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**Combination Therapy of Glucagon-like Peptide-1 Receptor Agonists and Insulin for
Patients who developed Diabetes after Partial Pancreatectomy**

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short running title : GLP-1 RA for T2DM after pancreatectomy

Abstract

Aims/Introduction: It is known that after pancreatectomy, patients experience hyposecretion of endogenous insulin and frequently develop diabetes. However, it has been unclear whether combination therapy with glucagon-like peptide-1 receptor agonists and basal insulin is effective for such patients. In this study, we evaluated the efficacy and safety of combination therapy with long-acting insulin glargine and the GLP-1 receptor agonist lixisenatide in patients who developed diabetes after pancreatectomy.

Materials and Methods: Japanese patients who developed diabetes after pancreatectomy were eligible for this study. Participants were treated with combination therapy of glargine and lixisenatide for 12 weeks. Fasting and postprandial plasma glucose, C-peptide immunoreactivity, HbA1c, body weight, visceral fat and subcutaneous fat were measured.

Results: At 12 weeks after initiation of lixisenatide, HbA1c levels decreased from $8.46\% \pm 1.64\%$ to $6.81\% \pm 1.15\%$. In addition, 1-h postprandial plasma glucose and 2-h PPG levels significantly decreased from 222.9 ± 56.2 mg/dl to 125.1 ± 37.5 mg/dl ($p < 0.001$) and from 247.5 ± 56.8 mg/dl to 115.1 ± 29.0 mg/dl ($p < 0.001$), respectively. Neither hypoglycemia nor clinically relevant adverse events occurred during this study.

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Conclusions: This study indicates that combination therapy with basal insulin and GLP-1 receptor agonists after partial pancreatectomy can be a useful therapeutic option for providing effective glycemic control with a reduced risk of hypoglycemia.

This study was registered with the University Hospital Medical Information Network (UMIN) (no. UMIN000014249).

Key words

glucagon-like Peptide-1 Receptor Agonists, lixisenatide, pancreatectomy

Introduction

It is known that patients who have undergone partial pancreatectomy frequently develop diabetes because secretion of endogenous insulin diminishes with the decreased mass of pancreatic parenchyma^{1,2}. Although the degree of severity depends on the area and volume of pancreas intensive insulin therapy is often introduced after the procedure, greatly affecting patients' quality of life (QOL).

Recently, development of insulin formulations that help basal secretion, including once-daily, long-acting, and minimally invasive insulins with a reduced risk of hypoglycemia, has progressed rapidly. Insulin glargine is one of these products and several studies, including clinical trials, have indicated that it shows stable and sustained blood insulin levels and glucose-lowering effect^{3,4}.

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While basal insulin treatment is effective for lowering diurnal variation in blood glucose by mainly controlling fasting plasma glucose (FPG) levels, combination therapy with additional insulin or an oral antidiabetic agent is often considered for controlling postprandial plasma glucose (PPG) levels because it would become difficult to achieve the HbA1c target once PPG levels elevate. Recently, combination therapy with glucagon-like peptide-1 (GLP-1) receptor agonists has gathered attention as an effective treatment to reduce HbA1c levels. GLP-1 receptor agonists have a distinctive feature of controlling hyperglycemia by stimulating glucose-dependent insulin secretion and suppressing glucagon secretion without promoting weight gain or hypoglycemia. Theoretically, combination therapy with GLP-1 receptor agonists and basal insulin is considered to provide effective glycemic control with complementary effects for FPG and PPG.

Combination therapy with GLP-1 receptor agonists and basal insulin has already been reviewed in several clinical trials. A meta-analysis of 15 randomized controlled trials suggested that this combination therapy has strong efficacy for decreasing blood glucose levels with a lower risk of hypoglycemia compared with other diabetes treatments. It has also been shown that this combination therapy prevents weight gain caused by insulin⁵. In particular, effectiveness of the GLP-1 receptor agonist lixisenatide in combination with basal insulin has been demonstrated in three studies: GetGoal-L-Asia, GetGoal-L, and GetGoal-Duo^{1,6-8}. A meta-analysis of these studies concluded that addition of lixisenatide has notable efficacy in improving PPG⁹.

