Effects of miglitol taken just before or after breakfast on plasma glucose, serum insulin, glucagon and incretin levels after lunch in men with normal glucose tolerance, impaired fasting glucose or impaired glucose tolerance

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ABSTRACT

Aims/Introduction: One of the reasons for the poor adherence to α-glucosidase inhibitor (αGI) treatment is the need to take medication three times a day. We hypothesized that the administration of miglitol might be effective for the next meal if the miglitol-induced inhibition of α-glucosidase activity persists until the next meal. In the present study, we evaluated whether the administration of miglitol just before or after breakfast was effective for postprandial glucose excursion after lunch without taking miglitol at lunch.

Materials and Methods: We measured the plasma glucose, serum insulin and glucagon, plasma active glucagon-like peptide-1 (GLP-1), and total glucose-dependent insulinotropic polypeptide levels in non-diabetic men. Miglitol was given to each patient according to four different intake schedules (control: no drug; intake 1: drug given just before breakfast [50 mg]; intake 2: drug given 30 min after the start of breakfast [50 mg]; intake 3: drug given at the same time as intake 2, but without eating breakfast [50 mg]).

Results: Both intake 1 and intake 2 had a smaller area under the curve (AUC) for plasma glucose excursion after lunch, compared with the control. Intake 2 had a larger AUC for active GLP-1 after lunch, compared with intake 1.

Conclusions: Intake 1 and intake 2 can improve postprandial hyperglycemia after lunch. The results of the present study raise the possibility that the administration of miglitol twice a day might be effective and might help to improve treatment adherence among diabetic patients. This trial was registered with UMIN Clinical Trial Registry (no. UMIN000002896). (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00129.x, 2011)

KEY WORDS: Miglitol, α-Glucosidase inhibitor, Postprandial hyperglycemia

INTRODUCTION

The regulation of postprandial hyperglycemia has a significant clinical relationship with the risk of diabetic complications[1]. However, medication non-compliance is prevalent among diabetic patients and is associated with adverse clinical outcomes[2]. Hertz *et al.*[3] reported that initial treatment using insulin or an α-glucosidase inhibitor (αGI) was a risk factor for early non-persistence and the discontinuation of treatment[3]. Recently, we reported that existing or newly manufactured supportive devices can enable handicapped patients to self-inject insulin, and this delivery route might improve adherence to insulin treatment[4]. At least three reasons exist for the poor adherence to αGI treatment: (i) the need to take the medicine just before meals; (ii) adverse gastrointestinal effects; and (iii) the need to take the medicine three times a day. To improve adherence to αGI treatment, these issues must be resolved.

In general, αGI should be taken just before meals[5]. However, we previously reported that the administration of miglitol after a meal was equally effective as when administered just before a meal[6–8]. We also compared the adverse gastrointestinal effects of acarbose and miglitol, and reported that the condition of the patient's stools and gastrointestinal symptoms should be taken into consideration when starting αGI therapy[9]. Such information might decrease adverse gastrointestinal effects. Another reason for the poor compliance with αGI treatment is the need to take the medicine three times a day. We previously reported the results of interviews with 100 diabetic patients who had been prescribed αGI; the interviews covered the frequency of missed doses and what the patients did if they forgot to take the drug

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before taking the first mouthful of their meal. Of the 100 patients, 48 forgot to take the medicine more than once a week, and 54% of these patients did not take the medicine at all if they missed taking it at the appointed time[7]. Of note, many patients forgot to take the αGI drug before lunch, but the influence of missing this dose has not been evaluated systematically.

Miglitol reportedly enhances glucagon-like peptide-1 (GLP-1) responses and reduces glucose-dependent insulinotropic polypeptide (GIP)[10–12]. We reported that the pre-meal administration of miglitol evoked a larger plasma GLP-1 response than post-meal administration[13]. The area under the curve (AUC) of the plasma GIP level was smaller in both the pre-meal and post-meal miglitol administration groups, compared with the control.

