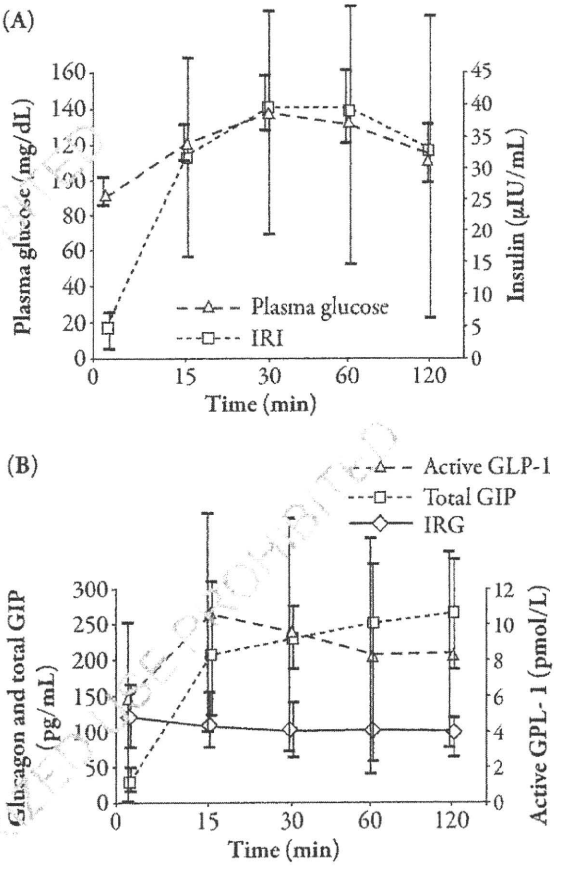
Table 1. Clinical characteristics of 30 Japanese subjects with normal glucose tolerance.

	Week 0
Age, years	24.7±2.3
Gender, *n*	
Men	20
Women	10
Height, m	1.67±0.08
Body weight, kg	60.8±11.6
BMI, kg/m^2	21.8±3.5
Waist circumference, cm	76.2±11.6
HOMA-R	1.1±0.8
HOMA-β, %	68.3±45.6
Insulinogenic index	0.8±0.5
Family history of diabetes* (presence [+]/absence [−]), *n*	[+]13/[−]17
Of the 13 subjects with the presence of a family history:	
Subjects with first-degree relative, *n*	4
Subjects with second-degree relative, *n*	8
Subjects with third-degree relative, *n*	1

*Defined as subjects with a first- to third-degree relative with T2DM.
BMI=body mass index; HOMA-R=homeostasis model assessment for insulin resistance; HOMA-β=homeostasis model assessment for insulin secretion; T2DM=type 2 diabetes mellitus.

Figure 1. Results of oral glucose tolerance test in (**A**) plasma glucose and insulin (**B**) glucagon, total glucose-dependent insulinotropic peptide, and active glucagon-like peptide-1. Data are calculated as mean±SD. GIP=glucose-dependent insulinotropic peptide; GLP-1=glucagon-like peptide-1; IRG=immunoreactive glucagon; IRI=immunoreactive insulin.



P<0.01) and Δ IRG between 0 and 30 minutes (*R*=–0.40, *P*<0.05), as shown in Figure 3A and B, respectively.

Body weight was correlated with HOMA-R (*R*=0.50, *P*<0.01), II (*R*=0.40, *P*<0.05), and HOMA-β (*R*=0.37, *P*<0.05). BMI was correlated with HOMA-R (*R*=0.50, *P*<0.01) and HOMA-β (*R*=0.37, *P*<0.05), and waist circumference was correlated with HOMA-R (*R*=0.44, *P*<0.05) and HOMA-β (*R*=0.39, *P*<0.05). However, body weight, BMI, waist circumference, height, and gender were not related to the secretory response of total GIP (Δ GIP between 0 minutes and 15, 30, 60, 120 minutes, and GIP-$AUC_{0\text{-}120}$), active GLP-1 (Δ active GLP-1 between 0 minutes and 15, 30, 60, 120 minutes, and active GLP-1-$AUC_{0\text{-}120}$), and IRG (Δ IRG between 0 minutes and 15, 30, 60, 120 minutes, and IRG-$AUC_{0\text{-}120}$).

The presence or absence of T2DM family history was not correlated with BMI, waist circumference, HOMA-R, II, HOMA-β, and IRI-$AUC_{0\text{-}120}$ as shown in Table 2. It was not correlated with the secretory response of active GLP-1 (Δ active GLP-1 between 0 minutes and 15, 30, 60, 120 minutes, and active GLP-1-$AUC_{0\text{-}120}$) and IRG (Δ IRG between 0 minutes and 15, 30, 60, 120 minutes, and IRG-

Figure 2. (**A**) Correlation between total glucose-dependent insulinotropic polypeptide (GIP) area under the curve $(AUC)_{0\text{-}120}$ and immunoreactive insulin (IRI)-$AUC_{0\text{-}120}$ (y=1.797x+205.79; R=0.39; P<0.05). (**B**) Correlation between total GIP-$AUC_{0\text{-}120}$ and insulinogenic index (y=7086.1x+21,774; R=0.40; P<0.05). (**C**) Correlation between total GIP-$AUC_{0\text{-}120}$ and ΔIRI between 0 and 120 minutes (y=140.35x+24,012; R=0.40; P<0.05). AUC=area under the curve; GIP=glucose-dependent insulinotropic peptide; II=insulinogenic index; IRI=immunoreactive insulin.

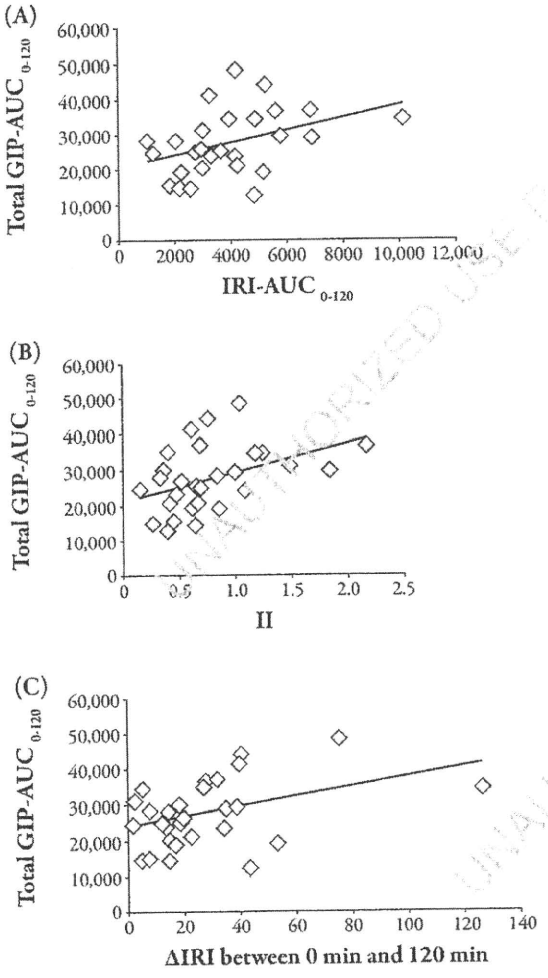
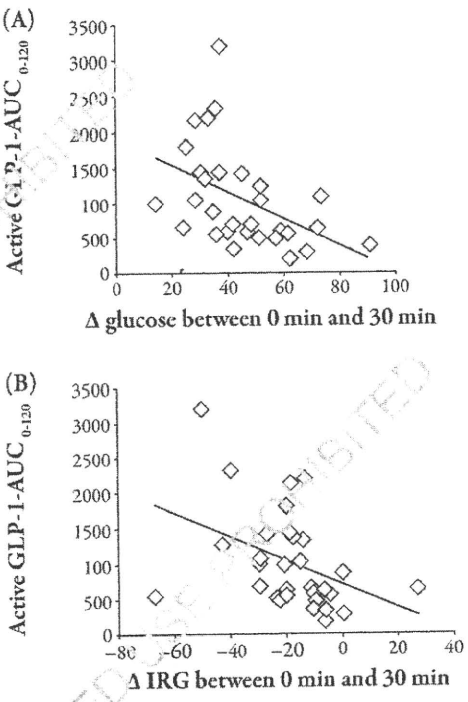


Figure 3. (**A**) Correlation between active glucagon-like peptide-1 (GLP-1) area under the curve $(AUC)_{0\text{-}120}$ and Δglucose between 0 and 30 minutes (y=−19.551x +1920.9; R=−0.47; P<0.01). (**B**) Correlation between active GLP-1-$AUC_{0\text{-}120}$ and Δ immunoreactive glucagon (IRG) between 0 and 30 minutes (y=−16.545x+720.37; R=−0.40; P<0.05). AUC=area under the curve; GIP=glucose-dependent insulinotropic peptide; IRG=immunoreactive glucagon.