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Few reports have evaluated combination therapy with GLP-1 receptor agonists and basal insulin for patients who develop diabetes after partial pancreatectomy. Therefore, we assessed the efficacy and safety of this combination therapy in patients with diabetes after partial pancreatectomy using long-acting insulin glargine and lixisenatide, a once-daily GLP-1 receptor agonist.

Materials and Methods

Study Population

Japanese patients who underwent pancreatectomy at Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital and who developed ~~hyposecretion of endogenous insulin~~ and diabetes were assessed for eligibility to participate in this study. Type 1 diabetes patients who had an absolute indication of insulin therapy and those who had undergone total pancreatectomy were excluded. All participants received both oral and written information and signed an informed consent form before entering the study.

Methods

The patients were monitored at the hospital and administration of glargine was started at the time of admission. The glargine dose was adjusted to achieve the target FPG levels of 100–130 mg/dl and lixisenatide was added when the target FPG levels were achieved and continued for 12 weeks. Glargine was administered at bedtime.

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Baseline was considered as the time when the target FPG levels were achieved. Plasma glucose levels and C-peptide immunoreactivity (CPR) were measured at pre-breakfast, 1-h post-breakfast, 2-h post-breakfast. HbA1c levels and body weight were measured at baseline and at the end of the 12-week combination therapy. In addition, a CT scan was conducted to measure visceral fat and subcutaneous fat. During follow-up, the patients adhered to a diabetic diet and the calorie component ratio of protein versus fat versus carbohydrate (PFC ratio) was 15:25:60. This study was conducted according to the tenets of the Declaration of Helsinki and was approved by the ethics committee of Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital. Also, it has been registered at the University Hospital Medical Information Network (UMIN) as UMIN000014249.

Outcomes and Statistical Analysis

The primary outcomes were changes in HbA1c, FPG, 1-h PPG and 2-h PPG after breakfast, and CPR levels from baseline to the end of the 12-week combination therapy. The secondary outcomes were frequency of hypoglycemia (serious and non-serious), frequency of gastrointestinal disorders, and changes in body weight.

Statistical analysis was performed using paired t-test. All the statistical tests were two-tailed, with a significance level of 0.05. All data were shown by the mean \pm standard deviation.

Results

Patient Characteristics at baseline

A total of 10 patients were included in this study, after exclusion of 1 patient with total pancreatectomy and withdrawal of 6 patients who declined to participate (Figure 1). Table 1 shows the baseline characteristics of the patients. Ten patients were analyzed (males: 8; females: 2). The mean age of the patients was 70.2 ± 6.6 years. The primary diseases were pancreas cancer (8 patients) and duodenal tumor (2 patients). The areas of resection were the pancreatic tail (6 patients) and pancreatic head (4 patients). ~~HbA1c levels were $8.46\% \pm 1.64\%$.~~ The mean HbA1c was $5.98\% \pm 0.39\%$ at pre-pancreatectomy and $8.46\% \pm 1.64\%$ at baseline. The mean glargine daily dose was 6.7 ± 3.6 units.

Changes in HbA1c and Blood Glucose Levels

HbA1c levels significantly decreased from $8.46\% \pm 1.64\%$ at baseline to $6.81\% \pm 1.15\%$ at the end of the 12-week combination therapy with lixisenatide (Figure 2, $p < 0.001$), and 80% of the patients (8 of 10 patients) achieved HbA1c levels of $<7.0\%$. Similarly, 1-h PPG and 2-h PPG levels significantly decreased from 222.9 ± 56.2 mg/dl and 247.5 ± 56.8 mg/dl at baseline to

125.1 ± 37.5 mg/dl and 115.1 ± 29.0 mg/dl, respectively (Figure 3, $p < 0.001$ for both). Individual blood glucose data indicated that 90% of the patients (9 of 10 patients) achieved 2-h PPG levels of <140 mg/dl, demonstrating that PPG was well controlled. FPG levels were also well controlled, without showing any changes before or after the combination therapy.

