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Effects of pre-meal *versus* post-meal administration of miglitol on plasma glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide levels in healthy men

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Abstract. We previously reported that the administration of miglitol after a meal was equally effective as administration before a meal. Since glucagon-like peptide-1 (GLP-1) reportedly promotes islet cell growth and inhibits apoptosis in animal models, an increase in GLP-1 secretion might also be beneficial for islet cell function and mass in humans. Miglitol reportedly enhances GLP-1 responses and reduces glucose-dependent insulinotropic polypeptide (GIP). However, whether the effect of miglitol on these incretins is comparable when miglitol is administered before or after a meal remains uncertain. Here, we compared the effects of the pre-meal versus post-meal administration of miglitol on the plasma active GLP-1 and total GIP levels in healthy men. Miglitol was administered according to three different intake schedules in each subject (control: no drug, intake 1: drug administered just before a meal [50 mg]; intake 2: drug administered at 30 min after the start of a meal [50 mg]). The area under the curve (AUC) of the plasma GLP-1 level for the intake 1 group was significantly greater than those of the control and intake 2 groups. The AUCs of the plasma GIP level for the intake 1 and 2 groups were significantly smaller than that of the control. The administration of miglitol just before a meal, rather than after a meal, is recommended in view of the up-regulation of GLP-1.

Key words: Miglitol, α-glucosidase inhibitor, Postprandial hyperglycemia

THE REGULATION of postprandial hyperglycemia has a significant clinical relation with the risk of microvascular and macrovascular complications [1]. In general, α-glucosidase inhibitors (αGIs) should be taken just before meals [2]. However, we previously reported that the administration of miglitol after a meal was equally effective as when administered just before a meal [3-5]. By contrast, miglitol reportedly enhances glucagon-like peptide-1 (GLP-1) responses and reduces glucose-dependent insulinotropic polypeptide (GIP) [6-8]. However, the effects of αGIs on incretin levels in pre-diabetic subjects are not reported. In addition, it remains also uncertain whether the effect of miglitol on these incretins is comparable when miglitol is administered before or after a meal. These conditions prompted us to compare the effects of the pre-meal versus post-meal administration of miglitol on the plasma GLP-1 and GIP levels in healthy subjects.

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Materials and Methods

After obtaining approval from the Institutional Ethics Review Committee, 10 healthy men aged 37.0 ± 1.8 years with a BMI of 24.2 ± 0.5 kg/m^2 who had never been diagnosed as having diabetes or IGT were enrolled in the present study. They were screened for diabetes on the basis of a questionnaire. Informed consent was obtained from each of the subjects prior to the start of the study.

Miglitol was administered according to three different intake schedules in each subject (control: no

drug, intake 1: drug administered just before a meal [50 mg]; intake 2: drug administered at 30 min after the start of a meal [50 mg]). Subjects were randomized to one of the three interventions using a crossover design. All the subjects received a standard breakfast (773 Kcal; protein: 27.0 grams; fat: 20.3 grams; carbohydrate: 121.5 grams). For the study, the subjects were requested to fast for at least 12 hours prior to breakfast on the following morning, and to finish their breakfast within 15 min. Blood samples were collected at 0, 30, 60, 120 and 180 min after the start of breakfast. The plasma glucose and serum insulin levels were measured, and the plasma active GLP-1 and plasma total GIP levels were measured using ELISA kits (Millipore Corporation, MA, USA) at SRL, Inc. (Tokyo, Japan).

Data were expressed as the mean ± SE. The analyses were performed using a two-way layout analysis of variance (ANOVA) with Tukey-type multiple comparisons. The areas under the curve (AUC) from just before a meal to 180 min after the start of a meal were calculated using the trapezoid method. Differences with P values of less than 0.05 were considered significant.

Results

The plasma glucose levels at 30 and 60 min after the start of the meal in the intake 1 group were significantly lower than those in the control (Fig. 1A). The AUCs of the plasma glucose levels in the intake 1 and 2 groups were significantly lower than that in the control (Fig. 1B). The serum insulin levels at 30 and 60 min after the start of the meal in the intake 1 group and at 120 and 180 min after the start of the meal in the intake 2 group were significantly lower than that in the control (Fig. 1C). Consequently, the AUCs of the serum insulin level for the intake 1 and 2 groups were significantly smaller than that in the control (Fig. 1D). These results were consistent with those of our previous report [3].

