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CLINICAL REVIEW

The current managements of pancreatic diabetes in Japan

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Abstract Pancreatic diabetes is secondary diabetes followed by progressions of pancreatic exocrine diseases, such as chronic pancreatitis, pancreatic neoplasm and post-pancreatectomy. Because of destruction and reduction of the pancreatic endocrine and exocrine functional compartments, patients with pancreatic diabetes frequently show malnutrition from maldigestion and malabsorption by insufficiencies in pancreatic digestive enzymes, and show unstable glycemic control and prolonged hypoglycemia by insufficiencies in synthesis and secretion of insulin and glucagon. Epidemiological studies have suggested that the incidence and development of pancreatic diabetes in patients with chronic pancreatitis (CP) depends on several risk factors, such as alcohol intake, the presence of pancreatic calcification and the long-term duration of CP. The clinical management of pancreatic diabetes is divided into two parts: one is the supplementation of pancreatic digestive enzymes and the other is the achievement of appropriate glycemic control. The appropriate and sufficient pancreatic exocrine replacement therapy is important for the maintenance of better nutrient conditions for patients with pancreatic diabetes. Furthermore, the intensive insulin therapy combined with short- or ultra-short-acting insulin and long-acting insulin glargine can be achieved for stable glycemic control and reduction of severe frequent hypoglycemia in patients with pancreatic diabetes. These current advanced management techniques against insufficiencies of pancreatic exocrine endocrine functions are beneficial for improving and maintaining the quality of life in patients with pancreatic diabetes.

Keywords Pancreatic diabetes · Chronic pancreatitis · Pancreatic digestive enzymes · Insulin · Glargine

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Introduction

Pancreatic diabetes is understood to be a secondary diabetes that appears and progresses with a primary pancreatic exocrine disease, such as acute and chronic pancreatitis, autoimmune pancreatitis, pancreatic neoplasm and post-pancreatectomy [1–4]. The report of the Committee of the Japan Diabetes Society concerning the classification and diagnosis of diabetes mellitus etiologically classified pancreatic diabetes into the subgroup (1) "exocrine pancreatic diseases—pancreatitis, trauma/pancreatectomy, neoplasm, hemochromatosis, and others" in the category 3B "diabetes associated with other pathologic conditions or diseases" [5]. Pancreatic diabetes is strictly defined as a diabetes that is newly diagnosed after the onset of a pancreatic exocrine disease or during post-pancreatectomy progress. However, in addition to the above classification, the aggravation of primary diabetes mellitus or impaired glucose tolerance followed by progressions of pancreatic exocrine diseases can be also generally and clinically regarded as pancreatic diabetes.

In the present clinical review, we focus on the pathophysiology, epidemiology and current management methods of exocrine and endocrine disorders in patients with pancreatic diabetes with reference to our own data and recent literature.

Pathophysiology of pancreatic diabetes

The common symptoms of pancreatic diabetes do not differ from other types of diabetes: polyuria, polydipsia and polyphagia. However, the pathophysiology of pancreatic diabetes (Fig. 1) is further complicated in comparison with that of primary diabetes. There is anatomically a close relationship between the exocrine and endocrine cells of the pancreas. Because of this anatomical relationship, the onset and development of pancreatic diabetes are caused by the progression of the primary pancreatic exocrine diseases [2, 6]. In morphological studies of chronic pancreatitis (CP), the impairment of pancreatic endocrine function is considered to be parallel with a destruction and spread of fibrosis inside the islet cells [3, 4, 7–9]. Furthermore, in our institutional data concerning the relationship between pancreatic exocrine function and glucose tolerance, the prevalence of diabetes was also parallel with the aggravation of pancreatic exocrine insufficiency (Fig. 2). In addition, parenchyma destruction and peri-insular fibrosis cause alterations of local blood flow and glucose diffusion in islet cells [1, 3, 4, 10]. Moreover, the surgical reduction of functional compartments in exocrine and endocrine pancreas is the cause of pancreatic diabetes after a pancreatectomy. Therefore, the patients with pancreatic diabetes show lack or insufficiencies in synthesis and secretion of not only insulin from B-cells, but also glucagon from A-cells by destruction and reduction of the islet cells. As a result, the management of glycemic control is thought to be considerably more difficult in patients with pancreatic diabetes because of unstable glycemic control and prolonged hypoglycemia. On the other hand, pancreatic diabetes is frequently complicated with malnutrition from maldigestion and malabsorption by lack or insufficiencies in pancreatic digestive enzymes due to destruction and reduction of the pancreatic exocrine cells. Moreover, diabetes with CP is considered to be the result not only of impaired production of endogenous insulin, but also of insulin resistance. These pathological conditions also contribute to the poor prognosis in patients with pancreatic diabetes [2, 4, 11].

