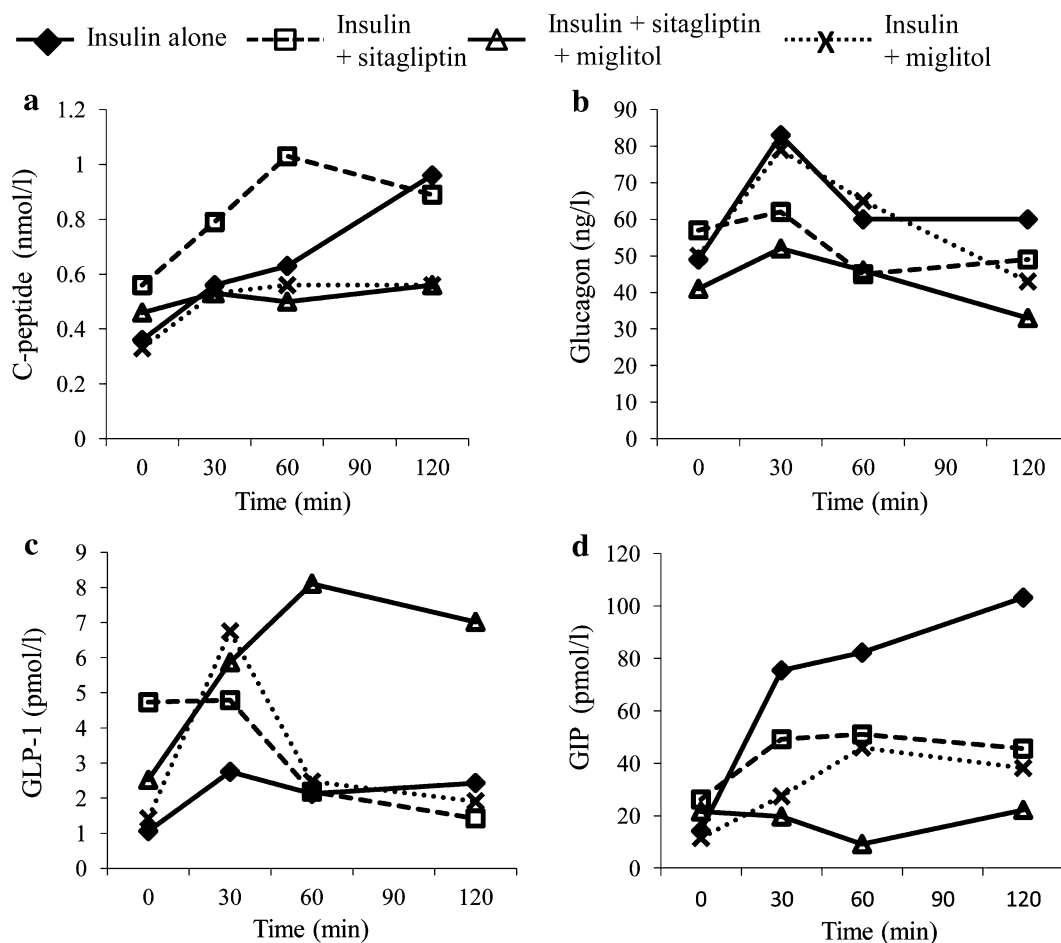


Fig. 2 Time course of plasma C-peptide (a), glucagon (b), active GLP-1 (c), and GIP (d) levels before and after food intake in the patient. *Thick line with filled diamond* insulin alone, *dashed line with square* insulin + sitagliptin, *thin line*

with triangle insulin + sitagliptin + miglitol, *dotted line with times symbol* insulin + miglitol. *GIP* glucose-dependent insulinotropic peptide, *GLP-1* glucagon-like peptide-1

combination of sitagliptin and miglitol was effective for reducing glucose fluctuations and stabilizing postprandial blood glucose levels in patients with type 2 diabetes receiving oral medication [19]. In the present study, the authors have demonstrated that both single administration and coadministration of these two drugs was also effective in an insulin-treated patient.