We hypothesized that the administration of miglitol might be effective for the next meal if the miglitol-induced inhibition of α-glucosidase activity persists until the next meal and the upregulation of GLP-1 persists throughout the next meal. The purpose of this study is to compare the effectiveness of the administration of miglitol just before breakfast or just after breakfast on the plasma glucose, serum insulin and glucagon, plasma active GLP-1, and plasma total GIP levels after lunch without taking miglitol at lunch.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Review Committee of Yokohama City University, the protocol was registered in the UMIN Clinical Trial Registry as UMIN000002896. A total of 10 non-diabetic men (six healthy men with normal glucose tolerance [NGT], two men with an impaired fasting glucose [IFG] level according to the definition of the World Health Organization [WHO], and two men with impaired glucose tolerance [IGT]), aged 39.7 ± 6.3 years and with a glycated hemoglobin (HbA_{1c}) level of 5.45 ± 0.15% and a body mass index (BMI) of 24.4 ± 2.8 kg/m^2, were enrolled. The HbA_{1c} (%) value was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by using the following formula: HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society [JDS]) (%) + 0.4%, considering the relational expression of HbA_{1c} (JDS) (%) measured by the previous Japanese standard substance and measurement methods and HbA_{1c} (NGSP)[14]. Informed consent was obtained from each of the patients before the start of the study. Miglitol was given to each patient according to four different intake schedules (control: no drug; intake 1: drug given just before a meal [50 mg]; intake 2: drug given at 30 min after the start of a meal [50 mg]; intake 3: drug given at the same time as intake 2, but without eating breakfast [50 mg]). The patients were randomized to one of the four interventions using a crossover design. The patients were asked to take each medication after a drug-free washout period of more than 1 week. All patients received a standard breakfast and lunch (773 Kcal; protein: 27.0 g; fat: 20.3 g; carbohydrate: 121.5 g). For the study, the patients were requested to fast for at least 12 h before breakfast.

Blood samples were collected before the start of breakfast and at 0 (180 min after the start of breakfast), 30, 60 and 120 min after the start of lunch. The plasma glucose, serum insulin and glucagon, plasma active GLP-1, and plasma total GIP levels were measured. The incretin levels were measured using an ELISA kit (Millipore Corporation, Billerica, MA, USA) at SRL, Inc. (Tokyo, Japan). We measured the total GIP level in the present study, because we could not obtain a commercially available kit capable of accurately measuring active GIP.

Because we previously reported the blood glucose levels for 30, 60 and 120 min after breakfast in groups with pre-meal or post-meal miglitol administration[13], we did not collect blood samples at 30, 60 or 120 min after breakfast in the present study. The glucose levels were measured using a self-monitoring blood glucose device (Glutest Neo Super; Sanwa Kagaku, Nagoya, Japan), and the intermediary value was used.

The data were expressed as the means ± SE. The AUC from just before lunch until 180 min after the start of lunch were calculated using the trapezoid method. The analyses were carried out using a two-way layout analysis of variance (ANOVA) with Tukey-type multiple comparisons. All statistical analyses were carried out using SPSS for Windows, Japanese version 16.0 (SPSS Institute Inc., Tokyo, Japan).

RESULTS

The time profiles of the plasma glucose levels, the AUC of the plasma glucose levels from after breakfast until 120 min after lunch, the AUC of the plasma glucose levels after lunch and the AUC of the plasma glucose excursion after lunch for each group are shown in Figure 1. The plasma glucose levels at 30 min after the start of breakfast in the intake 1 and intake 3 groups were significantly lower than those in the control and intake 2 groups (Figure 1a). The plasma glucose levels at 60 min after the start of breakfast in the intake 1 group were significantly lower than those in the control group, and the values in the intake 3 group were significantly lower than those in the control and intake 2 groups. The plasma glucose levels at 120 min after the start of breakfast in the intake 3 group were significantly lower than those in the control group. The plasma glucose levels at 180 min after the start of breakfast in the intake 2 and intake 3 groups were significantly lower than those in the intake 1 group. These results were consistent with our previously reported results[6,13].