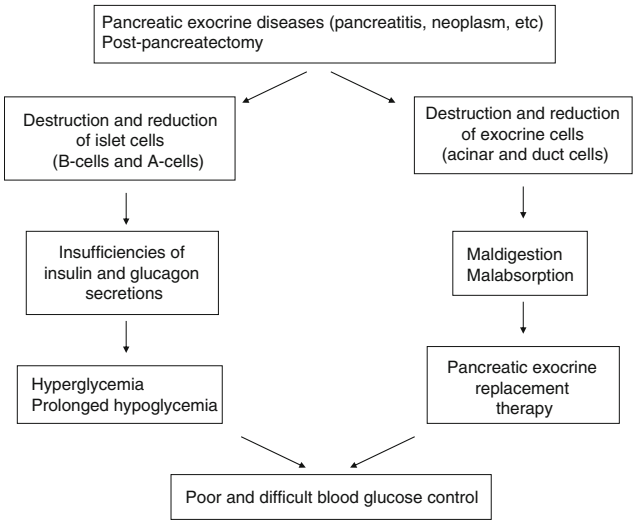

Fig. 1 The scheme of the pathophysiology of pancreatic diabetes

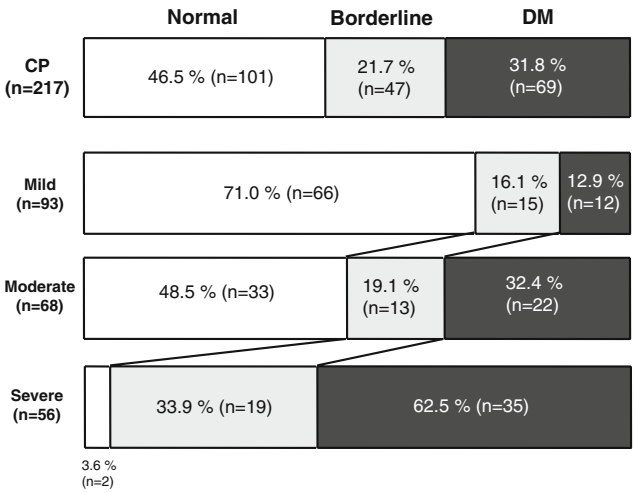

Fig. 2 Correlation between pancreatic exocrine function and glucose tolerance in patients with chronic pancreatitis (*CP*) in our hospital. A total of 217 patients with CP were divided into three groups: *Mild*, *Moderate* and *Severe* indicate mildly, moderately and severely abnormal groups of pancreatic exocrine function, respectively. *Normal* normal glucose tolerance, *boderline* borderline type glucose tolerance, *DM* diabetes mellitus

Epidemiology of pancreatic diabetes

Diabetes has been known to occur as a complication of various pancreatic exocrine diseases. In patients with CP, the incidence of diabetes depends on several factors, such as etiology, the presence or absence of pancreatic calcification, and the duration of the disease [3, 12, 13]. With respect to patients with pancreatic calcification, it is reported that approximately 60–70% of such patients have diabetes [2, 7]. However, the number of patients with pancreatic diabetes caused by pancreatic exocrine diseases is reported to be less than 1% of all patients with diabetes [2, 3]. On the other hand, in pancreatic surgery, the incidence of postoperative diabetes mellitus after Whipple's resection ranges from 20 to 50% [14, 15].

Recently, Ito et al. [4] published a circumstantial report on the long-term prognosis of pancreatic diabetes in patients with CP. This report shows the cumulative rate of diabetes and risk factors for diabetes in patients with CP over an 8-year follow-up period based on the data of a follow-up survey of CP by the Research Committee of Intractable Diseases of the Pancreas in Japan. As shown in

