【 CASE REPORT 】

Suppression of Extrapancreatic Glucagon by Octreotide May Reduce the Fasting and Postprandial Glucose Levels in a Diabetic Patient after Total Pancreatectomy

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Abstract:
A 52-year-old woman was treated with sensor augmented pump therapy after undergoing total pancreatectomy for a nonfunctional pancreatic neuroendocrine tumor (NET). The secretion of both endogenous insulin and pancreatic glucagon were completely depleted. Octreotide long acting repeatable (Oct-LAR) was administered for the treatment of liver metastasis of NET. Both the fasting and postprandial glucagon levels decreased immediately after the administration of Oct-LAR. In a continuous glucose monitoring analysis, episodes of nocturnal hypoglycemia was found to increase and an improvement of postprandial hyperglycemia was observed. This case suggests that octreotide may reduce the glucose level in both the fasting and postprandial states, in part by the suppression of extrapancreatic glucagon.

Key words: octreotide, glucagon, hypoglycemia, sensor augmented pump, total pancreatectomy

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Introduction

Octreotide (Oct) is a somatostatin analog that affects the somatostatin receptors (SSTR), with a strong affinity for SSTR2 and SSTR5 isoforms (1). Oct is widely used for the treatment of endocrine disorders, such as acromegaly and neuroendocrine tumors. Oct affects the glucose metabolism by controlling the secretion of insulin, glucagon, growth hormone (GH), and gastrointestinal hormones, as well as gastrointestinal motility (2). The effects of Oct on the glucose metabolism vary depending on the balance of suppression of each hormone, gastrointestinal motility, and postprandial glucose absorption, both hyperglycemia and hypoglycemia may develop after the administration of Oct (1, 3, 4).

Previous reports have shown both fasting and postprandial blood glucose levels during oral glucose tolerance test (OGTT) to decrease after the administration of somatostatin in patients with total pancreatectomy and whose suppressive effects of Oct on the endogenous pancreatic hormones can thus be ignored (5, 6). However, there is no previous report which evaluated the 24-hour glucose variability including nighttime using continuous glucose monitoring (CGM), thus describing the various hormones involved in the glucose metabolism before and after the administration of Oct in diabetic patients after total pancreatectomy.

We administered octreotide long acting repeatable (Oct-LAR) to a patient who had completely lost both insulin and pancreatic glucagon secretion following a total pancreatectomy, and investigated the long-term effects of Oct-LAR on 24-hour glucose variability including nocturnal glycemic control using a personal CGM and also investigated the changes in hormones related to the glucose metabolism. Our

Figure 1. Ethoxybenzyl-magnetic resonance imaging before the administration of Oct-LAR. The red arrow indicates a lower uptake region in the S7 region of the liver.

Table. General Examination Findings on Day 22.

[Urine]		UA	4 mg/dL
protein	(-)	Na	140 mEq/L
glucose	(-)	K	4.8 mEq/L
ketone	(-)	Cl	106 mEq/L
[Hematology]		Ca	10.1 mg/dL
WBC	9,400 /μL	AST	31 IU/L
Hb	12.4 g/dL	ALT	19 IU/L
RBC	460×10^4 /μL	γ-GTP	14 IU/L
Hct	39.8 %	T-Chol	177 mg/dL
Plt	42.7×10^4 /μL	TG	85 mg/dL
[Biochemistry]		HbA1c	7.9 %
TP	6.7 g/dL	BG	87 mg/dL
Alb	3.5 g/dL		
BUN	12 mg/dL		
Cr	0.64 mg/dL		

WBC: white blood cell, Hb: hemoglobin, RBC: red blood cell, Hct: hematocrit, Plt: platelet, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, UA: urea, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, T-Chol: total cholesterol, TG: triglyceride, HbA1c: hemoglobin A1c, BG: blood glucose

findings revealed that Oct-LAR decreases the extrapancreatic glucagon level, presumably resulting in an increased frequency of nocturnal hypoglycemic episodes and a decline in the postprandial glucose level.