The plasma glucose levels at 30 and 60 min after the start of lunch in the intake 2 group were significantly lower than those in the control and intake 3 groups (Figure 1a). As a result, the AUC of the plasma glucose levels from after breakfast until 120 min after lunch were smaller in the intake 1, 2 and 3 groups than in the control (Figure 1b). By contrast, the $AUC_{0–120\ min}$ of the plasma glucose levels after lunch in the intake 2 group were significantly lower than those in the control, intake 1 and intake 3 groups (Figure 1c).

We also evaluated the impact of the administration of miglitol on postprandial glucose excursion after lunch. The AUC of the

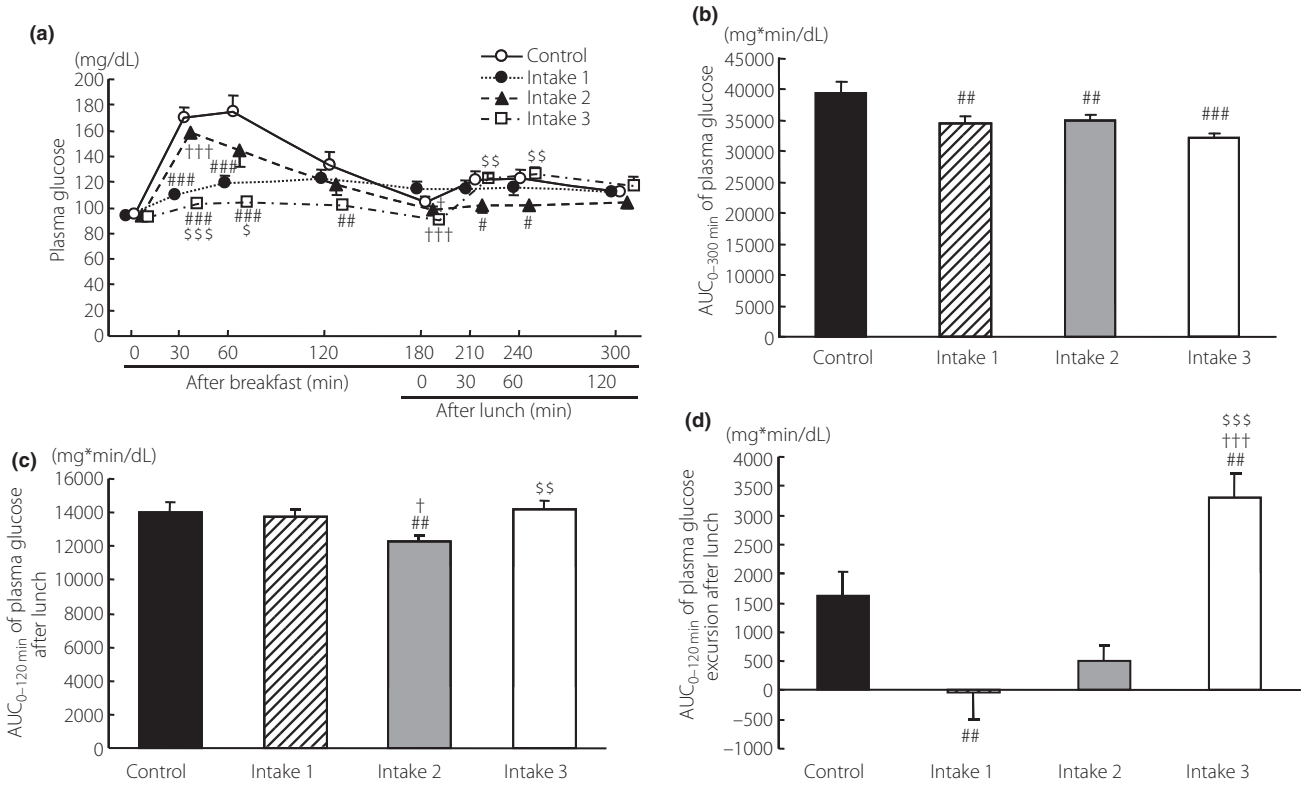

Figure 1 | Plasma glucose levels in the control and three miglitol intake groups. (a) Time profiles of the plasma glucose levels for each group. (b) Area under the curve (AUC) of the plasma glucose levels from after breakfast until 120 min after lunch for each group. (c) AUC of the plasma glucose levels after lunch for each group. (d) AUC of plasma glucose excursion after lunch for each group. The time data are presented as the mean ± SE. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs control, †$P < 0.05$, †††$P < 0.001$ vs intake 1, \$$P < 0.05$, \$\$$P < 0.01$, \$\$\$$P < 0.001$ vs intake 2.

plasma glucose excursion after lunch in the intake 1 group was lower than that of the control, and the AUC of the plasma glucose excursion after lunch in the intake 3 group was higher than that of the control, intake 1 and intake 2 groups (Figure 1d).

The serum insulin levels at 0 and 30 min after the start of lunch in the intake 3 group and at 30, 60 and 120 min after the start of lunch in the intake 2 group were significantly lower than those in the control group, and the serum insulin levels at 0, 60 and 120 min after the start of lunch in the intake 2 group and at 0 min after the start of lunch in the intake 3 group were significantly lower than those in the intake 1 group (Figure 2a). The $AUC_{0–120\ min}$ of the serum insulin levels in the intake 2 group was significantly