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ORIGINAL ARTICLE

Comparison of three α-glucosidase inhibitors for glycemic control and bodyweight reduction in Japanese patients with obese type 2 diabetes

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ABSTRACT

Aims/Introduction: α-Glucosidase inhibitors (αGIs) are widely used for the primary treatment of type 2 diabetes. We compared the clinical effects of three αGIs (miglitol, acarbose and voglibose) in patients with obese type 2 diabetes.

Materials and Methods: Japanese patients (n = 81) with obese type 2 diabetes (body mass index [BMI] ≥25 kg/m^2) were enrolled in this multicenter, open-label study. The participants were randomized into the miglitol (n = 18), acarbose (n = 22), voglibose (n = 19) or control (n = 22) groups. Glycemic control (fasting blood glucose and glycated hemoglobin [HbA1c]), bodyweight, BMI, serum insulin, serum lipids (low-density lipoprotein and high-density lipoprotein cholesterol, and triacylglycerols) and adipocytokines (leptin and adiponectin) were evaluated every 4 weeks for 12 weeks.

Results: In the miglitol group, HbA1c was improved significantly from the baseline at all points. The changes in HbA1c at 8 and 12 weeks from baseline were greater in the miglitol group than the control group. The voglibose group showed significant improvements in HbA1c at 12 weeks. Bodyweight and BMI were decreased significantly in the miglitol group. In addition, significant correlations were observed between the decrements in HbA1c and bodyweights over 12 weeks in the miglitol (r = 0.759, P < 0.001) and voglibose groups (r = 0.667, P = 0.002). Serum lipid and adipocytokine levels were not altered in any groups.

Conclusions: αGIs, especially miglitol, can effectively control blood glucose and bodyweight in obese type 2 diabetes. This study was registered with UMIN (no. UMIN000006465).

INTRODUCTION

Type 2 diabetes is a well-known risk factor for cardiovascular disease. Several experimental results suggest that postprandial hyperglycemic spikes contribute to the pathophysiology of diabetic cardiovascular complications. The suppression of postprandial hyperglycemia is therefore a promising approach for preventing cardiovascular disease in type 2 diabetes[1].

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α-Glucosidase inhibitors (αGIs) are widely used for the primary treatment of type 2 diabetes. They inhibit maltase, sucrase and other disaccharide hydrolases (i.e., suppress the degradation of disaccharides to monosaccharides) in the brush border membrane of the small intestine[2]. Therefore, αGIs can improve postprandial hyperglycemia by delaying carbohydrate absorption. The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus trial[3] showed that treatment with an αGI, acarbose, is associated with a significant risk reduction in cardiovascular

events in patients with impaired glucose tolerance or type 2 diabetes. Subsequently, much attention has been focused on αGIs as therapeutic agents for type 2 diabetes and its complications.

Weight gain in type 2 diabetes not only worsens diabetic control, but also increases the risk of diabetes-associated cardiovascular complications[4]. However, glycemic control with insulin or certain oral hypoglycemic agents (insulin secretagogues and thiazolidinediones) promotes weight gain[5]. In contrast, biguanides and incretin-related drugs (glucagon-like peptide 1 [GLP-1] analogs and dipeptidyl peptidase 4 inhibitors) have beneficial effects on bodyweight. Meanwhile, the effects of αGIs on bodyweight control remain unclear. Whereas some studies suggest that αGIs can reduce bodyweight in type 2 diabetes[3,6], a meta-analysis of randomized controlled trials with acarbose showed that it has minor effects for lowering bodyweight[7].

Three αGIs are now clinically available in Japan: acarbose, miglitol and voglibose. However, to our knowledge, there have been no reports comparing these drugs head-to-head. In the present study, we evaluated the effects of these three αGIs on glycemic control, weight management and other clinical measures in the treatment of Japanese patients with obese type 2 diabetes.

MATERIALS AND METHODS

The present study was a multicenter (Nippon Medical School Hospital; Saitama Medical Center, Jichi Medical University; Hachijo Municipal Hospital; Kashiwa City Hospital; and Otonari Medical Clinic), open-label, randomized study. The protocol was approved by each institutional ethics review board, and all participants were enrolled after being informed of the clinical trial and providing written consent.

Participants

The study included 81 outpatients (38 men and 43 women) with obese type 2 diabetes (aged ≥40 years; glycated hemoglobin [HbA1c] 6.4–8.4%; body mass index [BMI] ≥25 kg/m^2). HbA1c was measured by the latex agglutination method and expressed as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%)[8,9]. Patients who had received insulin therapy or αGI medication, or had a serious hepatic, renal, or cardiac disease were excluded.

Study Design

After the informed consent was obtained, an application form was sent to an external registration center by facsimile. Approved participants were allocated to one of four treatment groups using a random number list for miglitol (150 mg/day), acarbose (300 mg/day), voglibose (0.9 mg/day) and control (no additive medication). The dose of miglitol was not the maximum dose approved in Japan (225 mg/day), whereas acarbose and voglibose were used at maximum doses, because these doses are generally used in practice. All patients underwent a 12-week therapy with the assigned regimen, and were instructed to maintain their usual diet and medications over the study period.