The plasma active GLP-1 levels at 60 min after the start of a meal in the intake 1 group and at 180 min after the start of the meal in the intake 2 group were significantly higher than that in the control (Fig. 2A). The AUC of the plasma GLP-1 level for the intake 1 group was significantly greater than that in the control and intake 2 groups (Fig. 2B).

The total plasma GIP levels at 30 and 60 min after the start of the meal in the intake 1 group and at 60, 120 and 180 min after the start of the meal in the intake 2 group were significantly lower than that in the control (Fig. 2C). Consequently, the AUCs of the plasma GIP level in the intake 1 and 2 groups were significantly smaller than that in the control (Fig. 2D).

From the differences in the plasma glucose, serum insulin and plasma total GIP levels at 30 and 60 min after the start of the meal among the control, intake 1 and 2, it seems likely that the total GIP responses increase according to the glucose absorption in the upper intestine.

Discussion

The GLP-1 and GIP profiles of the subjects who took miglitol just before a meal were consistent with those of previous reports [6-8]. The most important finding of the present study was that the AUC of the plasma GLP-1 level was greater in the intake 1 group, but not in the intake 2 group, and that the AUC of GIP was smaller in both the intake 1 and 2 groups, compared with the control conditions.

Miglitol protects against carbohydrate absorption in the upper portion of the small intestine; therefore, a relatively higher amount of carbohydrate was absorbed in the lower portion of small intestine in the intake 1 group, and this might have increased GLP-1 secretion [6]. By contrast, miglitol was mixed with food in the small intestine in the intake 2 group, and carbohydrate was absorbed throughout the small intestine. The vagus nerve in the upper portion of the small intestine is suspected of being involved in GLP-1 secretion by L cells [9]. Therefore, the larger amount of unabsorbed nutrients remaining in the upper portion of the small intestine in the intake 1 group, compared with in the intake 2 group, might have activated GLP-1 secretion by the L cells through a mechanism involving the vagus nerve. Thus, the intake 1 may increase GLP-1 responses through vagus nerve system and direct stimulation, compared with intake 2 in spite of the same glucose lowering effect. In both the intake 1 and 2 groups, unabsorbed nutrients remaining in the upper intestine reduced the AUC of GIP, which is secreted from the upper portion of the small intestine.

Since GLP-1 reportedly promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats [10], an increase in GLP-1 secretion might also be beneficial