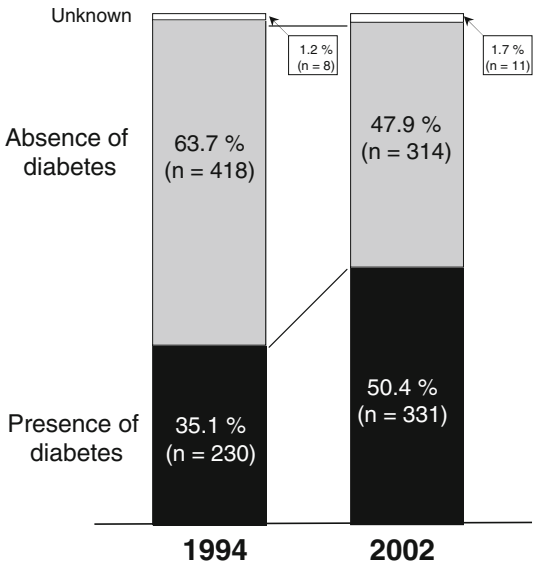

Fig. 3 Incidence of diabetes mellitus in 1994 and 2002 in 656 patients with chronic pancreatitis (CP) from data of the follow-up national survey of patients with CP by the Research Committee of Intractable Diseases of the Pancreas in Japan

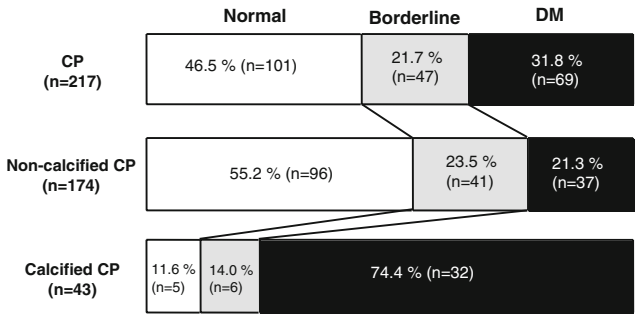

Fig. 4 Relationship between pancreatic calcification and glucose tolerance in our hospital. A total of 217 patients with CP were divided into two groups, calcified CP and non-calcified CP groups, respectively. *Normal* normal glucose tolerance, *boderline* borderline type glucose tolerance, *DM* diabetes mellitus

Fig. 3, in 1994, 35.1% of patients with CP were diagnosed with pancreatic diabetes. In 2002, however, the number of patients with pancreatic diabetes increased to 50.4%. In addition, among the CP patients with normal glucose tolerance in 1994, 28.9% were newly diagnosed with diabetes in 2002. Conclusively, in CP patients, continuous alcohol intake was the most common etiological factor that induced overt diabetes. Similarly, the other papers reported that pancreatic endocrine function is more disturbed in alcoholic CP than in nonalcoholic CP [2, 3], and that the incidence of overt diabetes was only 36.1% in nonalcoholic CP, compared with 53.7% in alcoholic CP [2]. Taken together, these reports suggested that alcohol intake aggravated CP and increased the risk for the development of diabetes in CP.

Furthermore, it has been reported that the secretion of both insulin and glucagon is more strongly disturbed in calcified CP than in noncalcified CP [16]. Bank et al. [13] reported pancreatic diabetes observed in 70% of patients with calcified CP, whereas the development of pancreatic diabetes with no calcified CP is only 30%. Additionally, our institutional data (Fig. 4) also showed that CP with impaired glucose tolerance occurred in 116 (53.5%) of all 217 cases of CP; 69 (31.8%) were complicated with diabetes and 47 (21.7%) with borderline type glucose tolerance. Pancreatic calcifications existed in 43 (19.8%) of 217 cases of CP. Patients with pancreatic diabetes were more frequently found in the calcified CP group (74.4%) than in the non-calcified group (21.3%). Meanwhile, Malka et al. [17] reported a more than three-fold increase in the risk of diabetes after the onset of pancreatic calcification in a follow-up study of CP over a mean period of 7.7 years. However, Ito et al. [4] demonstrated that the risk of diabetes in Japan increased approximately 1.32-fold after the onset of pancreatic calcification over an 8-year period. These reports suggested that it might be controversial whether the risk of development of diabetes in CP is closely related to pancreatic stones or not.

The management of pancreatic exocrine insufficiency in patients with pancreatic diabetes

Pancreatic diabetes is frequently complicated with a lack or insufficiencies in the pancreatic enzymes lipase, trypsin and amylase, because of destruction and reduction of pancreatic exocrine cells due to pancreatic exocrine diseases, such as compensated CP, pancreatic neoplasm, post-pancreatectomy complications, and so on. Consequently, patients with pancreatic diabetes suffer from excessive malnutrition, such as hypoglycemia, hypoproteinemia, hypoalbuminemia, hypocholesteremia and hypotryglicemia, caused by insufficiencies in digestion and absorption of fat, protein and carbohydrates. This condition is one of the reasons for the unstable glycemic control and poor prognosis in patients with pancreatic diabetes. Therefore, patients with pancreatic diabetes need to receive sufficient pancreatic exocrine replacement therapy for the supplementation of pancreatic enzymes.