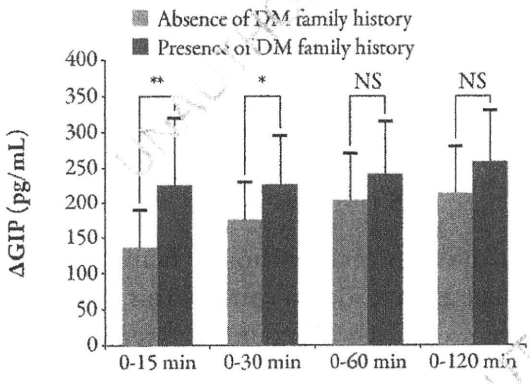
$AUC_{0\text{-}120}$), respectively. However, Δ total GIP between 0 and 15 minutes (R=0.54, P<0.01), Δ total GIP between 0 and 30 minutes (R=0.39, P<0.05), and the total GIP-$AUC_{0\text{-}120}$ (R=0.39, P<0.05) in subjects with a family history of diabetes were significantly higher than those subjects without a family history of diabetes. In order to confirm this, unpaired t-tests were used to examine whether there was a difference between the Δ total GIP between 0 and 15 minutes, Δ total GIP between 0 and 30 minutes, and GIP-$AUC_{0\text{-}120}$ in subjects with a family history of diabetes or no family history of diabetes. Total GIP-$AUC_{0\text{-}120}$ (P=0.039) in subjects with a family history of diabetes were significantly higher than those subjects without a family history of diabetes, and as shown in Figure 4, Δ total GIP between 0 and 15 minutes (P=0.0032) and Δ total GIP between 0 and 30 minutes (P=0.041) in subjects with a family history of

Table 2. Clinical characteristics of the enrolled subjects with or without a family history of diabetes.

	Family history of diabetes*		
	Presence (+)	Absence (–)	*P* value
Number of subjects	13	17	
Age, years	24.8±2.7	24.5±1.9	NS
BMI, kg/m^2	21.2±3.4	22.3±3.6	NS
Waist circumference, cm	73.8±12.6	78.1±10.8	NS
HOMA-R	1.1±0.9	1.2±0.6	NS
HOMA-β, %	64.3±49.8	71.4±43.4	NS
Insulinogenic index	0.8±0.5	0.8±0.5	NS
IRI-AUC$_{0\text{-}120}$, μU h/mL	3840.2±1493.0	4398.4±2321.5	NS

*Defined as subjects with first- to third-degree relatives with T2DM.
AUC=area under the curve; BMI=body mass index; HOMA-R=homeostasis model assessment for insulin resistance; HOMA-β=homeostasis model assessment for insulin secretion; IRI=immunoreactive insulin; NS=nonsignificant; T2DM=type 2 diabetes mellitus.

Figure 4. Correlation of Δglucose-dependent insulinotropic polypeptide (GIP) and a family history of type 2 diabetes mellitus (T2DM), defined as having a first- to third-degree relative with T2DM. **P<0.01. *P<0.05. DM=diabetes mellitus; GIP=glucose-dependent insulinotropic peptide; NS=nonsignificant.



diabetes were significantly higher than those subjects without a family history of diabetes.

DISCUSSION

The analytical data of incretin responses and kinetics of healthy Japanese subjects are scant;[5-7] therefore, in the present study 30 Japanese NGT subjects were recruited.

Nauck et al.[10] administered synthetic human GIP, GLP-1, and placebo under hyperglycemic clamp conditions in nine T2DM and nine age- and weight-matched NGT subjects. Both GIP and GLP-1 (7-36 amide) dose dependently augmented insulin secretion in both the T2DM and NGT group.[10] Cataland et al.[11] gave 75 g glucose to 21 healthy volunteers, and their serum GIP levels increased after oral glucose ingestion.

The present study shows that the total GIP-AUC$_{0\text{-}120}$ in healthy Japanese subjects positively correlated with the IRI-AUC$_{0\text{-}120}$ (P<0.05), II (P<0.05), and Δ IRI between 0 and 120 minutes (P<0.05). The present study has demonstrated that GIP clearly augmented insulin secretion in response to an oral glucose load in healthy subjects, which suggests that the secretory response of total GIP, which is secreted from K cells primarily in the proximal intestine after glucose ingestion, could be a potent trigger and/or stimulant of insulin secretion in healthy subjects.

Conversely, active GLP-1-AUC$_{0\text{-}120}$ was not related to IRI-AUC$_{0\text{-}120}$ and II. Active GLP-1 did not show any significant augmentation of insulin secretion in Japanese NGT subjects.

However, active GLP-1-AUC_{0-120} was correlated inversely both with Δ glucose between 0 and 30 minutes ($P<0.01$) and with Δ IRG between 0 and 30 minutes ($P<0.05$). This means that GLP-1 may exert its glucoregulatory action via the suppression of glucagon secretion rather than the stimulation of insulin secretion in healthy Japanese subjects. This effect of GLP-1 possibly contributes to lower the plasma glucose level as a result of reduction in hepatic glucose output.[1] The secretory response of GLP-1 has been reported to be decreased in T2DM,[3,4,12] which could weaken the incretin effect of GLP-1 on the reduction in hepatic glucose output.

In addition, GLP-1 may also lower plasma glucose levels by retarding gastric emptying, because there is an inverse relationship between gastric emptying of glucose and plasma GLP-1.[13] To establish the precise mechanism of the inverse relationship between GLP-1 secretion and plasma glucose, the function of gastric emptying of glucose needs to be examined.

The key factors regulating the GIP/GLP-1 response after glucose ingestion by NGT and abnormal glucose tolerant subjects are not well understood. Vollmer et al.[14] reported that female gender was positively related to GLP-1 concentration. Carroll conducted a study to determine the influence of BMI and gender on postprandial hormone responses such as insulin, leptin, ghrelin, active GLP-1, and glucagon. He found that men had significantly greater fasting ($P=0.02$) and postprandial ($P=0.03$) glucagon, and men tended to have higher GLP-1 concentrations ($P=0.06$). Obese subjects had higher fasting glucose and insulin concentrations, while BMI did not affect the postprandial GLP-1 response.[15] Several studies have demonstrated that gender did not influence glucagon responses to stimuli such as exercise and hypoglycemia.[16-18] Therefore, in the present study, the influence of gender, height, body weight, BMI or waist circumference on the incretin hormones and glucagon in healthy Japanese subjects was examined. However, no significant relationship among these factors in Japanese NGT subjects was found. Neither gender nor physical constitution affected the secretion of incretin hormones in the Japanese subjects.

In addition, we examined whether a family history of diabetes (presence or absence of T2DM patients within the third degree of kinship) was correlated with the level and/or the response of incretin hormones, because Japanese patients with T2DM usually have impaired insulin secretion even in the early phase of diabetes rather than insulin resistance.[19] In earlier studies in Western countries, the incretin effect in relatives of T2DM patients has been examined, and it is still controversial. In a German study, a lower insulin secretory response to exogenous GIP in first-degree relatives of patients with T2DM was shown,[20] and in a Danish study, the daytime (after meals) AUC for plasma GIP was significantly increased in the relatives of diabetes patients compared with control subjects without any family history of diabetes.[21] However, in another German study, the incretin effects were similar in first-degree relatives of patients with T2DM and healthy control subjects.[22] As there had been no attempt to reveal the relationship between a family history of diabetes and incretin response in Japanese subjects, we enrolled Japanese subjects who were NGT with or without a family history of diabetes. Interestingly, we found that Δ total GIP between 0 and 15 minutes ($R=0.54$, $P<0.01$), Δ total GIP between 0 and 30 minutes ($R=0.39$, $P<0.05$), and the total GIP-AUC_{0-120} ($R=0.39$, $P<0.05$) in the subjects with a family history of diabetes were significantly higher than those in the subjects without a family history of diabetes. Conversely, IRI, HOMA-R, HOMA-β, II, active GLP-1, and IRG were not correlated

with the presence or absence of a family history of diabetes.

It has been speculated that the loss of insulinotropic action of GIP in T2DM might occur as a result of either chronic desensitization of GIP receptors,[23] or a reduction in the expression of GIP receptors on pancreatic β cells.[24,25] Both abnormalities of GIP receptors might have already been induced in an NGT state with the presence of a family history, and a hypersecretion of GIP could potentially compensate for a reduced insulinotropic effectiveness of GIP, which could enhance insulin secretion particularly in the early phase in response to a glucose load.

Another hypothesis to account for the hypersecretion of GIP in NGT subjects with T2DM family history is the rapid gastric emptying. Since Phillips et al.[26] reported that recently diagnosed T2DM patients emptied their stomach more rapidly than nondiabetic control subjects, in the subjects with a family history of T2DM, the GIP secretion from the upper small intestine may already be augmented by rapid gastric emptying even in an NGT state. Furthermore, whether the background mechanism of the phenomenon would depend on the differences in the rate of glucose absorption in the small intestine and density of K cells should be examined in the future.

The augmented response of GIP after glucose load in subjects with a family history of T2DM in the present study could be related, in part, to the onset mechanism of Japanese T2DM patients, although further study is required. The low number of subjects is acknowledged as a limitation of the study.

In conclusion, the present study was designed to investigate the secretory patterns of two incretin hormones to OGTT and the relationship between incretin hormones and glucose, insulin, or glucagon response in healthy Japanese subjects. The results demonstrate that, at least in subjects enrolled in the study, GIP from the upper small intestine may play a role as an insulinotropic hormone and GLP-1 may play a role as a glucagonostatic hormone collaboratively. Furthermore, healthy subjects with a family history of diabetes who have normal glucose tolerance exert a significantly higher GIP response, especially in the early phase of GIP secretion in response to an oral glucose load compared with those without a family history of T2DM.

ACKNOWLEDGMENTS

The authors declare that there is no duality of interest associated with this manuscript.
Dr. Namba is the guarantor for this article, and takes responsibility for the integrity of the article as a whole.