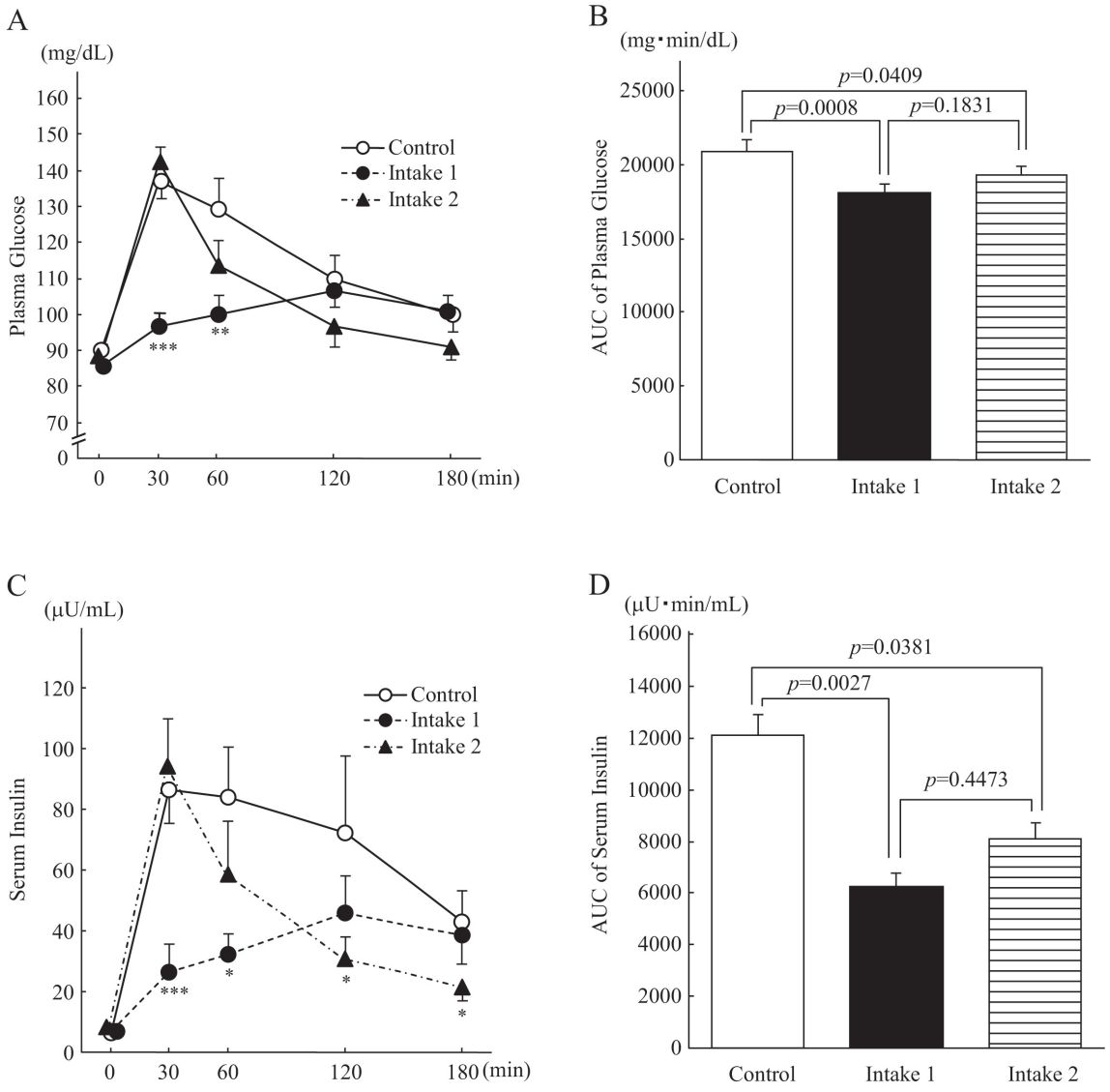

Fig. 1 Plasma glucose and serum insulin levels in the control and the two miglitol intake groups. A: Time profiles of the plasma glucose levels for each miglitol intake schedule. B: The AUC of the plasma glucose levels for each miglitol intake schedule. C: Time-profiles of the serum insulin levels for each miglitol intake schedule. D: The AUC of the serum insulin levels for each miglitol intake schedule. Data are expressed as the means ± SE. *$p<0.05$, **$p<0.01$, ***$p<0.001$ *vs.* control. Control: clear circles; Intake 1: filled circles; Intake 2: triangles.

for islet cell function and mass in humans. Given the fact that diabetes develops when insulin secretion by beta cells is insufficient to compensate for insulin resistance [11, 12], the increase in GLP-1 might be important for improving islet cell function. Postprandial hyperglycemia improved in both the intake 1 and the intake 2 groups, but the AUC of GLP-1 did not increase in the intake 2 group. αGIs decrease plasma glucose and serum insulin levels in healthy subjects [2, 13] and reduce the development of type 2 diabetes in subjects with impaired glucose tolerance (IGT) [14, 15]. However, their significance for protecting against the development of diabetes remains uncertain. Considering the up-regulation of GLP-1, the administration of miglitol just before a meal, rather than after a meal, might be preferable for the prevention of the development of type 2 diabetes. From the results of this study, we speculate that the administration of