lower than those in the control and intake 1 groups (Figure 2b). The AUC of the serum insulin excursion after lunch in the intake 1 group was lower than that in the intake 3 group, and the AUC of the serum insulin excursion after lunch in the intake 2 group was lower than those in the control and intake 3 groups (data not shown).

The serum glucagon levels at 0, 30, 60 and 120 min after the start of lunch in the intake 2 group were significantly higher than those in the control, intake 1 and intake 3 groups, although all the values were within the normal limits (Figure 3a). The $AUC_{0–120\ min}$ of the serum glucagon levels in the intake 2 group were significantly greater than those in the control, intake 1 and intake 3 groups (Figure 3b). There were no significant differences in the AUC of the plasma glucagon excursion after lunch among the four groups (data not shown).

The plasma active GLP-1 levels at 0, 30, 60 and 120 min after the start of lunch in the intake 2 group were significantly higher than those in the control, intake 1 and intake 3 groups (Figure 4a). The $AUC_{0–120\ min}$ of the plasma active GLP-1 levels in the intake 2 group were significantly greater than those in the control, intake 1 and intake 3 groups (Figure 4b). There were no significant differences in the AUC of the plasma GLP-1 excursion after lunch among the four groups (data not shown).

The plasma total GIP levels at 0, 30, 60 and 120 min after the start of lunch in the intake 2 group and the values at 0, 30 and 60 min after the start of lunch in the intake 3 group were significantly lower than those in the control group. The plasma total GIP levels at 0, 30 and 60 min after the start of lunch in the intake 2 group and the values at 0 and 30 min after the start of lunch in the intake 3 group were significantly lower than those in the intake 1 group (Figure 5a). The $AUC_{0–120\ min}$ of the plasma total GIP level in the intake 2 group was significantly lower than those in the control and intake 1 groups, and the $AUC_{0–120\ min}$ of the plasma total GIP level in the intake 3 group