Case Report

The patient was a 52-year-old woman. In January 2011, a total pancreatectomy was performed due to the presence of a pancreatic neuroendocrine tumor (PNET). The operative method of total pancreatectomy included distal gastrectomy, merger excisions of the duodenum, gallbladder, and spleen. The method of the intestinal tract reconstruction was the Billroth II method. Regarding the endocrinological findings, the insulin, glucagon, and gastrin levels at a fasting state before total pancreatectomy showed no abnormalities (data not shown) and immunohistochemical staining of the resected pancreas showed no hormone activity. As a result, the pancreas tumor was thus diagnosed to be a nonfunctional PNET. After the operation, continuous subcutaneous insulin infusion was introduced for the management of diabetes. Although HbA1c was maintained at a level ranging between 7% and 8%, asymptomatic hypoglycemia frequently occurred since 2015. To achieve a better management of diabetes, a sensor augmented pump (SAP) therapy was initiated in October 2015; consequently the frequency of severe hypoglycemia decreased. Basal and bolus dosages of insulin were 2.4 units/day and approximately 20 units/day by carbohydrate counting, respectively. In August 2016, a 6 mm tumor was found in the S7 region of the liver on magnetic resonance imaging (MRI) (Fig. 1). Since this tumor was suspected to be liver metastasis of the PNET, an intramuscular injection of Oct-LAR with a dosage of 30 mg was administered in September 2016 (Day 0). From Day 1, nausea and decreases in the blood glucose level were observed, resulting in the discontinuation of Oct-LAR after the first administration. The patient attempted to avoid hypoglycemia

by reducing the bolus insulin dose as calculated by carbohydrate counting. There were no changes in weight, appetite or the amount of meals before and after the administration of Oct-LAR. The weight and the amount of meals remained unchanged even during periods when the patient suffered from nausea. No abnormal values other than hypoalbuminemia were observed in the general examination findings on Day 22 (Table). Before undergoing total pancreatectomy, the serum albumin level was maintained at a level between 4.0 g/dL and 4.5 g/dL, but the level decreased to 3.0-3.5 g/dL after total pancreatectomy.