In order to reveal the importance of this pancreatic exocrine replacement therapy for patients with pancreatic diabetes complicated pancreatic exocrine insufficiency, an interesting and educational case in our hospital is presented (Fig. 5). The case concerned a 66-year-old Japanese male with frequent hypoglycemic attacks and malnutrition. His past medical history showed that he had undergone a total pancreatectomy for pancreatic body cancer 4 years before. After the total pancreatectomy, he had started insulin

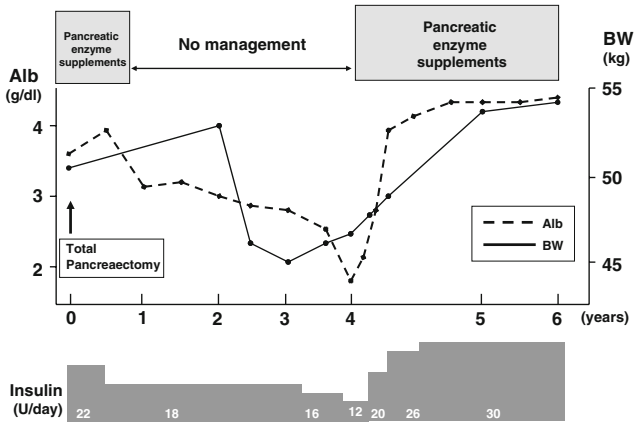

Fig. 5 Clinical course of a patient with pancreatic diabetes complicated with severe malnutrition. A 66-year-old Japanese male had undergone pancreatic exocrine replacement therapy (Berizym® 20 g/day) for 1 year just after total pancreatectomy. However, he had not received management for pancreatic exocrine insufficiency of long-term duration (as shown by *No management*), and this condition induced the decrease of body weight (*BW*) and serum albumin (*Alb*). After restarting the pancreatic exocrine replacement therapy (Pancreatin® 3 g/day plus Berizym® 5.4 g/day), body weight and serum albumin level immediately improved with the increase of the necessary daily dose of insulin

treatment against overt pancreatic diabetes. Upon admission to our hospital, the medication was only a low daily dose of insulin and ursodesoxycholic acid. Physical examination revealed emaciation and pitting edema at the lower extremities. Laboratory data showed steatorrhea, malnutrition, anemia, hypoproteinemia, hypoalbuminemia hypoglycemia, hypocholesterolemia and liver dysfunction. The imaging examinations demonstrated only pleural effusion and ascites, but no recurrent evidence of the pancreatic cancer. From the circumstantial investigation of the clinical course, it was thought that the lack of management for pancreatic exocrine insufficiency of long-term duration caused the malnutrition in this patient. In fact, this patient had not been prescribed any pancreatic exocrine supplements during the preceding 3 years.

Consequently, malnutrition and hypoglycemia in this patient were diagnosed as the result of maldigestion and malabsorption induced by the long-term lack of pancreatic exocrine replacement therapy. After medication with appropriate and sufficient pancreatic exocrine supplements, the clinical symptoms, such as emaciation, edema steatorrhea and malnutrition, gradually improved. Moreover, the necessary daily dose of insulin for glycemic control was increased after an improvement in the condition of malnutrition.

As presented above, it is possible to confirm the importance of this pancreatic exocrine replacement therapy in patients with pancreatic diabetes. However, it is difficult to determine the necessary and sufficient dose of pancreatic exocrine supplements for individual patients. In fact, the individual doses of supplement have to be determined in reference to individual pancreatic exocrine function (BT-PABA test, etc.) and clinical findings, for example, body weight, steatorrhea, anemia, leukocytopenia, liver function and serum profiles (protein, albumin, glucose, cholesterol, triglyceride, etc.).