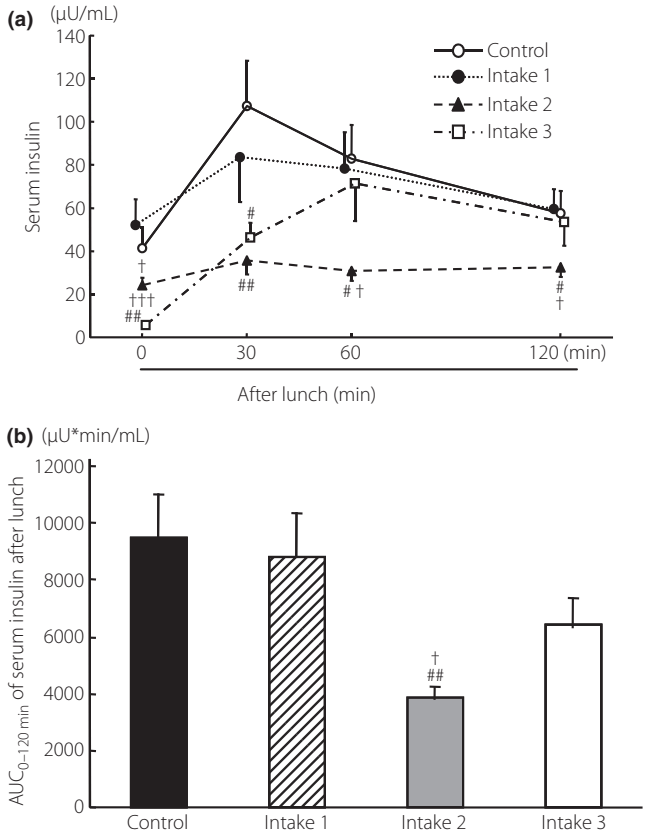

Figure 2 | Serum insulin levels after lunch in the control and three miglitol intake groups. (a) Time profiles of the serum insulin levels for each group. (b) Area under the curve of the serum insulin levels after lunch for each group. The time data are presented as the mean ± SE. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, †$P < 0.05$, †††$P < 0.001$ vs intake 1.

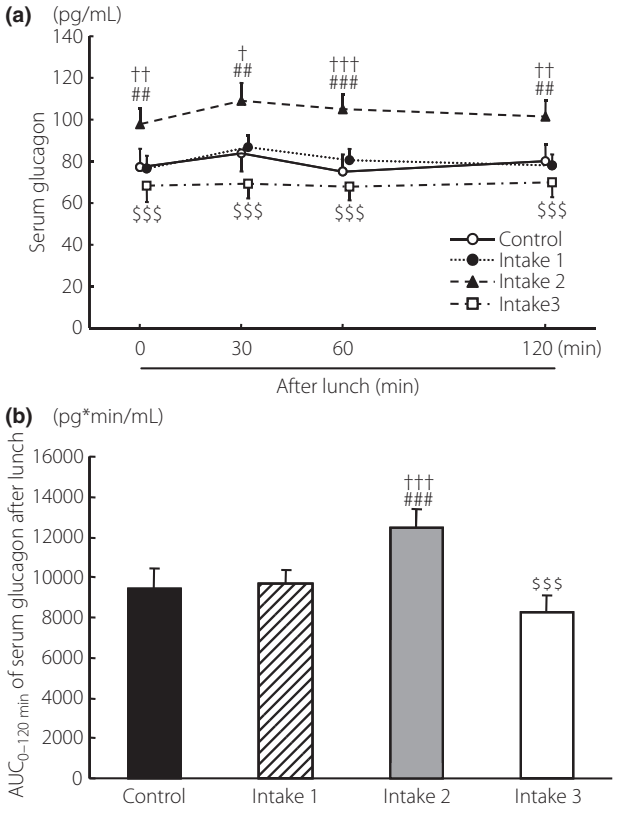

Figure 3 | Serum glucagon levels after lunch in the control and three miglitol intake groups. (a) Time profiles of the serum glucagon levels for each group. (b) Area under the curve of the serum glucagon levels after lunch for each group. The time data are presented as the mean ± SE. $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs control, †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ vs intake 1, $\$\$\$P < 0.001$ vs intake 2.

was significantly lower than that in the control group (Figure 5b). The AUC of the plasma total GIP excursion after lunch was significantly greater in the intake 3 group than in the control, intake 1 and intake 2 groups (data not shown).