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Effects of gliclazide on platelet aggregation and the plasminogen activator inhibitor type 1 level in patients with type 2 diabetes mellitus

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Received 10 February 2009; accepted 1 December 2009

Abstract

Vascular complications are a common factor determining morbidity and mortality of diabetic patients. In vitro studies have revealed that gliclazide has antiplatelet activities. To clinically assess this action, we measured the effects of gliclazide on platelet activities and abnormal fibrinolysis in patients with type 2 diabetes mellitus. We studied 14 patients aged 38 to 72 years (9 men and 5 women) with type 2 diabetes mellitus who have been treated with glibenclamide in our hospital for more than 6 months. We switched from glibenclamide to gliclazide using the average ratio of the respective doses, 2.5 vs 40 mg. We titrated the dose of gliclazide to keep the glycemic control at the same level as the previous (glibenclamide) treatment. We measured 10 μmol/L serotonin–induced or 0.5 μmol/L adenosine diphosphate (ADP)–induced platelet aggregate formation by particle counting using light scattering at baseline and up to 6 months after the switch. After switching to gliclazide, platelet aggregate formation induced by serotonin was significantly reduced ($P < .05$, compared with the levels observed after glibenclamide treatment). The body mass index, fasting plasma glucose, immunoreactive insulin, homeostasis model assessment of insulin resistance, hemoglobin A_{1c} (HbA_{1c}), total cholesterol, triglycerides, high-density lipoprotein cholesterol, prothrombin time, activated partial thromboplastin time, fibrinogen, thrombin-antithrombin III complex, plasmin-α2-plasmin inhibitor complex, and plasma plasminogen activator inhibitor type 1 (PAI-1) were not changed. In the group with improved HbA_{1c} (n = 5), ADP-induced platelet aggregate formation and plasma PAI-1 level were significantly reduced ($P < .05$, compared with the group with aggravated HbA_{1c}, n = 9). Multiple regression analysis showed that percentage change of ADP-induced platelet aggregate formation (standardized $\beta = 0.540$, $P < .05$) was independently associated with percentage change of plasma PAI-1 level in addition to percentage change of HbA_{1c} (standardized $\beta = 0.657$, $P < .05$) ($R = 0.939$, $P < .05$) after switching to gliclazide. The other independent variants, like the final dose of gliclazide, homeostasis model assessment of insulin resistance, percentage change of prothrombin time, activated partial thromboplastin time, and total cholesterol, were not significantly associated with the percentage change of plasma PAI-1 level. These results indicate that gliclazide inhibits platelet aggregation via the serotonin pathway, independently of the metabolic control per se. Furthermore, in the patients with improved glycemic control, gliclazide could inhibit ADP-induced platelet aggregation and reduce PAI-I level. Taken together, the results show that gliclazide may be more useful for the prevention of diabetic vascular complications than glibenclamide.

1. Introduction

Atherosclerotic complications play a crucial role in the prognosis of type 2 diabetes mellitus (DM). It is fully recognized that long-term macrovascular complications are common factors determining morbidity and mortality in the diabetic population. The Diabetes Control and Complications Trial and UK Prospective Diabetes Study indicate a consistent relationship between hyperglycemia and the incidence of chronic vascular complications in type 1 and type 2 DM, respectively [1,2]. Platelet function in DM patients is enhanced and is correlated with both agonist-induced and spontaneous aggregation [3]. It is thought that long-term exposure to high glucose levels may enhance

A part of this report has already been presented at The 40th European Association for the Study of Diabetes (EASD) Annual Meeting, Munich, Germany, 2004.

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doi:10.1016/j.metabol.2009.12.004

Table 1
Characteristics of enrolled patients

Age (y)	61.5 ± 2.6
Sex (M/F)	9/5
Height (cm)	165.3 ± 2.9
Weight (kg)	62.0 ± 3.1
BMI (kg/m^2)	22.5 ± 0.8
Duration of DM (y)	12.0 ± 1.8
HbA_{1c} (%)	7.4 ± 0.2
FPG (mg/dL)	165.0 ± 7.0
IRI (μU/mL)	7.8 ± 1.6
HOMA-R	3.0 ± 0.6

Data are expressed as mean ± SEM.

platelet function in DM patients. Moreover, rapid alterations of platelet aggregability in acute hyperglycemia have also been reported [4]. Intraplatelet serotonin (5-hydroxytryptamine; 5-HT) content is diminished and plasma levels of 5-HT are increased in DM patients [5].

This increase in plasma 5-HT may reflect enhanced release of platelet 5-HT by hyperactive platelets that may contribute to the pathogenesis of atherosclerosis. The measurement of 5-HT–induced platelet aggregation is therefore a useful method to evaluate the risk of diabetic complications in DM patients [5].

A technique for studying platelet aggregation by particle counting using light scattering may detect subtle changes in platelet activation [6]. Hypercoagulability and decreased fibrinolysis, including increased plasma plasminogen activator inhibitor type 1 (PAI-1) level, are often found and are considered to be risk factors of cardiovascular diseases and glucose intolerance, especially in patients with non–insulin-dependent DM [7]. Gliclazide is a second-generation sulfonylurea with the potency of free radical scavenger activity. Some studies have shown that gliclazide has beneficial effects on the hemorrheologic abnormalities seen in diabetic vascular disease [8-12].

To assess this clinically, we measured platelet activities and fibrinolysis in patients with type 2 DM treated with gliclazide; and we compared the results with those obtained in patients treated with glibenclamide.

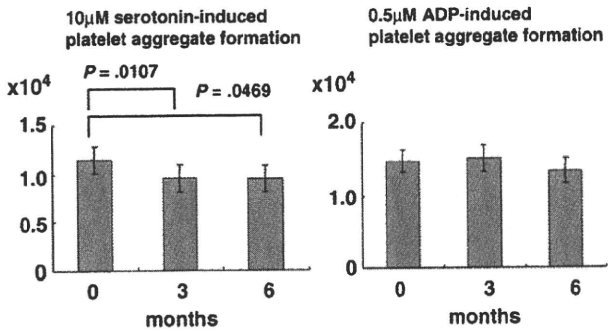

Fig. 1. Effects of gliclazide on platelet aggregation. Data are expressed as mean ± SEM.

2. Subjects and methods

2.1. Subjects

Fourteen patients with type 2 DM (9 men and 5 women; age [mean ± SEM], 61.5 ± 2.6) were randomly chosen as subjects. They were admitted to our metabolic ward between the years 2001 and 2002. Diagnosis of diabetes was based on World Health Organization 1998 criteria. All patients were treated with diet and glibenclamide. All the procedures in the study and the protection of the patients' private information were approved by the ethical committee of Hyogo College of Medicine. Informed consent was obtained from each patient before enrollment in the study.

2.2. Experimental protocol

We switched from glibenclamide to gliclazide using the average ratio of the respective doses, 2.5 vs 40 mg (1.25-20 mg in 2 patients, 2.5-40 mg in 6 patients, 5.0-80 mg in 2 patients, and 7.5-120 mg in 3 patients). We titrated the dose of gliclazide to keep the glycemic control at the same level as in the glibenclamide control. Patients' blood was assayed 3 times: before switching from glibenclamide to gliclazide and then 3 and 6 months after switching.

2.3. Blood sample preparation

Blood was collected in fasting condition on the respective mornings. Venous blood was drawn into 3.8% sodium citrate (1:9 vol/vol). Platelet-rich plasma (PRP) and platelet-poor plasma were obtained by centrifugation of the citrated blood at room temperature for 10 minutes at 150g and for 15 minutes at 3000g, respectively. The platelet count in PRP was adjusted to 2×10^{11}/L with platelet-poor plasma.

For the measurement of PAI-1, blood was centrifuged for 15 minutes at 3000g; and the supernatant was kept at −80 °C until assayed. Fasting plasma glucose (FPG), immunoreactive insulin (IRI), hemoglobin A_{1c} (HbA_{1c}), fasting serum concentrations of total cholesterol (T-Chol), triglycerides (TG), high-density lipoprotein cholesterol (HDL-Chol), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fbg), thrombin-antithrombin III complex (TAT), and plasmin-α2-plasmin inhibitor complex (PIC) were also measured. Total cholesterol, TG, and HDL-

Table 2
Effects of gliclazide on metabolic factors

	Before	3 mo	6 mo
BMI (kg/m^2)	22.5 ± 0.8	22.3 ± 0.8	21.9 ± 0.8
HbA_{1c} (%)	7.4 ± 0.2	8.0 ± 0.3	7.7 ± 0.3
FPG (mg/dL)	165.0 ± 7.0	166.0 ± 9.9	170.0 ± 8.0
IRI (μU/mL)	7.8 ± 1.6	7.5 ± 1.5	7.4 ± 1.1
HOMA-R	3.0 ± 0.6	3.0 ± 0.8	3.0 ± 0.4
T-Chol (mg/dL)	205.0 ± 8.3	205.0 ± 8.7	201.0 ± 9.4
TG (mg/dL)	121.0 ± 22.1	102.0 ± 10.6	135.0 ± 19.3
HDL-Chol (mg/dL)	50.0 ± 2.6	50.0 ± 2.3	48.0 ± 1.8

Table 3
Effects of gliclazide on coagulation test and PAI-1

	Before	3 mo	6 mo
PT-INR	0.93 ± 0.01	0.92 ± 0.01	0.92 ± 0.02
APTT (s)	25.8 ± 0.7	25.8 ± 0.6	26.6 ± 0.4
Fbg (mg/dL)	300.0 ± 20.7	301.0 ± 9.5	340.0 ± 11.8
TAT (ng/mL)	50.2 ± 22.2	15.3 ± 5.4	25.8 ± 7.8
PIC (μg/mL)	0.8 ± 0.1	0.8 ± 0.1	1.3 ± 0.3
PAI-1 (ng/mL)	42.0 ± 5.6	35.4 ± 4.9	36.4 ± 5.3

Data are expressed as mean ± SEM. INR indicates international normalized ratio.

Chol were assayed using an autoanalyzer (JCA-BM 2250; Nihon Denshi, Akishima, Tokyo, Japan), while HbA_{1c} was measured by high-performance liquid chromatography (HLC-723G7 system; Tosoh, Tokyo, Japan). The subjects were then divided into 2 groups depending on whether their HbA_{1c} levels were improved or aggravated 6 months after switching from glibenclamide to gliclazide.