Efficacy of intensive insulin therapy with insulin glargine in pancreatic diabetic patients

Insulin profiles in healthy individuals are characterized by relatively constant basal secretion with postprandial peaks. On the other hand, patients with pancreatic diabetes show the lack or defect in both basal and postprandial insulin secretion. To mimic physiological insulin secretion and achieve appropriate glycemic control in the patients with pancreatic diabetes, we should recognize that sufficient basal insulin supplementation is important. The ideal basal insulin preparations are considered to provide a constant and reliable 24-h basal insulin supply. The currently available intermediate-acting human NPH insulin is frequently used in insulin regimens. However, NPH insulin concentrations rise to a peak after 4–6 h and then steadily decline. In addition, NPH insulin treatment often results in nocturnal hypoglycemia events because inappropriate plasma insulin peaks occur at night [18, 19]. However, a new long-acting human insulin analog, insulin glargine (Lantus®, sanofi aventis, France), has characteristics of no pronounced peak and a 24-h time-action profile [20–23], and may be ideally suited to the constant basal insulin supplementation in patients with pancreatic diabetes.

Therefore, we examined the efficacy of the intensive insulin therapy in combination with long-acting insulin glargine as a basal requirement and pre-meal short- or ultra-short-acting insulin for postprandial hyperglycemia to mimic physiological insulin secretion and achieve glycemic control in patients with pancreatic diabetes (Fig 6).

A total of 15 patients with pancreatic diabetes in our hospital were evaluated in this study. The clinical profiles of patients are shown in Tables 1 and 2. There were 10 male and 5 female patients, and the average age was 58.1 ± 9.5 years old. The primary pancreatic diseases in these patients were three cases of CP, six cases of chronic calcifying pancreatitis, one case of autoimmune pancreatitis, three cases of pancreatic ductal carcinoma and two cases of intraductal papillary mucinous neoplasm of the pancreas. Additionally, the seven patients had undergone various degrees of pancreatectomy: total pancreatectomy, pylorus-preserved pancreatico-duodenectomy (PpPD), distal pancreatectomy and pancreatico-jejunostomy. All patients had to change to the intensive insulin therapy with

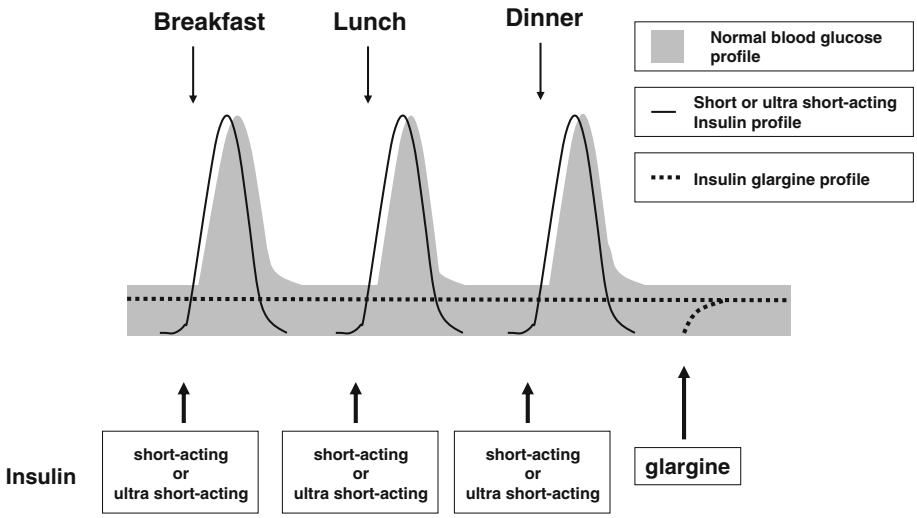

Fig. 6 The intensive insulin therapy in combination with pre-meal short- or ultra-short-acting insulin for postprandial hyperglycemia and a long-acting insulin glargine for basal requirement is a mimic of physiological insulin secretion and achieves better glycemic control in patients with pancreatic diabetes

Table 1 Clinical characteristics of pancreatic diabetic patients treated with intensive insulin therapy with glargine in our hospital

Patient (cases)	15
Male/female (cases)	10/5
Age (mean years)	58.1 ± 9.5
Primary pancreatic exocrine diseases (cases)	
Chronic pancreatitis	3
Chronic calcified pancreatitis	6
Autoimmune pancreatitis	1
Pancreatic ductal carcinoma	3
IPMC	2
Pancreatic surgery (cases)	
Total pancreatectomy	3
PpPD	2
Distal pancreatectomy	2
Pancreatico-jejunostomy	2
No surgery	6

IPMC intraductal papillary mucinous neoplasm of the pancreas, *PpPD* pylorus-preserved pancreatico-duodenectomy

glargine because they showed unstable control of blood glucose levels at baseline therapy.