DISCUSSION

We compared the effectiveness of the administration of miglitol just before breakfast or after breakfast on the plasma glucose, serum insulin and glucagon, and plasma incretins levels after lunch without taking miglitol at lunch. Here, we report several novel findings: the intake 1 and 2 schedules both decreased the AUC of the plasma glucose levels from after breakfast until 120 min after lunch, the intake 1 schedule decreased the plasma glucose excursion after lunch even without taking miglitol at lunch, and the intake 2 schedule also decreased the AUC of the plasma glucose levels after lunch, even without taking miglitol at lunch.

Both the intake 1 and the intake 2 schedules were effective for decreasing the plasma glucose level after lunch, even without taking miglitol at lunch. Based on the results of the present study, the administration of miglitol twice daily (at breakfast and at dinner) might be effective, and this might improve adherence to αGI treatment. The ultimate goal of the present clinical study is to examine the efficacy of administration of miglitol twice a day in subjects with type 2 diabetes. We would like to evaluate the effectiveness of miglitol on the next meal with a continuous glucose monitoring system (CGMS) in diabetic subjects in the future.

What is the impact of the administration of miglitol just before breakfast or after breakfast on the plasma incretin levels after lunch? The intake 2 schedule increased the AUC of active GLP-1 after lunch, compared with the intake 1 schedule; however, the intake 1 schedule further increased the AUC of the plasma active GLP-1 levels in the morning, compared with the intake 2 schedule[13]. Therefore, the total increment in active GLP-1 from the beginning of breakfast until 2 h after lunch is likely to be similar in the intake 1 and 2 groups. Given the fact that diabetes develops when insulin secretion by β-cells is insufficient to compensate for insulin resistance[15,16], the increase in GLP-1 might be important for improving β islet cell function. Because GLP-1 reportedly inhibits β-cell apoptosis in humans[17],

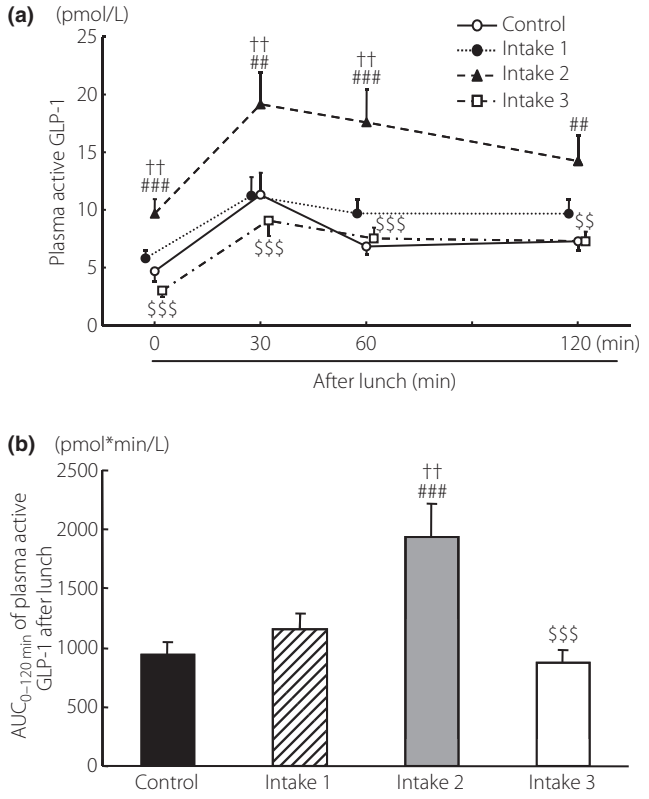

Figure 4 | Plasma active glucagon-like peptide-1 (GLP-1) levels after lunch in the control and three miglitol intake groups. (a) Time profiles of the plasma active GLP-1 levels for each group. (b) Area under the curve of the plasma active GLP-1 levels after lunch for each group. The time data are presented as the mean ± SE. $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs control, $\dagger\dagger P < 0.01$ vs intake 1, $\$\$P < 0.01$, $\$\$\$P < 0.001$ vs intake 2.