Changes in CPR Levels

It was demonstrated that insulin secretion was decreased. Fasting blood CPR level of each patient never exceeded 1.0 ng/ml from baseline to the end of the 12-week combination therapy with lixisenatide. Similarly, post-breakfast 1-h CPR and 2-h CPR levels did not show a marked change (from 1.37 ± 0.69 ng/ml to 1.50 ± 0.77 ng/ml and from 1.89 ± 1.16 ng/ml to 1.28 ± 0.78 ng/ml, respectively). Insulin secretion remained at a low level.

Changes in Body Weight, Visceral Fat Area, and Subcutaneous Fat Area

The patients' body weight decreased from 54.0 ± 9.0 kg at baseline to 49.9 ± 9.1 kg at the end of the 12-week combination therapy with lixisenatide, with a mean weight loss of approximately 4.1 kg ($p = 0.013$). Weight loss was seen in all patients. Furthermore, 50% of the patients (5 out of 10 patients) lost less than 2.0 kg, and the biggest weight loss was 14.5 kg (from 56.5 kg to 42.0 kg).

In terms of changes in visceral fat and subcutaneous fat area, the mean area changed from 75.5 cm² to 52.0 cm² and from 79.3 cm² to 55.1 cm², respectively ($p = 0.019$ and 0.017 , respectively).

Each loss was more than 20 cm²

Frequency of Hypoglycemia and Gastrointestinal Disorders

Neither hypoglycemia nor clinically relevant adverse events, including gastrointestinal disorders (nausea) uniquely caused by GLP-1 receptor agonists, were observed during this study.

Discussion

The study findings indicated that combination therapy with glargine and the GLP-1 receptor agonist lixisenatide was a useful treatment for patients with diabetes after partial pancreatectomy to achieve good glycemic control. Add-on lixisenatide decreased 1-h PPG, 2-h PPG, and HbA1c levels, which were insufficiently controlled by glargine monotherapy. As baseline fasting CPR levels were <1.0 ng/ml, insulin secretion of the patients in this study was decreased. Nevertheless, a tight glycemic control without hypoglycemic events was observed. Thus, glargine and the GLP-1 receptor agonist lixisenatide are considered to be an excellent combination not only in terms of efficacy but also safety.

According to the present GLP-1 receptor agonist classification method, which suggests that GLP-1 receptor agonists should be classified on the basis of duration of action, liraglutide and exenatide LAR (weekly) are classified as long-acting GLP-1 receptor agonists whose main action is decreasing FPG levels and exenatide (daily) and lixisenatide are classified as short-acting GLP-1 receptor agonists whose main action is decreasing PPG levels (Table 2) ¹⁰. GLP-1

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receptor agonists' duration of action is strongly associated with gastric emptying action, which affects the influence on PPG levels. As a possible mechanism, rapid desensitization (tachyphylaxis) against delayed action of gastric emptying has been considered. Allegedly, with long-acting GLP-1 receptor agonists, tachyphylaxis occurs more often and delayed gastric emptying action tends to wane. On the other hand, with short-acting GLP-1 receptor agonists, tachyphylaxis occurs less often and delayed gastric emptying action is sustained, which helps to decrease PPG levels¹¹. It is known that incretin has an extra-pancreatic effect of reducing peristaltic movement by affecting small and large intestine¹². Although we did not find any case in this study, the risk of ileus needs to be carefully monitored in the patients after abdominal surgery.

Lixisenatide used in this study is a short-acting GLP-1 receptor agonist and its duration of action is shorter than that of liraglutide, which is a recombinant¹³. Because it is highly effective for suppressing PPG levels, it is suggested that combination therapy with basal insulin, which mainly decreases FPG levels, would be highly useful due to its complementary mechanism of action as a new therapeutic option for type 2 diabetes. From this point of view, if additional therapy is needed to improve PPG levels, short-acting GLP-1 receptor agonists are considered more suitable in combination with basal insulin.