Compared to insulin therapy alone, the addition of sitagliptin to insulin therapy was associated with higher C-peptide and GLP-1 levels, and lower glucagon and GIP levels,

indicating that sitagliptin stimulated GLP-1 and endogenous insulin secretion, and suppressed glucagon and GIP levels. When miglitol was added to insulin therapy, GLP-1 levels during the early postprandial phase were higher than those seen with insulin therapy alone; however, unlike the case when sitagliptin was added, glucagon levels were not suppressed. However, GIP levels were suppressed to a level similar to that when sitagliptin was added to insulin therapy. These results are consistent with previous reports, which showed that miglitol enhances and prolongs GLP-1 release

and suppresses plasma GIP secretion [20–22]. The coadministration of sitagliptin and miglitol with insulin therapy was associated with a significant increase in GLP-1 secretion. The authors theoretically expected a postprandial increment in C-peptide levels as a result of the increased GLP-1 secretion; however, compared to insulin therapy alone, no remarkable changes in C-peptide levels were seen with sitagliptin and miglitol coadministration, which may be partly explained by the induced decrease in blood glucose levels. In contrast, the coadministration of sitagliptin and miglitol with insulin therapy was associated with significantly suppressed glucagon and GIP levels, indicating that the combination of these drugs acted synergistically to suppress glucose increments.

VilSBøll et al. [12] reported in a 24-week study that the addition of sitagliptin to ongoing insulin therapy resulted in significant improvements in glycemic control by improving beta-cell responsiveness relative to a placebo. The authors concluded that their findings were consistent with the mechanism of action of sitagliptin [6], and that in patients with more advanced disease and beta-cell failure, sitagliptin may still favorably impact glucose-dependent insulin secretion. In another report, Ahren et al. [23] demonstrated that vildagliptin, another DPP-4 inhibitor, enhanced alpha-cell responsiveness to both the suppressive effects of hyperglycemia and the stimulatory effects of hypoglycemia, concluding that these effects probably contributed to the improvement in glycemic control. Those reports support the authors' findings that the addition of a DPP-4 inhibitor to insulin therapy has beneficial effects on stabilizing glycemic control by stimulating endogenous insulin secretion and suppressing glucagon secretion. It is encouraging that these favorable effects were evident in a patient with a long history of diabetes, such as the

present patient. In addition, previous reports have demonstrated that in type 1 diabetes, exogenous GLP-1 lowered peak postprandial glucose levels regardless of residual beta-cell function [24], lowered fasting glycemia mainly by reducing glucose concentration [25], and presumably delayed gastric emptying and could normalize glycemic excursion after a meal when given in combination with insulin [26]. Vildagliptin has also been reported to be beneficial for decreasing postmeal glucagon excursion in insulinopenic patients with type 1 diabetes; this effect was not secondary to a change in endogenous insulin secretion [27]. These reports encourage the use of incretin-related agents in insulin-treated patients with type 1 or type 2 diabetes.

In addition to sitagliptin, the addition of miglitol to insulin therapy had favorable effects on stabilizing glycemic control, in a patient who had undergone gastrectomy, such as the present patient [14]. When both sitagliptin and miglitol were added to insulin therapy, the present patient experienced hypoglycemia that the patient was not completely aware of, but was revealed later by the CGM results. Therefore, caution should be exercised when these combinations are used and a reduction in the insulin dose should be considered. In other words, by adding these drugs to insulin therapy, the authors are able to reduce the insulin dose and are thus able to reduce the risk of undesired side effects of insulin treatments, such as severe hypoglycemia and increasing body weight [28, 29].

CONCLUSION

In conclusion, with the use of CGMS, the authors have shown that the addition of a DPP-4 inhibitor, such as sitagliptin, was effective in reducing glucose fluctuations and stabilizing postprandial blood glucose levels in

an insulin-treated patient. The addition of an alpha-GI, such as miglitol, to insulin therapy was also effective in this patient with diabetes who had undergone gastrectomy. Because the present patient was a thin man with very low C-peptide levels and the dynamics of glucose absorption were greatly influenced by gastric resection, the authors are unable to apply the present findings to a general population of individuals with type 2 diabetes. To verify the effectiveness of sitagliptin in insulin-treated patients, further studies in a larger number of patients are needed, including patients with other insulin regimens, for instance, once-daily injection of long-acting insulin or mixed insulin agents two or three times daily.

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Conflict of interest. The authors declare that they have no conflicts of interest.

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