Result of CGM analysis

We evaluated her glucose variability using a personal CGM before and after the administration of Oct-LAR (Fig. 2). The sensor glucose (SG) values (mean±SD) in the CGM analysis of SAP were 143±53, 126±51, and 131±58 mg/dL at one month before the Oct-LAR administration and one and two months after the administration, respectively. The daily insulin doses were 23.0±2.1, 18.0±2.5, 19.7±2.6 units/day at the respective months. The basal insulin dose remained unchanged, and the bolus insulin dose was reduced throughout the observation period. During the daytime (from 6 AM to 11 PM), in spite of the decreased bolus insulin dose by the patient as mentioned above, the frequency of hyperglycemic episodes (SG >180 mg/dL) decreased (23.7, 15.9, and 19.9% at one month before the Oct-LAR administration and one and two months after the administration), suggesting that postprandial hyperglycemia may be improved by the administration of Oct-LAR. During the nighttime (from 11 PM to 6 AM), the SG values were 137±49, 115±48, and 123±55 mg/dL at one month before the Oct-LAR administration and one and two months after
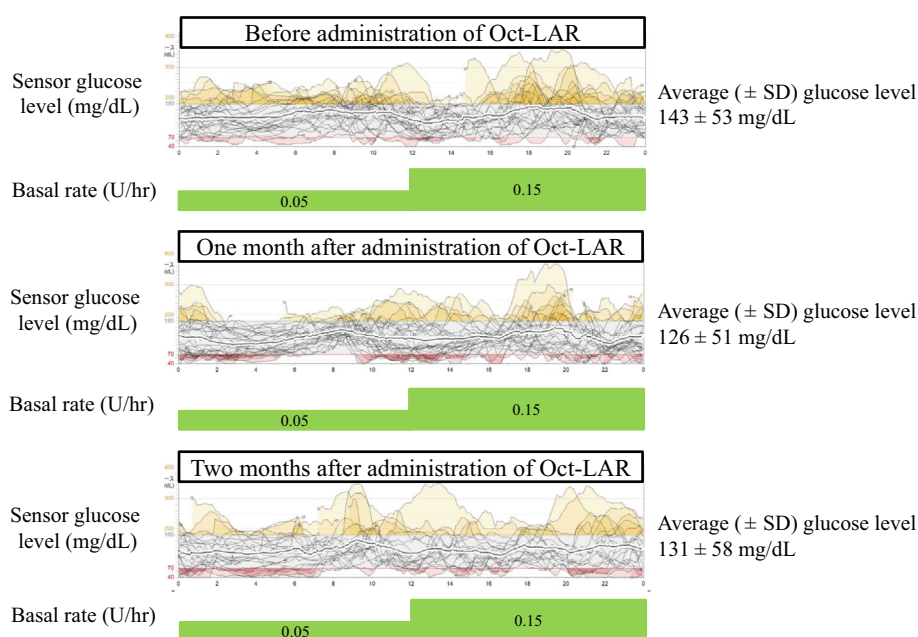
Figure 2. 24-hour glucose profiles before and after the administration of 30 mg octreotide LAR using a real-time continuous glucose monitoring system (Mini Med 620G® Medtronic). The upper, middle, and lower parts show the sensor glucose levels and the basal dose of insulin every each time from Day -31 to Day -1 (Before the administration of Oct-LAR), from Day 0 to Day 30 (one month after the administration of Oct-LAR), from Day 31 to Day 53 (two months after the administration of Oct-LAR). The black dotted lines indicate the average sensor glucose levels at each time point. The mean (±SD) of all sensor glucose levels are shown in the right part of the figure. The basal dose of insulin was 2.4 units/day during the observational period. Oct: octreotide, LAR: long-acting repeatable

the administration, resulting in an increased frequency of nocturnal hypoglycemic episodes (SG <70 mg/dL); 6.2, 20.9, and 17.5% at the respective months.
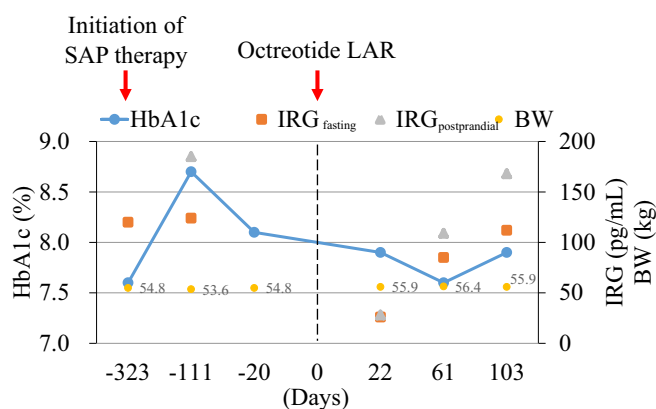
Clinical course including endocrinological findings

The clinical course including the endocrinological findings is shown in Fig. 3. During the observational period, the patient was only hospitalized for two weeks after the initiation of SAP therapy. As mentioned above, there were no changes in body weight before or after the Oct-LAR administration. Blood glucose, and endocrine hormones other than glucagon were measured in a fasting state. Glucagon was measured in both fasting and postprandial states. Postprandial glucagon was measured at 2 hours after breakfast. Before the administration of Oct-LAR, her endogenous insulin secretion had already been completely depleted. The HbA1c level gradually decreased after the administration of Oct-LAR. After administration of Oct-LAR, the fasting immunoreactive glucagon level decreased at one month, and then began to increase at two months, and later recovered to almost the same level as before the Oct-LAR administration. The postprandial glucagon level was decreased at one month and thereafter it recovered to the normal range at 3 months after the administration of Oct-LAR. Samples for a glucagon assay were collected in EDTA plus aprotinin tubes, then were immediately centrifuged and were stored at -80℃. Glucagon was measured by a double-antibody glucagon radioimmunoassay (Euro-Diagnostica AB, Malmö, Sweden)