Combination therapy with basal insulin and GLP-1 receptor agonists is highly useful in terms of

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QOL. At present, if patients fail to achieve the HbA1c target with basal insulin, basal plus or basal bolus therapy combined with additional insulin is suggested. Although these therapies are effective for glycemic control, there is concern regarding risks of hypoglycemia and body weight gain. In addition, given the influence on QOL due to their frequent dose, glargine and lixisenatide used in this study have greater advantages, such as less influence on QOL, because both doses are once daily and their dose timing can be set for the same time, such as before breakfast. Given the psychological status of diabetic patients after partial pancreatectomy, choosing a therapy with fewer burdens is very important to maintain their motivation for treatment.

In summary, this study suggested that combination therapy with basal insulin and short-acting GLP-1 receptor agonists for patients who develop diabetes after partial pancreatectomy provides effective glycemic control with a reduced risk of hypoglycemia. Although this was a single-arm study with a small study population, it is suggested that combination therapy with basal insulin and short-acting GLP-1 receptor agonists can be a useful therapeutic option to achieve good glucose control for patients who develop diabetes after partial pancreatectomy. More patients need to be selected and evaluated on a long-term basis.

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emptying in type 2 diabetes—relationship to postprandial glycemia. Regul Pept. 2013;

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Tables

Table 1. Patient Characteristics at baseline

Number of patients	10
Age (years)	70.2 ± 6.6
Gender (Male/Female)	8/2
Primary disease	
pancreas cancer	8
duodenal tumor	2
Areas of resection	
Pancreatic tail	6
Pancreatic head	4
BMI (kg/m ²)	20.53 ± 3.21
Glargine dose unit	6.7 ± 3.6 (range: 3–14)
the time from pancreatectomy to lixisenatide administration (days)	470.3 ± 483.1
FPG (mg/dl)	102.2 ± 19.3
Post-breakfast 1-h PPG (mg/dl)	222.9 ± 56.2
Post-breakfast 2-h PPG (mg/dl)	247.5 ± 56.8
HbA1c (%)	8.46 ± 1.64
Fasting CPR (ng/ml)	0.44 ± 0.31
Post-breakfast 1-h CPR (ng/ml)	1.37 ± 0.69
Post-breakfast 2-h CPR (ng/ml)	1.89 ± 1.16

All data are shown as the mean ± standard deviation.

BMI; body mass index, FPG; fasting plasma glucose, PPG; postprandial plasma glucose, CPR;

C-peptide immunoreactivity

Table 2. Classification and Characteristics of GLP-1 Receptor Agonists on the Basis of Duration of Action.

	Long-acting GLP-1 receptor agonists		Short-acting GLP-1 receptor agonists	
Medications	Liraglutide (Victoza®)	Exenatide LAR (weekly) (Bydurion®)	Exenatide (Daily) (Byetta®)	Lixisenatide (Lyxumia®)
Number of doses	1/day	1/week	2/day	1/day
Half-time in blood (h)	13–15	No data	1.3–1.4	2.12–2.45
Duration of action (h)	>24	No data	8	15
Fasting insulin secretion	Increased		Slightly increased	
Postprandial insulin secretion	Slightly increased		Decreased	
Glucagon secretion	Decreased		Decreased	
Delayed gastric emptying action	Waned with rapid desensitization (tachyphylaxis)		Sustained	

Partially revised from Reference 10

GLP-1 receptor agonists are classified on the basis of duration of action, such as long-acting GLP-1 receptor agonists and short-lasting GLP-1 receptor agonists. The main action of long-acting agents is decreasing FPG levels, whereas that of short-lasting agents is decreasing PPG levels.

Figure legends

Figure 1. Participant flow diagram.

Figure 2. Changes in HbA1c Levels.

The black lines show each patient's data, and the red line and numbers in red show the mean of each data.

Figure 3. Transition of Mean Blood Glucose Levels.

The blue line indicates the transition at baseline, and the red line indicates the transition after 12-week combination therapy with lixisenatide.