2.4. Platelet aggregation

Platelet aggregation was monitored with an AG10 aggregometer (Kowa, Tokyo, Japan) that determines the size and number of platelet aggregates based on particle counting using light scattering [6,13]. A laser beam (675 nm) is passed through a platelet suspension, and the intensity of light scattering provides information on the number and size of aggregates. Data were recorded as a 2-dimensional graph showing the change over time of total light intensity expressed as cumulative summation. The total light intensities of small aggregates were determined. Particles with an intensity of 25 to 400 mV represent small aggregates consisting of less than 100 platelets. Platelet-rich plasma (180 μL) was placed in a cuvette and incubated for 3 minutes at 37°C while rotating at 1000 rpm. Subsequently, 20 μL of 5-HT (final concentration, 10 μmol/L) or adenosine diphosphate (ADP) (0.5 μmol/L) was added; and the formation of platelet aggregates was monitored for 5 minutes. For this experiment, we determined the peak level of aggregate formation.

2.5. Statistical analysis

Values are presented as means ± SEM. Correlations were assessed using Spearman rank correlation test. Multiple regression analysis was performed to assess the combined influence of variables on percentage change of plasma PAI-1 levels. The Wilcoxon signed rank test or the Mann-Whitney *U* test were used for comparison. Differences were considered significant at $P < .05$. All the statistical analyses were performed using StatView J-5.0 software (SAS Institute, Berkeley, CA).

3. Results

3.1. Clinical characteristics of the patients

The clinical characteristics of the enrolled patients in the study are summarized in Table 1. The mean FPG was 165.0 ± 7.0 mg/dL (reference range, 70-110 mg/dL), and HbA_{1c} was 7.4% ± 0.2% (reference range, 4.0%-5.4%).

3.2. Change of platelet aggregation and metabolic factors after switching to gliclazide

After switching from glibenclamide to gliclazide, platelet aggregate formation induced by serotonin was significantly reduced ($P = .0107$, compared with glibenclamide treatment) after 3 months and ($P = .0469$, compared with glibenclamide treatment) after 6 months, although the ADP-induced platelet aggregate formation was not changed at all (Fig. 1). The switch from glibenclamide to gliclazide did not modify body mass index (BMI), FPG, IRI, homeostasis model assessment of insulin resistance (HOMA-R), HbA_{1c}, T-Chol, TG, and HDL-Chol (Table 2).

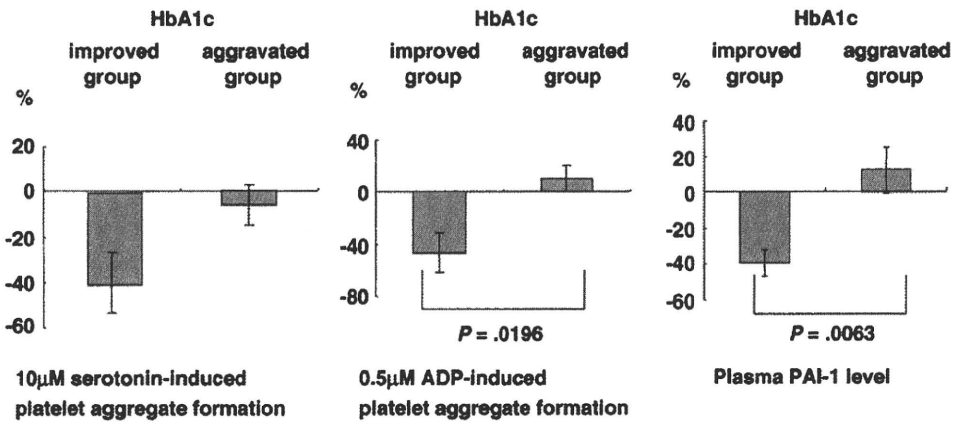

Fig. 2. Percentage change of platelet aggregate formations by 10 μmol/L serotonin or 0.5 μmol/L ADP and plasma PAI-1 level depend on the change of glycemic control after switching to gliclazide. Data are expressed as mean ± SEM.

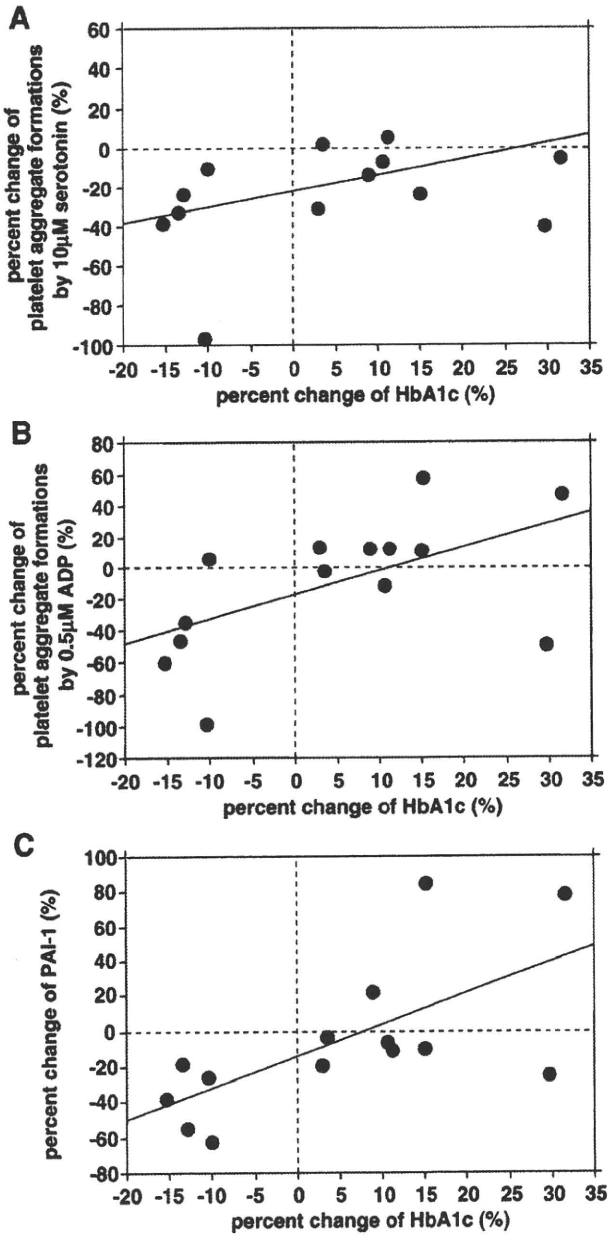

Fig. 3. A, Correlation between percentage change of HbA_{1c} and platelet aggregate formations by 10 μmol/L serotonin after switching to gliclazide (r = 0.39, P = .1712). B, Correlation between percentage change of HbA_{1c} and platelet aggregate formations by 0.5 μmol/L ADP after switching to gliclazide (r = 0.56, P = .0370). C, Correlation between percentage change of HbA_{1c} and PAI-1 after switching to gliclazide (r = 0.65, P = .0115).

3.3. Change of the levels of coagulation factors and PAI-1 after switching to gliclazide

After switching from glibenclamide to gliclazide, PT, APTT, Fbg, TAT, PIC, and PAI-1 were not changed significantly, although PAI-1 would tend to decrease (Table 3).

3.4. Relationship between platelet aggregate formation, plasma PAI-1, blood pressure, and glycemic control

At the end of the 6-month gliclazide treatment and compared with the group of patients with aggravated levels of HbA_{1c} (n = 9), patients with improved HbA_{1c} levels (n = 5) had significantly reduced ADP-induced platelet aggregate formation (P = .0196) and plasma PAI-1 levels (P = .0063) (Fig. 2).

Linear regression analysis showed that percentage change of HbA_{1c} correlated positively with both percentage change of platelet aggregate formation by 0.5μmol/L ADP (r = 0.56, P = .0370) (Fig. 3B) and percentage change of PAI-1 (r = 0.65, P = .0115) (Fig. 3C) after switching to gliclazide.

The mean systolic blood pressure (135.9 ± 3.9 mm Hg) in the group of patients with aggravated levels of HbA_{1c} was not significantly different from the mean systolic blood pressure (124.0 ± 9.2 mm Hg) in the group of patients with improved HbA_{1c} levels. The mean diastolic blood pressure (76.7 ± 2.4 mm Hg) in the former group was not significantly different from the mean diastolic blood pressure (70.2 ± 6.2 mm Hg) in the latter group. Percentage change of mean systolic blood pressure (−5.6% ± 4.3%) in the former group was not significantly different from percentage change of the mean systolic blood pressure (2.1% ± 2.5%) in the latter group. Percentage change of mean diastolic blood pressure (−2.0% ± 3.1%) in the former group was not significantly different from percentage change of the mean diastolic blood pressure (6.8% ± 2.7%) in the latter group.

3.5. Relationship between plasma PAI-1 and various factors

Multiple regression analysis showed that, after switching to gliclazide, the percentage change of ADP-induced platelet aggregate formation (r = 0.540, P = .0401) was independently associated with the percentage change of plasma PAI-1 level in addition to the percentage change of HbA_{1c} (r = 0.657, P = .0310) (R = 0.939, P = .0188) (Table 4). The other independent variants including the final dose of gliclazide, HOMA-R, percentage change of PT–international normalized ratio, APTT, and T-Chol were not significantly associated with percentage change of PAI-1.