Eleven cases showed hyperglycemia and a high value of hemoglobin A1c (HbA1c), and four cases showed frequent hypoglycemia. The baseline regimens of insulin therapy were a total of eight cases of short- (six cases) or ultra-short-acting (two cases) insulin before meals with once daily NPH insulin, two cases of only short- or ultra-short-acting insulin, two cases of short-acting insulin with once daily premixed insulin and two cases of oral hypoglycemic agents (sulfonylurea plus alpha-glucosidase inhibitor).

After the induction of the intensive insulin regimen with glargine, all of the hyperglycemic patients indicated reductions of HbA1c (Fig. 7a). The reduction rates of HbA1c after 6 months and 1 year were 15.6 and 17.6%, respectively, compared to the baseline therapies (Fig. 7b). Furthermore, the long-term outcome of the intensive insulin regimen with glargine produced a stable control of blood glucose and HbA1c levels for 3 years (Fig. 7c).

A representative case of hyperglycemia involved a 58-year-old Japanese female who had undergone a PpPD for a duodenal papillary carcinoma. Two years after the operation, her postoperative pancreas showed atrophic and decompensated pancreatic function. Because the exocrine and endocrine (insulin and glucagon secretion) pancreatic function was decreased, she had to start insulin therapy against overt pancreatic diabetes. The initial regimen of insulin therapy in this patient was short-acting insulin before meals with once daily NPH insulin. After 18 months from beginning the insulin therapy, the control of blood glucose levels became worse, so the insulin regimen was changed from NPH insulin to glargine. After the change to a regimen with insulin glargine, the control of blood glucose levels became better and stabilized (Fig. 8).

Next, we examined the efficacy of insulin glargine in the frequent hypoglycemic cases of patients with pancreatic diabetes. The frequency of hypoglycemia successfully declined from 8.2 times per week down to 2.1 times per week on average after intensive insulin therapy with insulin glargine. Furthermore, the intensive insulin therapy with insulin glargine reduced the amount of insulin from 18.4 units per day to 12.5 units per day (Fig. 9).

Another representative case of hypoglycemia involved a 67-year-old Japanese male who had suffered from chronic calcifying pancreatitis and insufficiency of exocrine and endocrine pancreatic functions. The patient received insulin therapy for treatment in pancreatic diabetes. The initial regimen of insulin therapy for this patient was composed of short-acting insulin before meals with once daily NPH insulin. This initial regimen caused instability in the control of blood glucose levels and frequent hypoglycemia

Table 2 The lists of pancreatic diabetic patients treated with intensive insulin therapy with glargine in our hospital

No.	Sex	Age (years)	Pancreatic disease	Surgery	Baseline treatment	Baseline HbA1c (%)
1	F	60	IPMC	TP	Rx3 + N	8.1
2	F	47	PK	TP	Rx3 + N	9.4
3	F	57	CP	None	Rx3 + N	10.2
4	M	53	CP	DP	SU + α-GI	14.6
5	M	67	CCP	P-J	R + 50R	5.7
6	F	56	Vater Ca, CP	PpPD	Rx3 + N	10.4
7	M	68	PK	PpPD	Rx3	5.3
8	M	66	IPMC	TP	Rx3 + N	7.9
9	M	68	AIP	None	Rx3 + N	10.3
10	M	67	CCP	None	Rx2 + 50R	6.9
11	F	57	CCP	None	Rx3 + N	10.2
12	M	61	PK	None	Qx3	8.1
13	M	44	CCP	DP	SU + α-GI	9.8
14	M	37	CCP	P-J	Qx3 + N	8.8
15	M	63	CCP	None	Nx2 → Qx3 + N	11.0

CP chronic pancreatitis, *CCP* chronic calcifying pancreatitis, *PK* pancreatic ductal carcinoma, *AIP* autoimmune pancreatitis, *IPMC* intraductal papillary mucinous neoplasm of the pancreas, *TP* total pancreatectomy, *DP* distal pancreatectomy, *PpPD* pylorus-preserved pancreatico-duodenectomy, *P-J* pancreatico-jejunostomy, *R* short acting insulin, *N* NPH insulin, *Q* ultra-short acting insulin, *SU* sulfonylurea, *α-GI* α-glucosidase inhibitor

