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REVIEW

Usefulness of antidiabetic alpha-glucosidase inhibitors: a review on the timing of administration and effects on gut hormones

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Abstract. Elevation of postprandial plasma glucose is correlated with an increase in cardiovascular events, and alpha-glucosidase inhibitors (αGIs) are effective at reducing postprandial glucose levels. In Japan, the αGIs acarbose, voglibose, and miglitol have been available since 1993, 1994, and 2006, respectively. Dipeptidyl peptidase-4 (DPP-4) inhibitors are also effective at reducing postprandial glucose levels, and they have been available in Japan since 2009. A combination therapy of αGI, miglitol, and the DPP-4 inhibitor, sitagliptin, is more effective at decreasing postprandial glucose levels than monotherapy with either miglitol or sitagliptin. Moreover, the combination therapy of miglitol and sitagliptin is more effective at increasing postprandial active glucagon-like peptide-1 (GLP-1) levels than monotherapy. Peptide YY (PYY) has appetite-suppressing and gastric-emptying effects similar to GLP-1. In healthy individuals, miglitol increases the postprandial total PYY; however, combination therapy of miglitol and vildagliptin does not change postprandial total PYY levels. αGIs are typically prescribed to be taken just before a meal, which can result in decreased drug adherence. Different patterns of αGI intake were examined, and the results showed that miglitol or acarbose administration after a meal is effective. The effects of taking miglitol dissolved in water during a meal appeared to be similar to that of taking miglitol as a tablet just before a meal. The long-term effects of taking miglitol dissolved in water should be evaluated in future studies. αGIs may be effective even when they are not taken before a meal, and a more flexible administration may improve drug adherence.

Key words: Alpha-glucosidase inhibitor, Dipeptidyl peptidase-4 inhibitor, Gut hormone, Intake pattern

A LARGE NUMBER OF PATIENTS have type 2 diabetes worldwide, including in Japan. Treatment is important as to prevent severe complications from diabetes. Elevation of postprandial plasma glucose levels is significantly correlated with an increase in cardiovascular events [1, 2]. Anti-diabetic drugs, such as alpha-glucosidase inhibitors (αGIs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glinides, GLP-1 analogs, and short-acting insulin, are effective at reducing postprandial glucose levels. We focused on αGIs and DPP-4 inhibitors, which are associated with incretin regulation.

In Japan, there are three types of approved αGIs: acarbose, voglibose, and miglitol. αGIs delay the absorption of glucose by inhibiting brush border enzymes in the small intestine, thereby decreasing postprandial plasma glucose and insulin levels [3]. DPP-4 inhibitors have been available in Japan since 2009, after which αGI use declined. However, αGIs are still important for the treatment of diabetes patients.

Miglitol reduces serum insulin levels and has anti-obesity effects [4]. The Study to Prevent Noninsulin-Dependent Diabetes Mellitus trial showed that acarbose therapy prevents progression to diabetes in individuals with impaired glucose tolerance (IGT) and reduces the risk of cardiovascular events compared with placebo [5]. Voglibose also reduces the development of type 2 diabetes in individuals with IGT [6]. Moreover, a meta-analysis of studies on type 2 diabetes (MeRIA[7]) revealed that acarbose reduces the risk of cardiovascular events compared with placebo [7].

DPP-4 inhibitors improve hyperglycemia by inhibiting cleavage of incretins. αGIs also affect incretins; therefore, the effect of combination therapy of an αGI and a DPP-4 inhibitor on gut hormones is interesting.

αGIs should be taken just before a meal according to

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Table 1 Production organ and cell of gut hormones and their effect on appetite and gastric emptying

	GLP-1	GIP	PYY	CCK	Ghrelin
Organ	Small intestine	Small intestine	Small intestine	Small intestine	Stomach
Cell name	L cell	K cell	L cell	I cell	X/A-like cell
Appetite	Decrease	None	Decrease	Decrease	Increase
Gastric emptying	Inhibit	None	Inhibit	Inhibit	Stimulate

GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; PYY, peptide YY; CCK, cholecystokinin

the package insert. However, this can result in decreased drug adherence. Allowing patients to take αGIs after a meal would create more flexibility of the timing of administration of αGIs and likely increase drug adherence. Therefore, it is important to determine the efficacy of αGIs when taken after a meal.