with an analytical sensitivity of 16.3 pg/mL. The assay is standardized according to the World Health Organization International Standard 69/194. There was no interaction with the mainly structurally related peptides, including glucagon-like peptide (GLP)-1, GLP-2, glucose-dependent insulinotropic polypeptide (GIP), vasoactive intestinal peptide (VIP), and very low cross-reactivity with 19-29 as well as 22-29 human glucagons. No information on the cross-reactivity with oxyntomodulin and glicentin, which include glucagon arrangement, was available in the package insert.

IGF-1 was within the normal range (155 ng/mL) before total pancreatectomy in January 2011, but it decreased to approximately 60 ng/mL and remained unchanged after the operation. In addition, the gastrin level was shown to be low (25 pg/mL) at the second month after Oct-LAR administration, but it recovered to the normal range (80 pg/mL) at the third month after the administration. Neither the GH nor IGF-1 levels were affected by Oct-LAR. No abnormal findings were found in the pituitary MRI (image not shown). In addition, no adrenal insufficiency was observed before or after the administration of Oct-LAR.

At three months or later after the administration of Oct-LAR, the episodes of hypoglycemia gradually decreased, and the HbA1c level recovered to almost the same level as that observed before the administration of Oct-LAR. Oral multitargeted tyrosine kinase inhibitor (sunitinib) or transcatheter arterial chemoembolization are thus considered to be a second treatment for liver metastasis associated with

Figure 3. The clinical course before and after the administration of 30 mg of octreotide LAR. We defined the day on the administration of octreotide LAR as Day 0. LAR: long-acting repeatable. ACTH: adrenocorticotropic hormone, CPR: C-peptide, FPG: fasting plasma glucose, GH: growth hormone, IGF-1: insulin-like growth factor 1, IRG fasting: fasting immunoreactive glucagon, IRG postprandial: postprandial immunoreactive glucagon (2-hour after breakfast), SAP: sensor augmented pump, BW: body weight

Hormones	(Reference)	Day-323	Day-111	Day 22	Day 61	Day 103
FPG (mg/dL)	(73-109)	265	122	87	119	169
CPR (ng/mL)	(0.6-1.8)	<0.1	<0.1	<0.1	<0.1	<0.1
IRG fasting(pg/mL)	(70-174)	120	124	26	85	112
IRG postprandial(pg/mL)	(70-174)		185	28	109	168
GH (ng/mL)	(0.13-9.88)	2.19	3.03	3.35	3.58	1.38
IGF-1 (ng/mL)	(78-213)	60	61	68	62	63
ACTH (pg/mL)	(7.2-63.3)		7.2	9.5	8.6	9.4
Cortisol (μg/dL)	(6.4-21.0)		16.3	20.9	18	10.3
Gastrin (pg/mL)	(37-172)		55		25	80

PNET.

Discussion

We observed substantial and sustained decreases in both the fasting and postprandial glucose levels by Oct-LAR using CGM in a diabetic patient with total pancreatectomy. Regarding the effects of Oct-LAR on the endocrine function, Oct-LAR reduced both the fasting and postprandial glucagon levels without affecting the hypothalamic-pituitary-adrenal (HPA) or GH/IGF-1 axes. This case is unique in that the effects of Oct-LAR on the glucose metabolism were able to be determined without the need to consider its impact on the pancreatic hormones, including insulin and pancreatic glucagon because she had already undergone a total pancreatectomy. We believe that this is the first study to precisely determine the effects of Oct on 24-hour glucose variability, using CGM and to identify the various kinds of hormones related to the glucose metabolism in a patient with a total pancreatectomy.