Table 4
Multiple regression analysis with percentage change of plasma PAI-1 level

	Regression coefficient	SEM	Standardized regression coefficient	P
Percentage change of ADP-induced platelet aggregate formation	0.539	0.207	0.540	.0310
Percentage change of HbA_{1c}	1.809	0.645	0.657	.0401

4. Discussion

We found that platelet aggregate formation induced by 5-HT was significantly reduced after switching from glibenclamide treatment to gliclazide under the same conditions of metabolic control. Serum advanced glycation end products (AGEs) are significantly higher in DM subjects compared with healthy subjects [14], and our previous study indicated that enhancement of 5-HT–induced platelet aggregation in DM is dependent on the increased level of AGEs [15]. Gliclazide may therefore decrease the effect of AGEs on the enhancement of 5-HT–induced platelet aggregate formation in type 2 DM patients. When we switched from glibenclamide to gliclazide, BMI, FPG, IRI, HbA_{1c}, T-Chol, and TG were not changed at all. These results indicate that gliclazide inhibits platelet aggregation via the serotonin pathway, independently of the metabolic and/or glycemic control per se. Although gliclazide is a more potent ADP-induced platelet aggregation inhibitor than glibenclamide [16], ADP-induced platelet aggregate formation was not changed in our study when we switched from glibenclamide to gliclazide. We reported that ADP-induced platelet aggregation is increased by AGEs; but this increment is diminished by addition of sarpogrelate, a selective 5-HT receptor antagonist [15]. In the group with improved HbA_{1c}, ADP-induced platelet aggregate formation and plasma PAI-1 level were significantly reduced compared with the group with aggravated HbA_{1c}. Although a relationship between the level of blood pressure (particularly hypertensive levels) and platelet activation has been reported, there was no significant difference of hypertensive levels between the groups with aggravated and improved HbA_{1c} levels. The percentage change of ADP-induced platelet aggregate formation was independently associated with the percentage change of plasma PAI-1 level in addition to percentage change of HbA_{1c} after switching to gliclazide by multiple regression analysis. In some reports, an improved metabolic control of type 2 DM could significantly decrease the elevated concentrations of PAI-1. The decrement in PAI-1 is induced by drugs with dissimilar effects on insulin secretion (ie, glipizide gastrointestinal therapeutic system and metformin), emphasizing the important contribution that metabolic control has on this process [17].

Furthermore, in patients with improved glycemic control, gliclazide could inhibit ADP-induced platelet aggregation and PAI-1 level. Gliclazide rather than glibenclamide has been reported to attenuate the progression of carotid intima-media thickness in subjects with type 2 DM [18]. Furthermore, in a population-based case-control and follow-up study, the risk of myocardial infarction would appear to be higher among users of old sulfonylureas including glibenclamide (adjusted odds ratio, 2.07; 95% confidence interval, 1.81-2.37) than among users of new sulfonylureas including gliclazide (adjusted odds ratio, 1.36; confidence interval, 1.01-1.84) [19]. Recently, in the ADVANCE trial (Action in Diabetes and Vascular disease: preterAx and diamicroN modified release Controlled Evaluation), an intensive glucose-control strategy using gliclazide (modified release) and other drugs as required lowered the average HbA_{1c} value to 6.5% in a broad range of patients with type 2 DM and reduced the incidence of the combined primary outcome of major macrovascular or microvascular events [20]. We should have listed the limitations of the study in the interpretation of the results. All patients were switched from glibenclamide to gliclazide. Although we have claimed that the subjects were under the same conditions of metabolic control, at the end of the 6-month period, there was a group with aggravated levels of HbA_{1c} and a group with improved HbA_{1c} levels. To compare the 2 drugs, half the patients should have continued on glibenclamide; or, more practicable with the small number, a cross-over design could have been used. This would permit comparing the 2 drugs in the patients with matching HbA_{1c} levels.

In conclusion, the study results demonstrate that gliclazide inhibits serotonin-induced platelet aggregation independently of glycemic control, although being less effective on ADP-induced aggregation, and may have a better effect on the reduction of platelet aggregability than glibenclamide. Very importantly, this study supports previous results showing the reduction in platelet aggregability and reduction in PAI-1 level with the improvement in glycemic control. Therefore, gliclazide may be more useful for the prevention of diabetic vascular complications than glibenclamide via beneficial and pleiotropic effects on the hemorrheologic abnormalities.

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IV-1

IV. インクレチンの関連薬剤の糖尿病治療における展望

1 型糖尿病治療への可能性

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インクレチン治療薬にはGLP-1受容体作動薬と，内因性GLP-1濃度を上昇させるDPP-4阻害薬が存在し，インクレチン作用以外に膵内外でマルチポテンシャルな作用を示して血糖改善作用を発揮する新たな糖尿病治療薬として期待されている．なかでも，実験動物で確認されている既存β細胞の増殖促進作用およびアポトーシス抑制作用，およびβ細胞分化・新生誘導作用は，これまでの糖尿病治療薬では期待できない作用であり，このような作用がヒトで存在するのであれば，1型糖尿病治療においても治療効果が期待される．GLP-1あるいはGLP-1受容体作動薬による現在までの知見からは，そのような薬理作用は実証できないが，残存β細胞機能改善作用に加え，食欲・摂食量の低下，胃排泄運動の抑制，グルカゴン分泌の抑制（肝臓のグルコース過剰産生抑制）などだけでも，血糖コントロールの安定化やインスリン注射量の減量は期待できる．また，GLP-1は免疫系にも作用して自己免疫によるβ細胞傷害機構にも影響を与える可能性も秘めており，GLP-1受容体作動薬は1型糖尿病治療への可能性を十分有するものと考えられる．

注目を浴びるインクレチン治療

近年，インクレチン治療（incretin-based therapy）が従来にない作用機序に基づく新たな糖尿病治療として注目を浴びている．「インクレチン」は，食物（とりわけ炭水化物）の摂取（消化管内への食物流入刺激）に対して，消化管からなんらかの因子によるシグナルが膵島細胞に伝達され，β細胞に対して血中グルコース濃度上昇による直接的な刺激をはるかに上回るインスリン分泌増強作用を発揮する消化管由来の因子として，従来から知られている．後に，このようなインクレチンシグナルの主役を演じているのが，消化管内分泌ホルモンであるGIP（glucose-dependent insulinotropic polypeptide）とGLP-1（glucagon-like polypeptide-1）であることが明らかにされ，糖尿病治療薬としての標的となっていたが，両ペプチドホルモンの半減期がきわめて短いこと，GIPを外因性に投与しても糖尿病患者においてインクレチン作用が回復しないことから，より半減期の長いGLP-1受容体作動薬が模索されてきた．最近，ようやく半減期の長いGLP-1受容体作動薬が開発され，2回/日～1回/週の皮下注射による糖尿病治療が可能，あるいは可能となりつつある．わが国においてもリラグルチド（liraglutide，Victoza®，Novo）および合成exendin-4であるエキセナチド（exenatide = exendin-4，Byetta®，Lilly）が申請中であり，2010年には承認されると予測されている．

GLP-1の多面的な生理作用

GLP-1の生理作用は多面的であり，GLP-1受容体作動薬

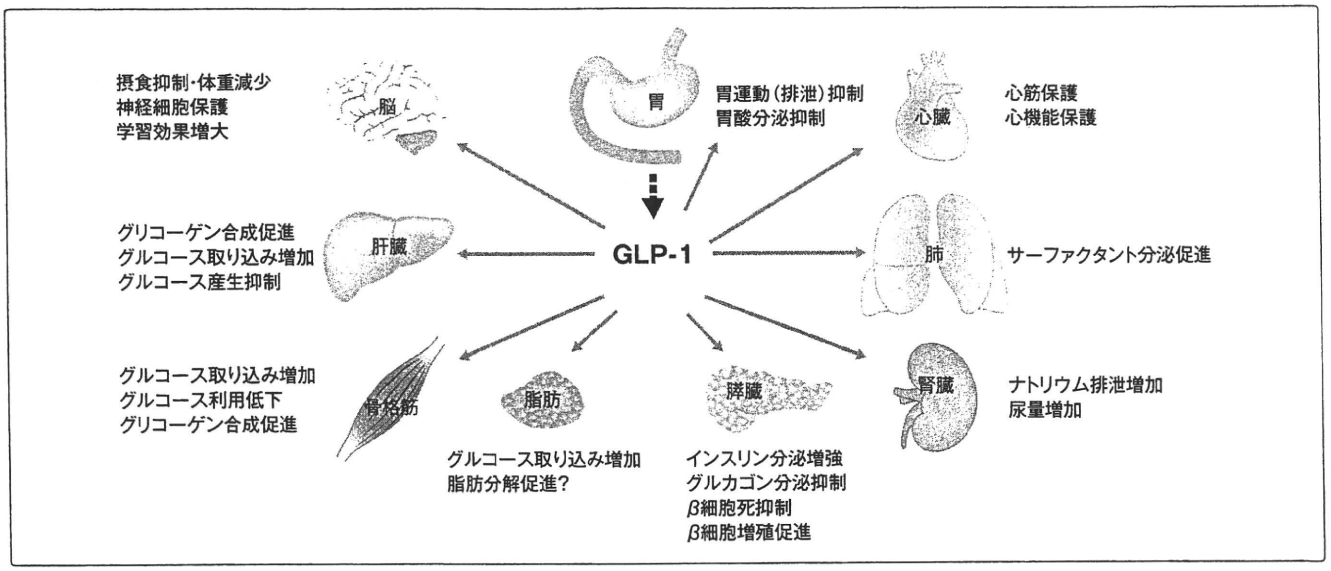

図1 GLP-1の多彩な生理作用(文献3)
ただし，ヒトにおいて実証されていない作用も含む

においても，β細胞におけるグルコース濃度依存性インスリン分泌増強作用(インクレチン作用)以外に，ヒトでは確証が得られていないが，既存β細胞に対する増殖促進作用やアポトーシス抑制作用，β細胞分化・新生誘導促進作用を有する．また，α細胞に対してはグルコース濃度依存性グルカゴン分泌抑制作用も存在する．さらに膵外作用として，食欲抑制，胃排泄運動抑制作用，肝臓におけるグルコース産生抑制およびグルコース取り込み促進作用，脂肪組織や骨格筋細胞におけるグルコース取り込み促進作用など，糖尿病治療においてマルチポテンシャルな抗糖尿病作用を発揮しうることが明らかにされている(図1)[1-3]．