In this review, we aimed to analyze the effects of combination therapy of an αGI and a DPP-4 inhibitor on gut hormones. We also aimed to analyze patients' levels of glycemic control based on the pattern of αGI intake. As αGIs have many beneficial effects, improving drug adherence should be considered in the timing of αGI administration to patients.

Effect of Combination Therapy of αGI and DPP-4 Inhibitor on Gut Hormones

Summary of gut hormones

Several gut hormones, secreted by the stomach or the small intestine, that regulate appetite and gastric emptying are shown in Table 1. Gut hormones including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretins. After food intake, GLP-1 is secreted by L cells located in the lower part of the small intestine, and GIP is secreted by K cells in the upper part of the small intestine. GLP-1 and GIP stimulate glucose-dependent insulin secretion; GLP-1 also inhibits glucagon secretion [8]. GLP-1 can reduce appetite and food intake and has a protective effect on the pancreatic β-cell function in animal models [8, 9]. GIP has additional effects on adipocytes and bone [8]. The peptide YY ($PYY_{1–36}$) is mainly secreted by L cells in the intestine [10, 11]. Cleavage of the N-terminal tyrosine-proline residues of $PYY_{1–36}$ by DPP-4 results in the production of $PYY_{3–36}$, which constitutes approximately 63% of the total PYY after a meal and approximately 37% after fasting [12, 13]. $PYY_{3–36}$ administration in mice and humans reduces food intake [14]. Cholecystokinin (CCK) is secreted from I cells in the duodenum and jejunum [15]. CCK stimulates pancreatic enzyme secretion and gall bladder contraction, and delays gastric emptying and food intake by stimulating the vagus nerve [16, 17]. Ghrelin is an orexigenic peptide secreted by the stomach [18]. Plasma ghrelin concentrations increase with fasting and decrease after eating [19]. Obestatin has been isolated from the rat stomach and is encoded by the ghrelin gene [20]. Obestatin reduces food intake and gastrointestinal motility; however, the effects of obestatin remain controversial [21, 22].

Effect of αGIs or DPP-4 inhibitors on gut hormones

Miglitol increases the GLP-1 secretion and decreases the GIP secretion [23-26]. These effects are due to a change in the location of glucose absorption from the upper portion to the lower portion of the small intestine. Kaku *et al.* reported that patients who received a single dose of miglitol showed higher postprandial plasma total PYY levels and lower postprandial active ghrelin levels after 180 min (% of basal levels) compared with the control group (no medication) [27]. Additionally, in the study by Kaku *et al.*, miglitol suppressed appetite, maintained satiety, and delayed gastric emptying. Treatment with acarbose resulted in delays in gastric emptying and increase in CCK, GLP-1, and PYY levels [28].

DPP-4 inhibitors increase active GLP-1 and active GIP by inhibiting DPP-4 activity and improve hyperglycemia in a glucose-dependent fashion by increasing serum insulin and decreasing serum glucagon levels in patients with diabetes [29]. Administration of vildagliptin for 10 days decreased total PYY levels in patients with type 2 diabetes [30], and administration of sitagliptin for 3 months also reduced total PYY and $PYY_{3–36}$ levels and increased $PYY_{1–36}$ levels [31]. Sitagliptin decreased the fasting total ghrelin levels in patients with type 2 diabetes, but did not change the postprandial total ghrelin levels in healthy individuals [32, 33]. Moreover, vildagliptin did not change the postprandial active ghrelin levels in patients with type 2 diabetes [34].