Glucose variability after administration of Oct

Oct can widely affect the glucose metabolism by controlling insulin, counter-regulatory hormones such as glucagon, gastrointestinal motility, and postprandial glucose absorption (1, 2). Therefore, either hyperglycemia or hypoglycemia may develop after the administration of Oct. The frequency of hyperglycemia has been reported to be 7-15% and that of hypoglycemia was 2% as side effects of Oct (3). While previous studies suggest that hypoglycemia is a rare condition related to Oct, there is one case report of hypoglycemia after the administration of Oct-LAR to treat metastasis of insulinoma (4). In that case, both the glucagon and GH levels were shown to be more strongly suppressed than insulin with a long effective period for Oct-LAR. In a case series of 8 patients with acromegaly who were administered 30 mg of Oct-LAR, the mean period in which Oct reached the maximum blood concentration (Cmax) was 20 days, and the concentration was decreased to 50% of Cmax on the 56th day. In addition, the biological half-life of 30 mg of Oct-LAR was about 6 days (Novartis Pharma in-house document, unpublished data). Given these findings, it is possible that hypoglycemia by Oct may be associated with the suppression of counter-regulatory hormones including glucagon.

Association of Oct with the extrapancreatic glucagon and glucose levels in the fasting state

Extrapancreatic glucagon has recently attracted attention due to the possibility that it may be secreted from the gut, in which enteroendocrine L cells are found. It is reported that extrapancreatic glucagon may play a role in the pathophysiology of diabetes secondary to a total pancreatectomy (7), suggesting that the suppression of extrapancreatic glucagon could be associated with hypoglycemia. Indeed, a

recent case report of patients with a total pancreatectomy showed decreases in both the fasting and postprandial blood glucose and glucagon levels during OGTT after the subcutaneous injection of somatostatin (5); however, neither any detailed observation of glucose variability, including the nighttime use of CGM, nor measurements of other hormones, such as GH and IGF-1, have do far been reported in the literature. Our case with a total pancreatectomy showed a decrease in the glucose level during the nighttime in parallel with a reduction in the fasting glucagon level by the Oct-LAR, suggesting that Oct may suppress the extrapancreatic glucagon level, thus leading to an increase in nocturnal hypoglycemia. When considering the effective period of Oct on the endocrine function, we found a reduction in the fasting glucagon concentration on Days 22 and 61. At the second month after the administration of Oct-LAR, the fasting blood glucose level and insulin dose were lower than those before the administration of Oct-LAR (Fig. 2). Since the effects of Oct-LAR persist for 2 months after the administration (refer to data of Novartis as described above), it was considered in the present case that the reduced fasting glucagon concentration on Days 22 and 61 were thus influenced primarily by Oct-LAR. The prolonged effects of Oct-LAR may be supported by the fact that serum gastrin concentration as well as the glucagon level both declined at the second month.

Suppression of extrapancreatic glucagon by Oct may reduce the postprandial glucose level

In terms of the relationship between the extrapancreatic glucagon and postprandial blood glucose levels, it has recently been demonstrated that endogenous glucagon secretion during OGTT increased in patients who have undergone total pancreatectomy, suggesting that postprandial hyperglycemia may develop, in part, due to an increased extrapancreatic glucagon level in post-pancreatectomy patients (7). In our case, CGM revealed the presence of uncontrolled postprandial hyperglycemia before the administration of Oct-LAR which is consistent with the findings of a previous report (7). As the report above mentioned (5), Oct-LAR robustly reduced the postprandial glucose levels in parallel with the reduction in postprandial glucagon in spite of a reduction in the insulin dosage in this patient. In addition, there were no changes in weight, appetite, the amount of meals, or the subjective gastrointestinal motility, all of which could affect the postprandial blood glucose level, bolus dose of insulin and also glucagon concentration, before and after Oct-LAR administration. These findings suggest that postprandial extrapancreatic glucagon may be suppressed by the Oct-LAR, thus leading to an improvement of postprandial hyperglycemia. In contrast to the findings in our case, a previous report demonstrated that the administration of intravenous somatostatin improved glucose tolerance without any clear suppression of glucagon in diabetic patients after total pancreatectomy (6). This discrepancy might be based on the route of the administration of somatostatin

and a non-specific assay available at the time of the study (5).