1型糖尿病治療におけるGLP-1受容体作動薬の可能性

1型糖尿病は，成因分類的にはType 1A，自己免疫性1型糖尿病およびType 1B，特発性1型糖尿病に分類され，通常は膵β細胞の破壊により絶対的なインスリン不足，すなわちインスリン依存状態に陥る．自己免疫性1型糖尿病では，従来から知られている膵島内への単核細胞浸潤，すなわち膵島炎（insulitis）が病理組織学的な特徴であり，Tリンパ球（$CD8^+$ T細胞を主体とするリンパ球）やマクロファージの浸潤が観察され，自己反応性の細胞傷害性Tリンパ球による直接的なβ細胞破壊に加えて，膵島に浸潤したリンパ球やマクロファージが産生する液性因子，IFN-γ (interferon-γ)，IL-1β (interleukin-1β) やTNF-α（tumornecrosis factor-α）などの炎症性サイトカインによってもアポトーシス細胞が惹起される．Type 1Bでは1～2週間の急激な経過で発症に至る（インスリン依存状態に陥る）劇症1型糖尿病 (fulminant type 1 diabetes mellitus) といわれる亜型が存在するが，いずれも膵β細胞数，いわゆる「β-cell mass」の著しい減少が基本病態として存在する．このような糖尿病，すなわち，既存β細胞が著しく減少した病態においてGLP-1受容体作動薬を投与しても，インクレチン作用に基づく血糖改善効果は2型糖尿病で認められるほどには期待できないと考えられるが，わずかでもβ細胞が残存していれば内因性インスリン分泌を増加させ，血糖コントロールの不安定さ（brittleness）が改善されるかもしれないし，インスリン必要量が減少するかもしれない．また，α細胞や膵島構造そのものに対する作用および膵外作用などは，2型糖尿病と同様に期待しうると考えられる．さらに，GLP-1受容体はリンパ球の一部にも発現しており，1型糖尿病モデルマウスにおける検討からは，自己免疫現象そのものにも影響を与える可能性も指摘されている．本稿ではこのような知見あるいは可能性を踏まえ，1型糖尿病治療へのGLP-1受容体作動薬の可能性を探ってみたい．

1型糖尿病モデル動物における知見

1型糖尿病におけるGLP-1の血糖値改善・糖尿病発症抑制効果

2型糖尿病モデルマウスやラットにおいては，GLP-1やGLP-1受容体作動薬を投与すると膵β細胞数が温存あるいは増加し，膵内分泌保護作用を有することが明らかにされており，DPP-4（dipeptidyl peptidase-4）阻害薬においても同様の効果が観察されている[4-6]．ヒト2型糖尿病においてもそのような薬理作用が実証されれば，これは従来の糖尿病治療薬では期待できなかった作用である．そのため，インクレチン関連薬が新たな糖尿病薬として期待されている理由のひとつとなっている．

発症時すでにβ細胞数が著しく減少している1型糖尿病においてわずかでもこのような作用が認められるとすれば，インスリン注射から解放される可能性は低いとはいえ，少なくとも血糖日内変動の安定性には大きく寄与しうると推測される．そのような観点から，筆者らは自己免疫性1型糖尿病モデルマウスであるNOD（non-obese diabetic）マウスで検討を行った[7]．同マウスでは生後5～6週で膵島へのリンパ球やマクロファージなどの細胞浸潤，すなわち膵島炎（insulitis）が認められ，雌では25週ごろに1型糖尿病発症率が約80％に達する．このようなマウスに8週齢（未発症）から浸透圧ポンプを用いてヒトGLP-1の持続皮下注入（4週間，あるいは8週間．コントロール群は生理食塩水の投与）を行った．その結果，NODマウスの血中活性型GLP-1の濃度は持続的に50～60 pmol/l程度に維持され，随時血糖値の上昇を抑制，糖尿病発症の抑制あるいは遅延が認められた（図2）．GLP-1によるNODマウスの血糖値改善および糖尿病発症抑制効果がいかなる機序によるのか，膵組織を免疫組織学的に検討すると，膵β細胞量（relative β-cell area）が増加しており，GLP-1投与群では，既存β細胞の増殖促進（BrdU labeling法）に加え，β細胞死（アポトーシス）の抑制（TUNEL法）が認められた．さらに，膵導管細胞配列における分化・新生誘導現象も増加していた（図3～図6）[7]．すなわち，糖尿病発症前NODマウスに対してヒトGLP-1の持続皮下投与を行うと，既存β細胞の増殖活性増強，アポトーシスの抑制，膵組織幹細胞ないし内分泌前駆細胞に対する分化・新生誘導促進が起こり，膵β細胞量が増加した結果，内因性インスリン分泌能が改善して血糖上昇が抑制され，糖尿病発症の抑制あるいは遅延が起こったものと考えられた．もちろん，本マウスの糖尿病発症基盤にはβ細胞に対する自己免疫が存在するため，GLP-1投与を中止するとβ細胞傷害が進行するため，最終的には血糖値の上昇や糖尿病発症が認められるようになるが，興味深いことに，GLP-1投与中止後も随時血糖値は少なくとも5週間にわたり上昇が抑制されていた（図2）．GLP-1そのもの以外にも，GLP-1受容体作動薬のひとつであるエキセナチド，エキセナチドと抗リンパ球抗体（anti-lymphocyte serum；ALS）あるいは抗CD3モノクローナル抗体（anti-CD3 monoclonal antibody）やガストリンの併用によるNODマウス糖尿病発症後の耐糖能改善効果についての報告がみられる[8-11]．

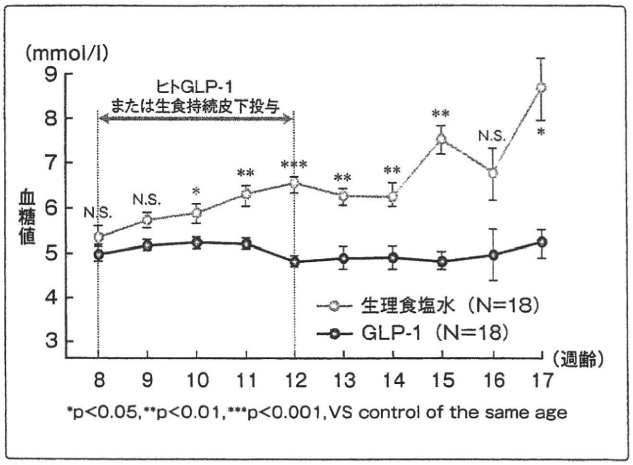

図2 NODマウスにおけるGLP-1持続皮下投与中の随時血糖値の推移（文献7改変）

GLP-1の免疫系への作用

GLP-1受容体はリンパ球にも発現しており，外因性のGLP-1やGLP-1受容体作動薬の投与により自己免疫現象に影響を及ぼす可能性も否定できない．実際，GLP-1が免疫系にも生理活性を有することが明らかになりつつあり，最近の検討によると，自己免疫性1型糖尿病におけるβ細胞傷害機構に影響を与えている可能性が示されてい