Combination therapy of αGI and DPP-4 inhibitor

Human studies

The specific changes in gut hormones that occur in individuals who received a combination of an αGI and a DPP-4 inhibitor have not been fully elucidated; therefore, the effects of αGIs, DPP-4 inhibitors, and combina-

Table 2 Effects of miglitol, sitagliptin, or vildagliptin as monotherapy and combination therapy on gut hormones

	Active GLP-1	Total GIP	Total PYY	CCK	Active Ghrelin
Miglitol	↑	↓	↑	→	→
Sitagliptin or vildagliptin	↑	↓	↘	→	→
Combination therapy	↑↑	↓↓	→	→	→

Effects of miglitol, sitagliptin, or vildagliptin as monotherapy and combination therapy on postprandial gut hormones in healthy individuals [35, 36].

Two arrows represent combination therapy: two upward arrows indicate that combination therapy increased the level of a specific variable compared with monotherapy, while two downward arrows indicate that combination therapy decreased the level of a specific variable compared with monotherapy. Slanting arrow indicates the tendency to decrease (statistically significant).

tion therapy on gut hormones in healthy men were evaluated [35]. Miglitol and sitagliptin were administered to healthy individuals as a single drug or as a combination therapy, and the results were compared to those of the control group (no drug). The postprandial active GLP-1 level was higher in the group treated with miglitol, sitagliptin, and miglitol plus sitagliptin compared with the control group (Table 2). More specifically, combination therapy of miglitol plus sitagliptin resulted in higher postprandial active GLP-1 levels than monotherapy with miglitol or sitagliptin. The postprandial total GIP levels in the miglitol plus sitagliptin group were lower than those in the control group, miglitol group, or sitagliptin group. As GLP-1 reduces appetite and food intake [8], the increase of active GLP-1 may be beneficial for obese patients with type 2 diabetes. However, the exact effects of increased active GLP-1 after combination therapy in diabetes patients remain unknown; therefore, further research is needed to study this aspect.

Subsequently, the effect of another combination therapy of an αGI and a DPP-4 inhibitor on gut hormones, such as total PYY ($PYY_{1–36}$ plus $PYY_{3–36}$), CCK, ghrelin, and obestatin, were evaluated (Table 2) [36]. Miglitol and vildagliptin were administered to healthy men either as monotherapy or combination therapy, and the results were compared to those of the control group (no drug). The postprandial serum total PYY was significantly increased in the group treated with miglitol compared with the control group, whereas patients treated with vildagliptin exhibited a non-significant decrease in serum total PYY compared with the control group. As expected, the serum total PYY levels of patients treated with combination therapy remained unchanged compared with the control group. In addition, the postprandial plasma CCK, plasma active ghrelin, plasma obestatin, and ghrelin/obestatin levels of patients who received combination therapy remained unchanged compared with the control group. These results suggested that combination therapy of miglitol and vildagliptin has no effect on appetite-regulating hormones, such as total PYY, CCK, active ghrelin, and obestatin. In the future, it will be interesting to study the appetite and gastric emptying of patients with type 2 diabetes after receiving a combination therapy.

Mikada *et al.* reported on the use of combination therapy of miglitol and sitagliptin for 24 weeks in overweight patients with type 2 diabetes [26]. Postprandial active GLP-1 levels of patients treated with combination therapy after a meal tolerance test were increased compared with those treated with miglitol or sitagliptin. Postprandial total GIP was decreased after treatment with miglitol, but remained unchanged after treatment with sitagliptin. Additionally, combination therapy was more effective in decreasing total GIP than monotherapy with miglitol or sitagliptin.

We also reported the effectiveness of the miglitol monotherapy when received just before breakfast on the plasma glucose and incretin levels in sitagliptin-treated patients with type 2 diabetes [37]. Miglitol was not administered on the first day; it was only administered on the second day just before breakfast. Miglitol was only administered just before breakfast, but was not administered before lunch in order to increase the postprandial active plasma GLP-1 levels after lunch. This finding suggests that miglitol, in combination with sitagliptin, can act as a "GLP-1 enhancer," even in combination with sitagliptin. As mentioned previously, the effects of high active GLP-1 levels in diabetes patients treated with combination therapy remain unknown.