Impact of Oct on the other counter-regulatory hormones

Oct, which is used for the treatment of acromegaly, generally suppresses the GH/IGF-1 levels (3, 4). However, the GH/IGF-1 levels were not affected by Oct-LAR and the IGF-1 level remained in the normal range in our case. MRI showed no abnormality in the pituitary gland and neither a worsening glycemic control nor liver dysfunction were observed. Thus, it is possible that the low IGF-1 level observed in this case might have been caused by malnutrition due to malabsorption after total pancreatectomy. It is also theoretically possible in this case that a somatostatin analog could not suppress the GH/IGF-1 levels due to the low or lack of SSTR2 expression in the pituitary gland as reported in the cases of acromegaly (8). Therefore, the expression profile of the SSTR subtypes in the normal pituitary might influence this mechanism.

Oct can also be used for the treatment of Cushing disease, but Oct has not been reported to induce adrenal insufficiency. Actually, in our case, adrenal insufficiency was not observed before or after the administration of Oct-LAR.

Other factors related to glucose metabolism in this case

After total pancreatectomy, the gastrointestinal anatomy is dramatically changed, including the removal of the pyloric sphincter and the duodenum and the reconstruction of the gastrointestinal tract. The above mentioned research paper (7) reported that after the ingestion of a meal, nutrients are rerouted and delivered directly from the stomach to the jejunum, where L cells are more abundant, possibly explaining the increased GLP-1 and oxyntomodulin concentrations observed in the totally pancreatectomized patients after OGTT. Thus, GLP-1 and oxyntomodulin are important factors when discussing the glucose metabolism in patients with total pancreatectomy. Unfortunately, these hormone levels were not measured in our case. In our case, it is also necessary to address whether the liver metastasis of PNET could induce hormone-production and thereby affect the endocrine function. As an increase in the hormone level, including insulin, glucagon, and gastrin, was not observed after the diagnosis of liver metastasis, we diagnosed the liver tumor to be non-functional liver metastasis from PNET.

Limitations in this report

Some of the limitations associated with this case report include that impact of Oct on the gastrointestinal motility and the fact changes in postprandial glucose absorption could not be completely ruled out although there were no changes in the weight, appetite, amount of meals, or subjective gastrointestinal motility, all of which could affect the postprandial blood glucose level, bolus dose of insulin, before and after the administration of Oct-LAR. A second

limitation is the problem of the glucagon assays used in our case. The specificity of glucagon immunoassays, which rely on C-terminal or side-viewing antibodies toward the various circulating glucagon-like peptides, including oxyntomodulin and glicentin, remains unclear for many of the currently applied glucagon assays (9).

However, the more recently developed glucagon assays, sandwich ELISA targeting the N- and C- terminal regions of glucagon simultaneously, can eliminate those specificity problems (10), and therefore such new assays should be used in the future.

Conclusion

We herein reported the case of a diabetic patient with total pancreatectomy who showed a decrease in both the fasting and postprandial glucose levels according to the findings of a personal CGM after the administration of Oct-LAR in parallel with a reduction of both the fasting and postprandial glucagon levels. This case suggests that extrapancreatic glucagon may influence both fasting and postprandial glycemic control and octreotide could reduce the glucose levels in both the fasting and postprandial states, in part, by the suppression of extrapancreatic glucagon.

The authors state that they have no Conflict of Interest (COI).

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