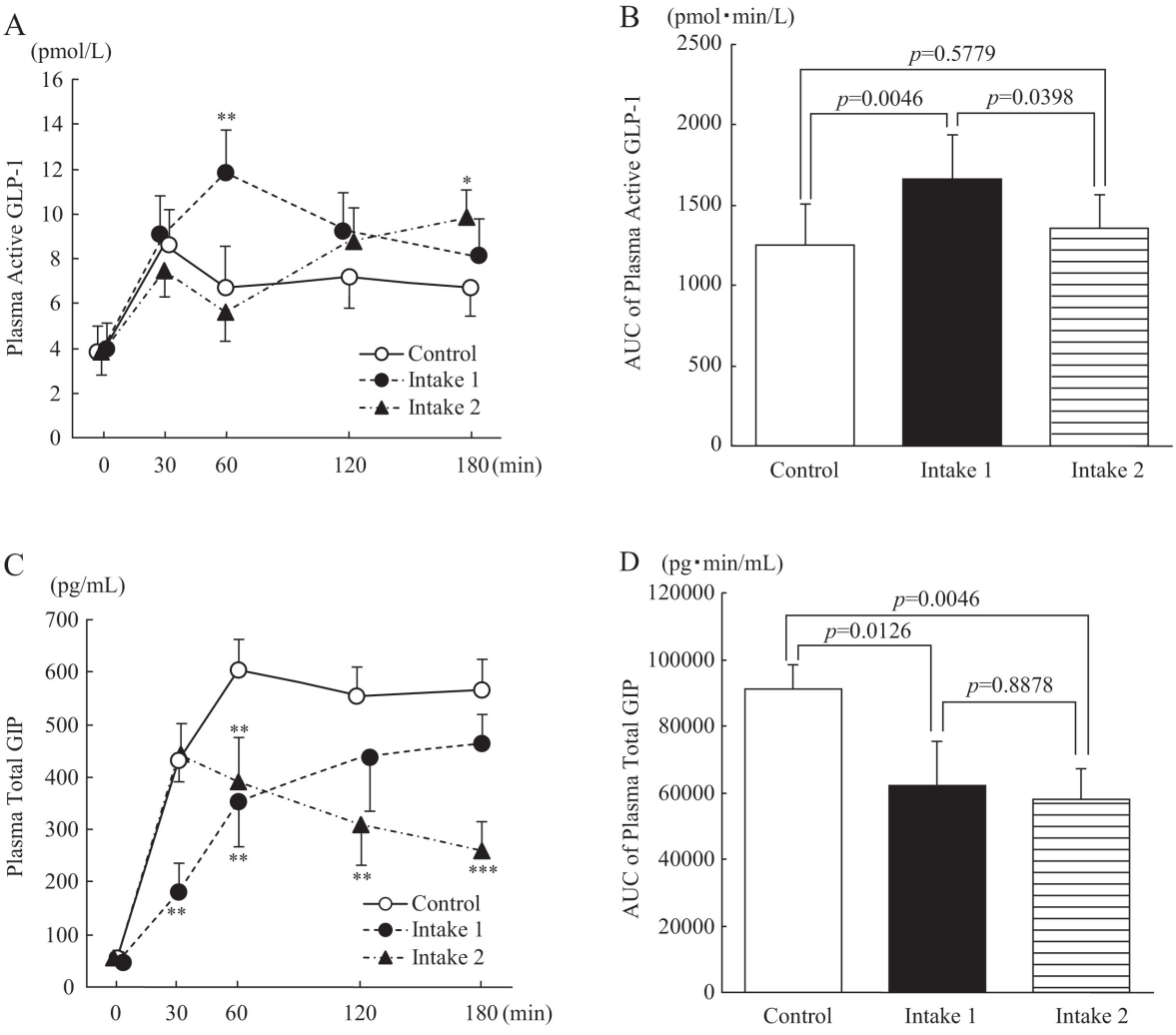

Fig. 2 Plasma active glucagon-like peptide-1 (GLP-1) and total glucose-dependent insulinotropic polypeptide (GIP) levels in the control and two miglitol intake schedules. A: Time profiles of the plasma GLP-1 levels for each miglitol intake schedule. B: The AUC of the plasma GLP-1 levels for each miglitol intake schedule. C: Time-profiles of the plasma GIP levels for each miglitol intake schedule. D: The AUC of the plasma GIP levels for each miglitol intake schedule. Data are expressed as the means ± SE. *p<0.05, **p<0.01, ***p<0.001 *vs.* control. Control: clear circles; Intake 1: filled circles; Intake 2: triangles.

miglitol just before a meal, rather than after a meal, may be recommended in view of the up-regulation of GLP-1 in type 2 diabetic patients. As we previously reported in [5], we would like to compare the incretin levels of pre- *vs.* post-meal administration of miglitol for long time in type 2 diabetic patients in future. We would also like to measure serum glucagon and total GLP-1 levels because we were unable to measure these parameters in the present study.

In conclusion, pre-meal administration of miglitol induced better plasma GLP-1 response rather than post-meal administration. The AUC of plasma GIP was smaller in both the groups of pre- and post-meal administration of miglitol, compared with the control.

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