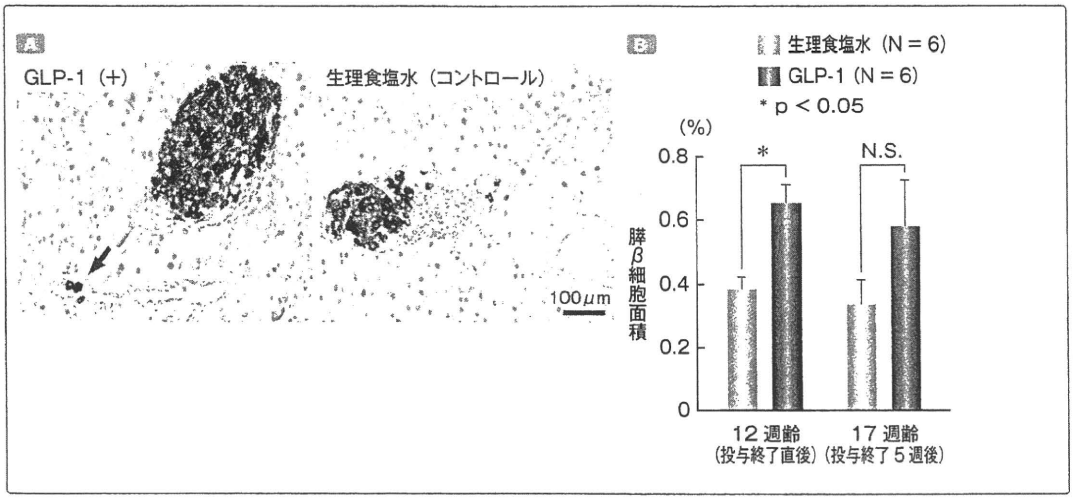

図3 NODマウス膵島におけるGLP-1持続皮下投与（4週間）の効果（文献7）

A：NODマウス膵島の変化．茶；インスリン／B：β細胞面積の変化（morphometric analysis）

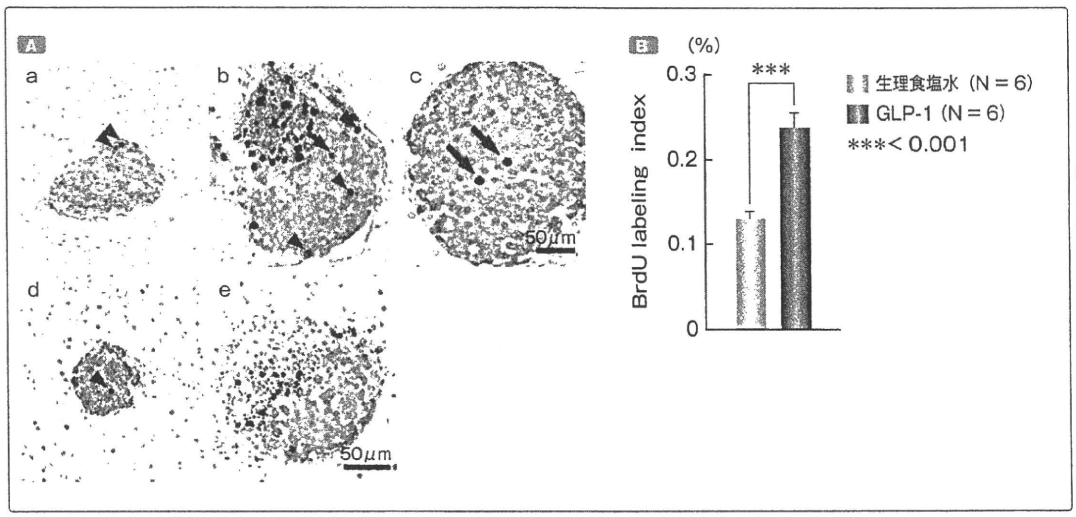

図4 GLP-1の既存β細胞に対する増殖促進作用（投与4週後）（文献7）

A：NODマウス膵島の変化（GLP-1投与4週後）．a～c：GLP-1（+）群（a：膵島炎の存在しない膵島，b：膵島炎の存在する膵島，c：強拡大像）／d・e：GLP-1（−）群（d：膵島炎の存在しない膵島，e：膵島炎の存在する膵島）．Blue-gray：インスリン，→・▶：BrdU陽性細胞．

B：NODマウス膵島のBrdU陽性β細胞数の変化

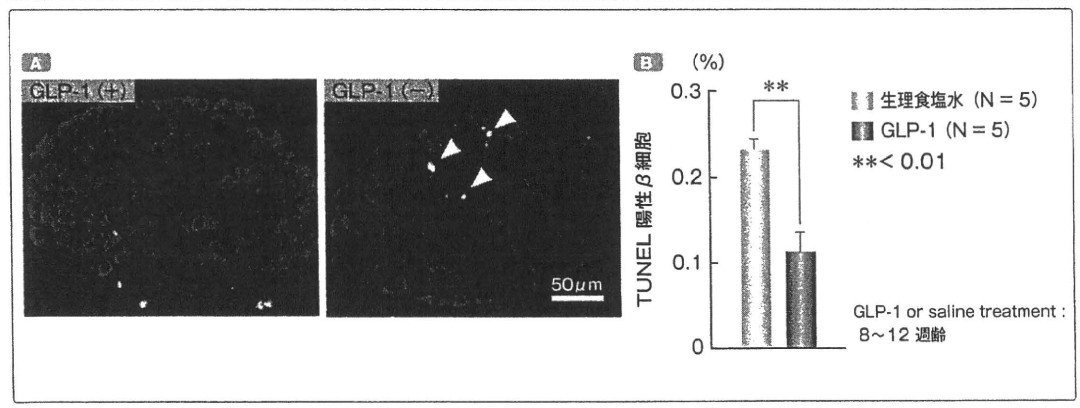

図5 NODマウスのβ細胞死に及ぼすGLP-1持続皮下投与の効果（投与終了5週後，TUNEL法）（文献7）

A：赤；インスリン，緑；TUNEL陽性細胞／B：TUNEL法によるapoptotic β-cellの検出

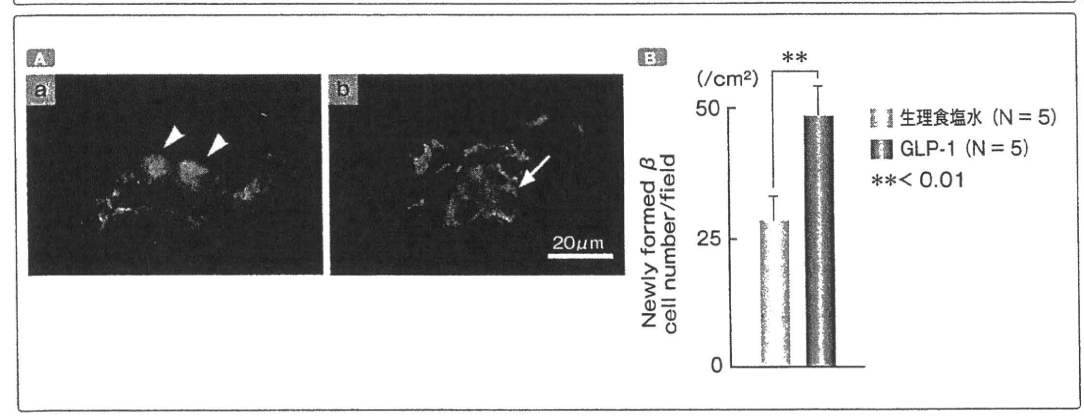

図6 GLP-1投与によるβ細胞分化・新生促進作用（文献7）

A：導管細胞配列内（a），ないし密接して存在する新生β細胞（b）．赤；インスリン，緑；導管細胞特異的cytokeratin／B：導管細胞配列内，ないし密接して存在する新生β細胞の出現頻度

る．糖尿病発症直後のNODマウスにエキセナチドを投与すると，エフェクターT細胞（Teff）の活性化や増殖の抑制に関わっているとされる調節性Tリンパ球（regulatory T cell；Treg）の機能が増強ないし数が増加する傾向がみられる．また，IL-10の産生が増加してTh1/Th2バランスを変化させる可能性がある[12]．GLP-1受容体ノックアウトマウス由来の免疫担当細胞を用いて機能解析を行うと，エキセナチドはSDF-1α（stromal-derived factor -1α）の存在下でリンパ球の遊走能を高めるようである[13]．

このように，少なくとも動物モデルにおいては，自己免疫性1型糖尿病においてもGLP-1ないしGLP-1受容体作動薬による耐糖能改善作用が実証され，自己免疫によるβ細胞傷害機構にも好ましい方向に関与するかもしれないという知見も見いだされつつあることから，ヒト1型糖尿病への臨床応用の可能性についても大規模な治験などにより検討されるべき時期にきていると考えられる[14]．

ヒト1型糖尿病におけるGLP-1受容体作動薬の臨床効果

ヒト自己免疫性1型糖尿病の予防あるいは治癒（＝cure）をめざすなら，病態の基盤となるβ細胞に対する自己免疫反応を阻止する必要があるが，残念ながらいまだその域に達していない．臨床的に最も多く試みられているのは，抗CD3モノクローナル抗体を用いたimmunomoduration therapyであるが，その効果も長期的には残存β細胞機能（≒β-cell mass ？）に左右されてしまい，これのみでは限界がある[15,16]．前述のNODマウスを中心としたモデル動物の成績では，自己免疫反応は阻止できないにしても，β-cell massの増加～維持あるいは減少の抑制が期待され，さらにインクレチン作用以外の多面的作用の一部，すなわち，α細胞によるグルカゴン分泌抑制および，それに関連した肝臓からのグルコース過剰産生の抑制，胃排泄運動抑制作用，食欲抑制作用などは，1型糖尿病においても有効であるはずである．

わが国においては，1型糖尿病における治験成績などは見当たらないが，欧米においては小規模ながら1型糖尿病における臨床効果についての報告がみられる．内因性インスリン分泌がほとんど消失している1型糖尿病患者9名に対し，エキセナチドを朝食前投与し，血糖値，膵ホルモン分泌やアセトアミノフェンを用いた胃排泄能の変化を検討したところ，食後血糖値がほぼ正常化し，日内変動の改善が認められた．食事開始15分前の注射で0.03 μg/kg体重が最も効果的で，それ以上の投与量になると，インスリン注射量を変更しなかった場合，低血糖が出現する患者がみられた．血糖値の改善は主に，グルカゴン分泌の抑制およびその結果としての肝臓におけるグルコース過剰産生の抑制，および胃排泄運動の抑制によるものと推測され，内因性インスリン分泌能の増加は確認されていない[17]．

最近，長い罹病歴（21.3±10.7年）ながら，内因性インスリン分泌能がわずかながら残存している1型糖尿病患者20名（39.5±11.1歳，HbA_{1c} 7.3±1.1 %）に対するエキセナチドの効果を検討した報告がなされた[18]．基礎値ないし食事負荷，あるいはアルギニン負荷後のCペプチド≧0.3 ng/ml）となる患者を選択して4ヵ月間インスリン治療を十分行って血糖コントロールを最善の状態にしておき（Run-in period），遂行可能となった14名に対して，6ヵ月間（Study period A），A：インスリンのみ，B：インスリン＋Daclizmab，C：インスリン＋エキセナチド，D：インスリン＋エキセナチド＋Daclizmabの群に分けて治療した後，さらに6ヵ月間（Study period B），各群をA：インスリン＋エキセナチド，B：インスリン＋Daclizmab＋エキセナチド，C：インスリンのみ，D：インスリン＋Daclizmabの群とするクロスオーバー試験を実施し，終了後，同様のメニューで3ヵ月の延長期間（Extension period）を設けてさらに治療効果を観察している（表1）．各治療期間の前後で血糖コントロール，グルカゴン，GLP-1，食事負荷およびアルギニン負荷後のCペプチド反応（β細胞機能の変化），β細胞抗原に対するTリンパ球の反応性（β細胞障