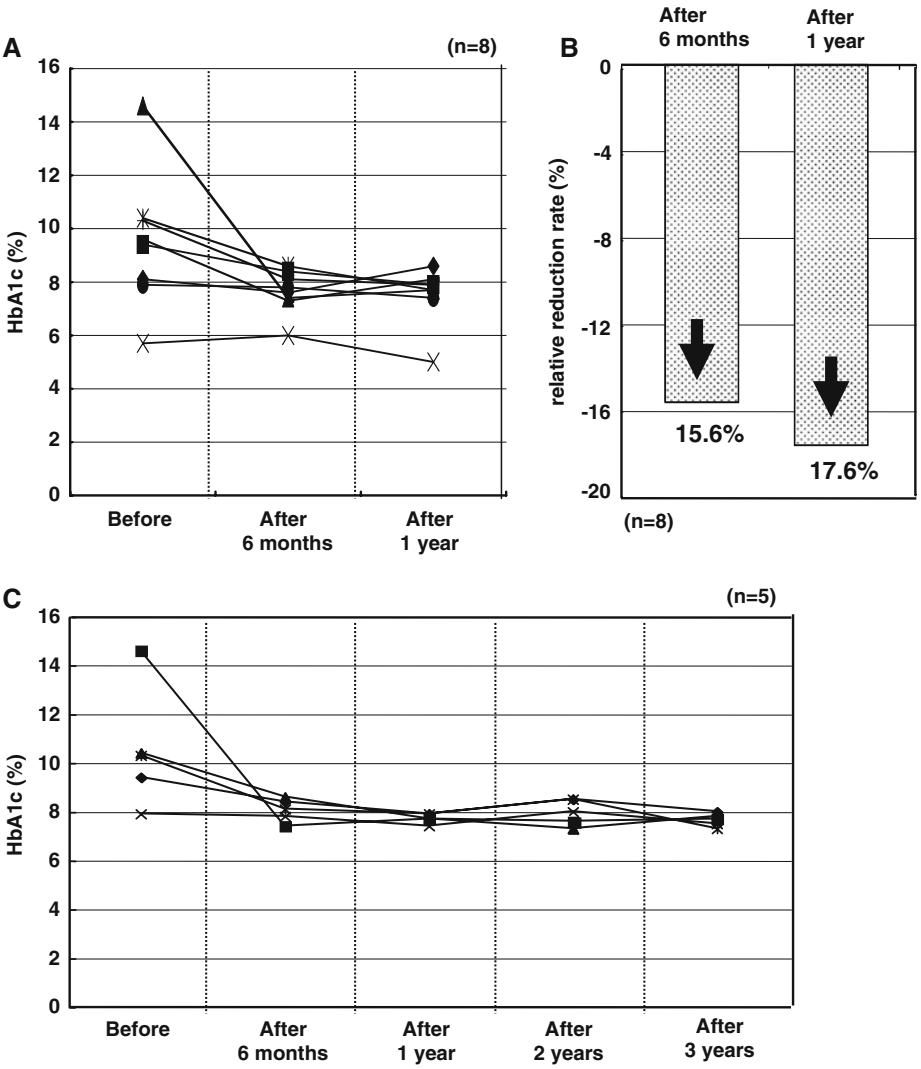

Fig. 7 Efficacy of the intensive insulin regimen with glargine in patients with pancreatic diabetes. **a** In all cases for eight patients ($n = 8$) with pancreatic diabetes induced by the intensive insulin regimen with glargine indicated reductions of HbA1c. **b** The averages of reduction rates of HbA1c after 6 months and 1 year were 15.6 and 17.6%, respectively, compared to the baseline therapies in cases of eight patients ($n = 8$). **c** The long-term effects of the intensive insulin regimen with glargine achieved the stable control of blood glucose and HbA1c levels over 3 years in five patients ($n = 5$)