Animal studies

db/db mice, an animal model of diabetes, were under combination therapy with voglibose and alogliptin for 3 weeks [38]. The combination therapy increased insulin and active GLP-1 secretion, decreased glucagon secretion, prevented the onset of diabetes, and preserved pancreatic beta-cell in prediabetic db/db mice. The authors suggested that these effects were due to the increased active GLP-1 levels and improved hyperglycemia by the combination therapy. Combination therapies of three different αGIs (acarbose, voglibose, or miglitol) and sitagliptin were administered to C57BL/6J mice [39], and all three combinations resulted in a synergic increase of

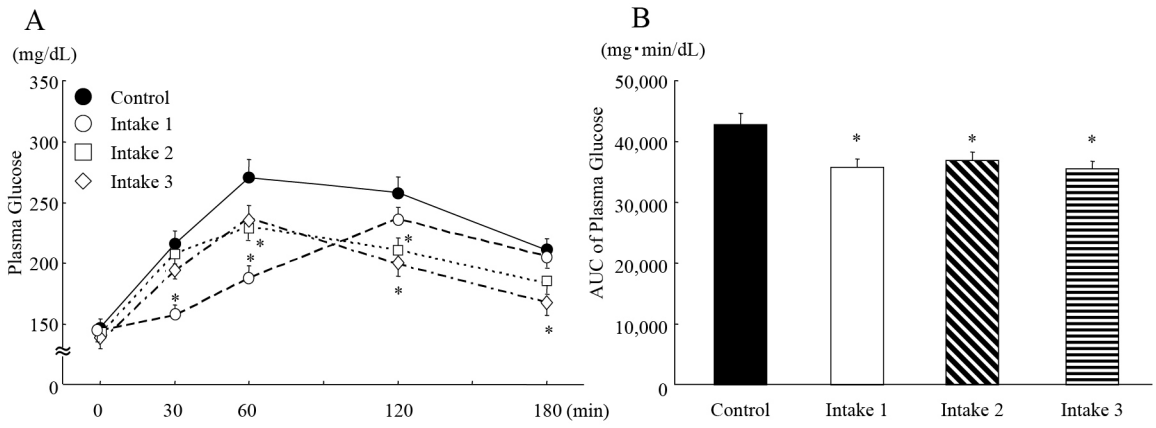

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Fig. 1 The effects of miglitol intake pattern on postprandial plasma glucose levels

Miglitol was administered once using four different intake patterns. Control: no miglitol, intake 1: just before breakfast, intake 2: 15 min after the beginning of breakfast, intake 3: 30 min after the beginning of breakfast. A: Effects of the intake patterns on plasma glucose levels from mealtime (0 min) to 180 min after the meal. B: The area under the curve (AUC) of plasma glucose from 0 min to 180 min after the meal. $*p < 0.05$ compared with the control group.

active GLP-1. The combination therapy of miglitol and sitagliptin resulted in a stronger inhibition of early phase of postprandial hyperglycemia compare with other combinations.

Combination therapy of αGI and other antidiabetic drugs

The combination therapy of miglitol and metformin improved the glycemic control of patients with type 2 diabetes compared with metformin monotherapy [40]. The combination therapy of miglitol and mitiglinide also improved the glycemic control of patients with type 2 diabetes compared with monotherapy [41]. The addition of dulaglutide to the αGI treatment resulted in a decrease in HbA1c levels and body weight [42]. The combination therapy of premixed insulin and acarbose or metformin improved the glycemic control of the patients with type 2 diabetes to some extent [43]. Thus, the combination of αGI and other antidiabetic drugs is also effective in improving glycemic control. In addition to αGI and DPP-4 inhibitor, metformin can also increase endogenous active GLP-1 levels in the patients with type 2 diabetes [44]. However, it remains unclear whether a combination of αGI and metformin is more effective in increasing active GLP-1 levels than monotherapy. As the effects of αGI and DPP-4 inhibitor combination therapy on incretin levels have already been validated, those of αGI and metformin combination therapy should also be investigated in future studies.