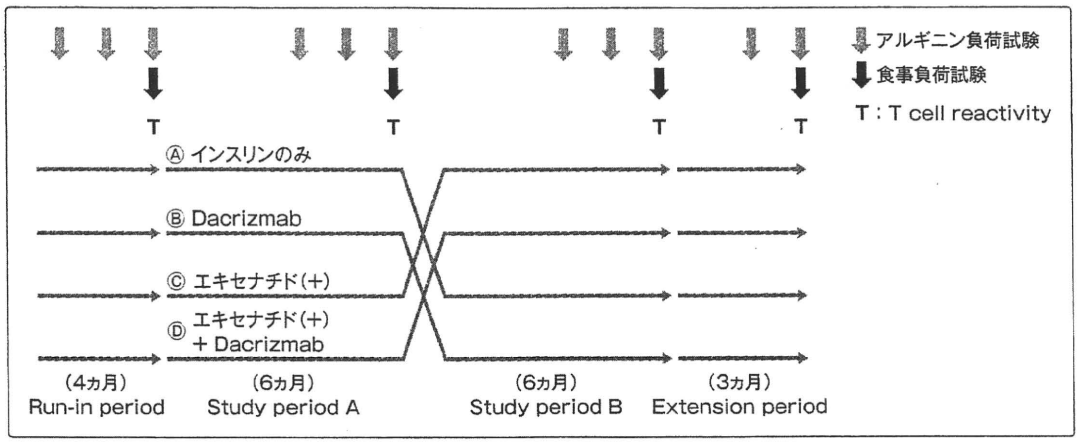

図7 長い罹病歴ながら内因性インスリン分泌能がわずかに残存している1型糖尿病患者に対するエキセナチドの効果（文献17より作図）

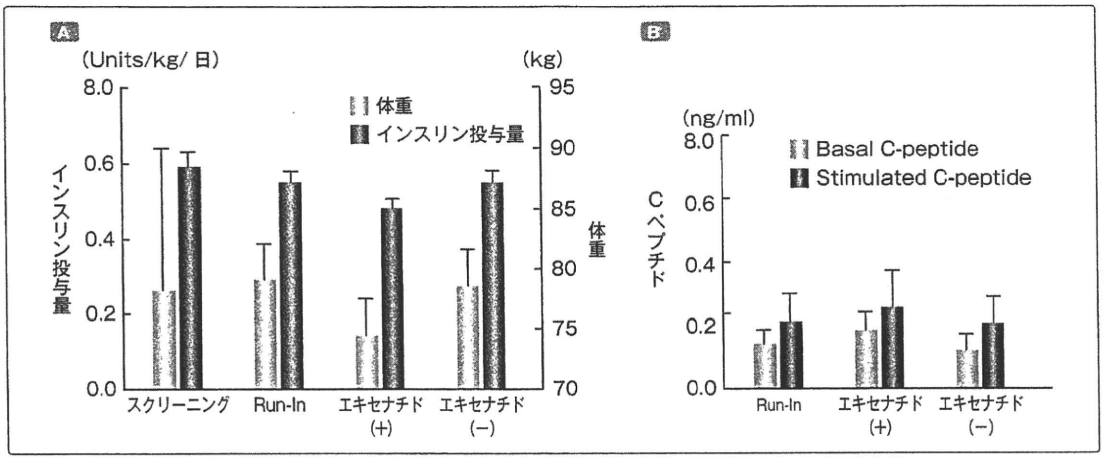

図8 エキセナチドの血糖コントロール改善効果とその機序（文献17改変）
A：エキセナチド併用の有無によるインスリン投与量および体重の変化／B：アルギニン負荷試験におけるCペプチド分泌反応の変化

害機構への影響）などを実施して，エキセナチドの血糖コントロール改善効果とその機序について検討している[18]．その結果，エキセナチド（+）群の6ヵ月後の体重（74.2±12.6 kg）とエキセナチド（−）群の体重（78.4±12.1 kg）に差を認め，体重減少作用が観察された．この効果は消化器系副作用である悪心の有無とは無関係で，食欲低下作用によるものと考えられた．開始時の血糖コントロールがかなり良好であったためか，エキセナチド(+)群とエキセナチド(−)群で有意な差は認められなかった(6.51±0.56 % vs 6.64±0.64 %）が，低血糖の頻度を増加させることなく，総インスリン使用量を30 %低下させている（図8-A）．アルギニン負荷試験によるCペプチドの反応は明らかに存在し，外因性GLP-1受容体作動薬がわずかに残存するβ細胞におけるインスリン分泌を増強しうることが確認された．しかし，エキセナチドを投与(+)時には増加する傾向がみられるが，エキセナチドを投与(−)となると投与前のレベルに戻ってしまうことから，期待されたβ-cell massの増加についての証拠は得られなかった（図8-B）．また，食事負荷試験の結果では，エキセナチド(+)群では胃排泄運動の抑制が認められ，その結果と考えられるグルコース吸収（血糖値の上昇）は抑制されたが，グルカゴン分泌の抑制は2型糖尿病でみられるほどには抑制されていない（図9-A～C）．興味深いことに，内因性GLP-1はエキセナチド(−)群では健常者より反応が強いが，エキセナチド(+)群では有意に抑制されている（図9-D）．以上の結果から，1型糖尿病におけるGLP-1受容体作動薬による血糖コントロールあるいは日内変動パターンの改善は，主に食欲・摂食量低下作用，食後のグルカゴン分泌抑制作用，肝臓におけるグルコース過剰産生抑制作用などによるものと考えられる．しかし，わずかに残存し，インクレチンに反応するβ細胞の存在も重要である．これまでの検討によると，ヒト1型糖尿病においては，残念ながら動物モデルで明らかにされているβ-cell massの増加についての確証は得られていないが，投与期間や検出方法の困難さも存在することから，完全に否定されるものではないだろう．

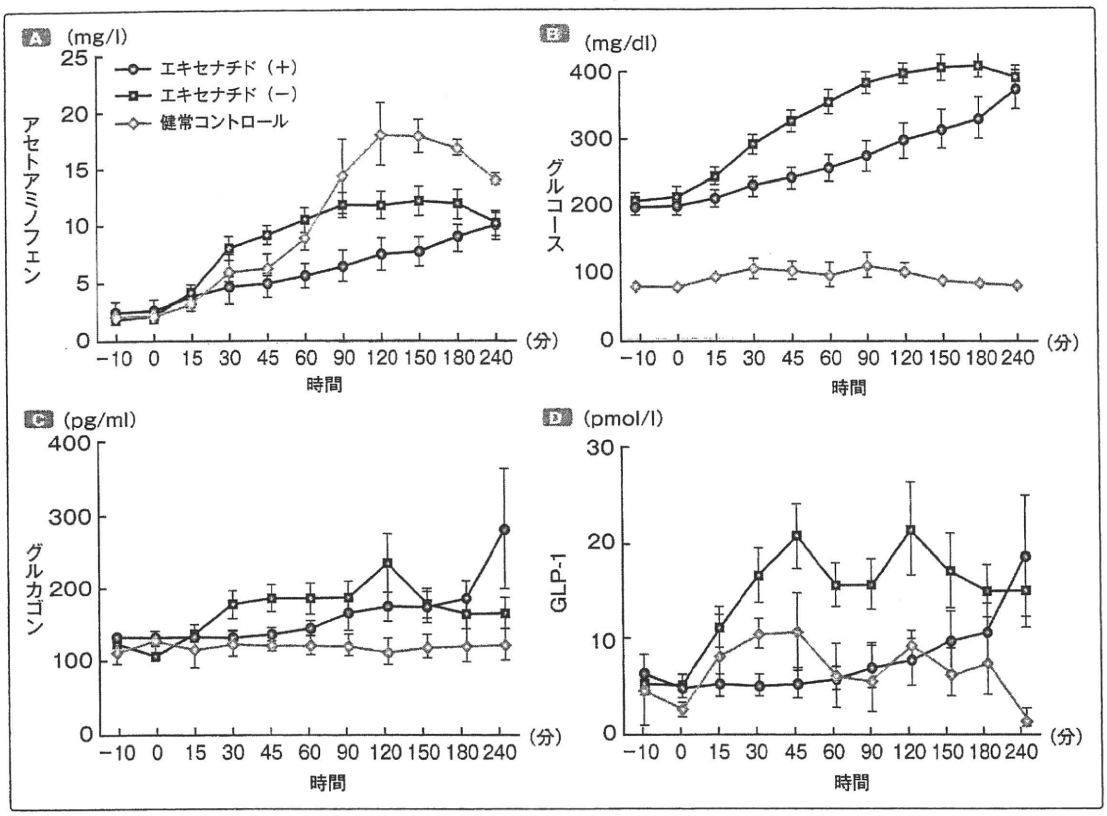

図9 食事負荷試験の結果（文献17改変）
A：胃排泄運動の変化／B：血糖値（グルコース吸収）の変化／C：グルカゴン分泌の変化／D：Total GLP-1分泌の変化

おわりに

インクレチン治療薬，とくにGLP-1受容体作動薬は，血糖コントロール改善に対してこれまでにない複数の薬理作用を発揮することから，糖尿病治療に変革をもたらすのではないかと大きな期待が寄せられている．そのなかの作用のひとつがβ-cell mass増加作用であるが，現状ではそのような現象がヒトで見いだせないとしても，残存β細胞機能や膵島構築の維持に好ましい作用を発揮している可能性は，膵島移植における検討からも推測される．また，自己免疫によるβ細胞傷害機構を弱めるかもしれないという可能性に加えて，GLP-1本来のマルチポテンシャルな作用は，1型糖尿病におけるインスリンとの併用療法の可能性を十分持っていると考えられる．

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糖尿病の最新治療 Current Diabetology

Vol.1 No.3 別刷

特集

インクレチン治療の夜明け ― GLP-1受容体作動薬

GLP-1 受容体作動薬
―エキセンジン-4

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フジメディカル出版
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