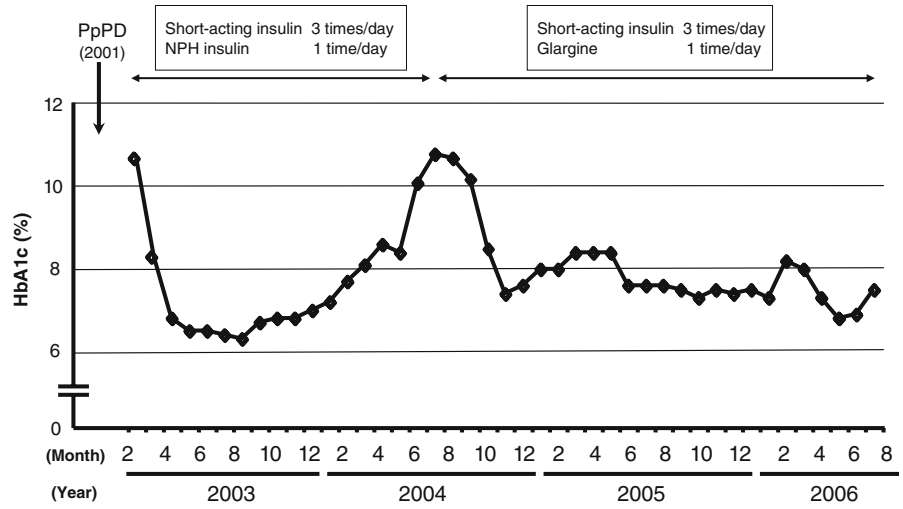

Fig. 8 The clinical profile of glycemic control in a pancreatic diabetic patient with the intensive insulin regimen using glargine. A 58-year-old Japanese female had undergone a pylorus-preserved pancreatico-duodenectomy (*PpPD*) for a duodenal papillary carcinoma. Two years after PpPD, she started the insulin therapy (the initial regimen was short-acting insulin before meals with once daily NPH insulin) for overt pancreatic diabetes. After 18 months, the insulin regimen was changed from NPH insulin to glargine, because the control of blood glucose levels became worse (increase of HbA1c levels). After the change to glargine, the control of blood glucose levels improved and stabilized

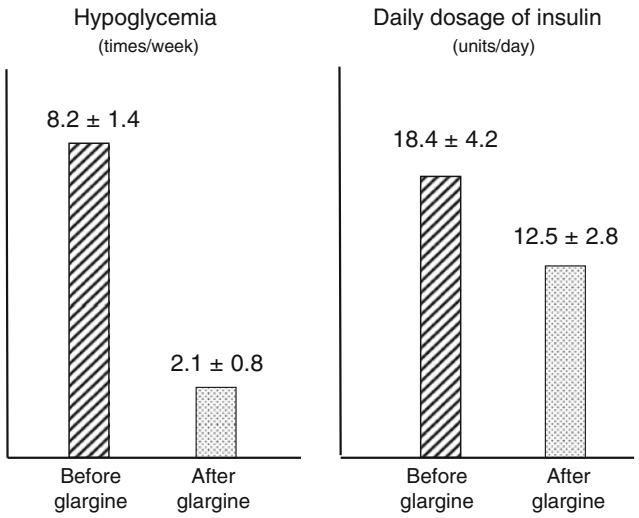

Fig. 9 Efficacy of an intensive insulin regimen with glargine for frequent hypoglycemic cases in the patients with pancreatic diabetes. After the induction of the intensive insulin therapy with glargine, the frequency of hypoglycemia (*Hypoglycemia*) declined from 8.2 times per week to 2.1 times per week on average. Also, the intensive insulin therapy with glargine reduced the amount of insulin from 18.4 units per day to 12.5 units per day (daily dosage of insulin)

(ten times per a week). After changing the insulin regimen to ultra-short-acting insulin before meals with once-daily insulin glargine, hypoglycemia dramatically disappeared and the control of blood glucose levels was improved and stabilized in this patient.

In conclusion, intensive insulin therapy using insulin glargine is effective and useful for achieving better glycemic control and reduction of severe frequent hypoglycemia in patients with pancreatic diabetes.

Future directions

Pancreatic diabetes in patients with pancreatic exocrine diseases and post-pancreatectomy was characterized by unique clinical findings, such as significant malnutrition due to pancreatic exocrine insufficiency and an unstable control of blood glucose levels due to defects in multiple pancreatic glucose-regulatory hormones. The management of patients with pancreatic exocrine insufficiency, leading to improved digestion and absorption, required high doses of oral pancreatic enzyme supplements. However, in Japan, popular pancreatic enzyme supplements are inadequate, so patients have to take a high dose of supplements. Presently, the clinical trial of a high-potency enteric-coated microsphere preparation of porcine pancreatin (Solvay Pharma, Germany) in patients with pancreatic steatorrhea is in progress in Japan. In the near future, this preparation will be available for treatment and lead to good compliance in treating patients.

On the other hand, intensive insulin therapy with the long-acting basal insulin, glargine, is effective in glycemic control in patients with pancreatic diabetes. Recently, in addition to glargine, a new long-acting insulin analog, detemir (Levemir®, Novo Nordisk Pharma, Denmark), can be utilized in Japan and is expected to be useful in the managements of diabetic patients [24].

The increase of available treatment options is beneficial in improving and maintaining the quality of life in patients with pancreatic diabetes.

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