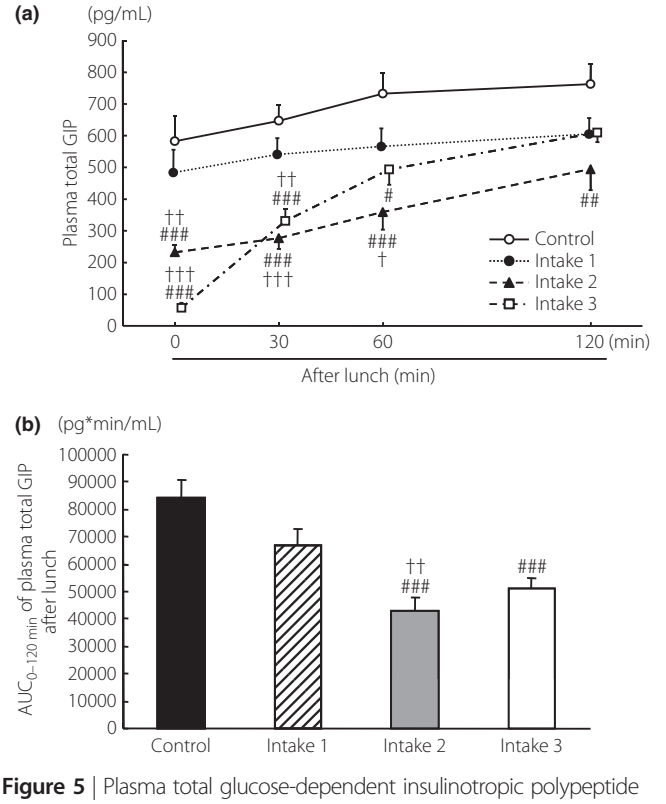

Figure 5 | Plasma total glucose-dependent insulinotropic polypeptide (GIP) levels after lunch in the control and three miglitol intake groups. (a) Time profiles of the plasma total GIP levels for each group. (b) Area under the curve of the plasma total GIP levels after lunch for each group. The time data are presented as the mean ± SE $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs control, $\dagger P < 0.05$, $\dagger\dagger P < 0.01$, $\dagger\dagger\dagger P < 0.001$ vs intake 1.

an increase in GLP-1 secretion might also be beneficial for β-cell protection in humans.

The intake 3 schedule failed to decrease the AUC of the plasma glucose level after lunch and instead increased the AUC of glucose excursion after lunch. The intake 1 schedule was less effective with regard to the serum insulin, plasma GLP-1 and GIP levels than the intake 2 schedule. Therefore, miglitol likely mixes with the food in the intestine, protecting against glucose uptake after lunch.

The $AUC_{0–120\ min}$ of the serum glucagon levels after lunch was significantly greater in the intake 2 group than in the control, intake 1 and intake 3 groups (Figure 3b). The effect of acarbose on the serum glucagon levels has been controversial[18–20]. In addition, GLP-1 has been shown to suppress glucagon secretion when the plasma glucose levels are above the fasting level[21]. However, the decreased insulin levels might at least partly explain the increased glucagon levels in the intake 2 group, compared with in the control and intake 1 groups.

In conclusion, miglitol taken either just before or after breakfast remains in the intestine and improves postprandial hyperglycemia after lunch. Our results suggest the effectiveness of the administration of miglitol twice a day, possibly improving the treatment compliance of diabetic patients.

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