Intake Pattern of αGI

Administration of αGI after a meal

In Japan, patients with type 2 diabetes are instructed to take αGI just before a meal; however, it is often difficult to take these drugs just before a meal. A gastric emptying test was conducted in patients with diabetes using a ^{99m}TC-labeled solid meal. The mean gastric retention rates at 150 min after starting the meal in patients without or with autonomic neuropathy were 33% and 65%, respectively [45]. Therefore, αGI is effective in patients with diabetes when administered after a meal. Rosac *et al.* reported that acarbose is effective in type 2 diabetes patients when taken 15 min after starting a meal [46]. Asakura *et al.* reported that acarbose is effective in healthy or IGT individuals when taken 30 min after starting a meal [47]. Miglitol is partially absorbed at the upper portion of the small intestine, resulting in a higher effectiveness at reducing blood glucose levels at 30 min after a meal than voglibose or acarbose [48, 49]. Therefore, it was interesting to examine the effect of miglitol treatment after a meal in patients with type 2 diabetes. As shown in Fig. 1, administration of miglitol at 15 and 30 min after the start of a meal decreased the postprandial glucose levels to same level as when the drug was administered just before a meal [50]. Another study showed that the administration of miglitol after meals for a duration of 3 months decreased the HbA1c level and increased the 1,5-anhydroglucitol (1,5-AG) level to the same extent as when miglitol was administered just before a meal [51]. The effect of a single administration of voglibose just after a meal was also evaluated in indi-

viduals with or without IGT [52]. The administration of voglibose just before breakfast decreased the postprandial plasma glucose levels, but the administration of voglibose after a meal did not decrease the postprandial plasma glucose levels. It was reported that the administration of voglibose after a meal tends to decrease postprandial serum insulin levels ($p = 0.07$). Hence, a long-term observational study using a larger sample size is required to further evaluate the effects of administering voglibose after a meal. In summary, administration of miglitol or acarbose after a meal is effective and this may improve drug adherence of patients with diabetes.

Dissolved-dose regimen of αGI

The administration of miglitol after a meal decreased the postprandial plasma glucose to the same level as administration just before a meal; therefore, it was evaluated whether a divided-dose of miglitol might improve postprandial glucose excursions. Administration of a divided-dose of miglitol just before and 15 min after the start of a meal smoothed the postprandial glucose and insulin excursions in healthy men [53].

More recently, the efficacy and safety of miglitol dissolved in water taken during a meal and a miglitol tablet taken just before a meal were compared [54]. Postprandial plasma glucose and insulin levels were significantly lower when miglitol was taken just before breakfast and when miglitol dissolved in water was consumed during breakfast compared with not taking the medication at all. The efficacy of taking miglitol dissolved in water during a meal appeared to be similar to taking a miglitol tablet just before a meal. Interestingly, the coefficient of variation of plasma glucose was significantly lower for the dissolved-dose regimen than taking miglitol just before a meal or not taking miglitol at all. Therefore, the results of this study suggest that a dissolved-dose regimen is useful, but longer effects of taking miglitol dissolved in water on glycemic control need to be studied further.

Summary

In this review, we described the effects of combination therapy of αGIs and DPP-4 inhibitors on gut hormones. The combination therapy of miglitol and sitagliptin increases active GLP-1 levels. As the exact effects of increased active GLP-1 levels after combination therapy in diabetes patients are unknown, further studies are warranted to examine the effects of combination therapy on other gut hormones.

In addition, we evaluated the effect of intake pattern of αGIs on glycemic control. The administration of miglitol or acarbose after a meal is effective, and this may improve the drug adherence of patients with diabetes. The effects of drinking water with dissolved miglitol during a meal appeared similar to taking a miglitol tablet just before a meal. Thus, we propose the possible usefulness of this dissolved-dose regimen, and the long-term effects of taking miglitol dissolved in water should be evaluated.

In conclusion, miglitol increases GLP-1 levels even in combination with sitagliptin. Improving drug adherence should be considered when discussing the intake pattern of αGIs with patients.

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