Anthropometric measurements and blood sample tests were carried out after an overnight fast at baseline, and 4, 8 and 12 weeks after the treatment. The primary end-points were HbA1c, bodyweight and BMI, as well as their changes from baseline after drug treatment. The secondary end-points included other glycemic parameters (fasting plasma glucose [FPG] and serum insulin), serum lipids (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C] and triacylglycerols [TG]) and adipocytokines (leptin and adiponectin). All patients completed questionnaires about their digestive symptoms (borborygmus, abdominal distension, flatulence and fecal condition), appetite and drug compliance every 4 weeks.

Statistical Analyses

The clinical characteristics of patients were analyzed by the χ^2-test or one-way analysis of variance (ANOVA). The changes over the study period were analyzed by two-way ANOVA with Bonferroni correction. Intergroup differences were analyzed by two-way repeated-measures ANOVA with Bonferroni correction. The questionnaire results were analyzed by the Friedman test with Bonferroni correction. The level of statistical significance was set at $P < 0.05$. Associations between changes in HbA1c and bodyweight were evaluated by Pearson's correlation coefficient analysis. All statistical analyses were carried out using SPSS for Windows, Japanese version 16.0 (SPSS Institute Inc., Tokyo, Japan).

RESULTS

Of the 81 enrolled patients, 78 had sufficient baseline and follow-up data to evaluate the primary end-points (Figure 1). Two patients in the control group and one in the acarbose group with insufficient data were excluded from the statistical analysis. The baseline characteristics of the study participants are shown in Table 1. There were no significant differences in the clinical characteristics among the four groups.

Primary Endpoints

Table 2 shows HbA1c, bodyweight, and BMI in the four groups. In the control group, HbA1c increased significantly from baseline at 12 weeks of treatment. In the miglitol group, HbA1c decreased significantly from baseline at 4 weeks, and the decreased HbA1c level was kept over the study period. In the voglibose group, a significant decrease was observed in HbA1c after 12 weeks of treatment. HbA1c did not change significantly in the acarbose group over the study period (Table 2). In addition, the changes in HbA1c from baseline (ΔHbA1c) in the miglitol group were greater than those in the control group at 8 and 12 weeks of treatment (Figure 2a).

The bodyweight of the miglitol group decreased significantly from baseline at 4, 8 and 12 weeks of treatment, whereas no significant bodyweight changes were observed in any other groups over the study period (Table 2 and Figure 2b). Conse-

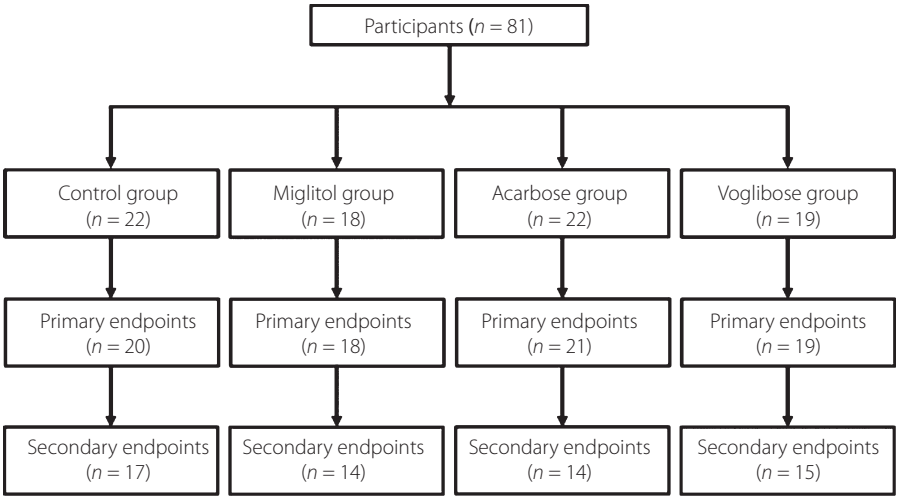

Figure 1 | Flow diagram of the study.

Table 1 | Baseline characteristics of the participants

	Control	Miglitol	Acarbose	Voglibose	Significance
No. of patients	22	18	22	19	
Male/female	7/15	10/8	13/9	8/11	NS
Age (years)	66.6 ± 13.0	66.3 ± 9.3	61.8 ± 13.7	66.7 ± 12.3	NS
Height (cm)	155 ± 9.5	156 ± 9.8	159 ± 10.3	157 ± 8.4	NS
Bodyweight (kg)	69.6 ± 14.3	67.8 ± 11.2	72.7 ± 11.5	70.8 ± 11.3	NS
BMI (kg/m^2)	28.7 ± 3.1	28.2 ± 3.1	28.6 ± 2.7	28.9 ± 5.3	NS
HbA1c, NGSP (%)	7.26 ± 0.79	7.08 ± 0.61	7.11 ± 0.66	7.14 ± 0.59	NS
FPG (mmol/L)	7.55 ± 1.34	7.10 ± 1.05	7.71 ± 1.63	7.00 ± 1.32	NS
Total cholesterol (mmol/L)	5.00 ± 0.74	5.07 ± 0.79	5.21 ± 1.26	4.75 ± 0.72	NS
LDL cholesterol (mmol/L)	3.06 ± 0.86	3.08 ± 0.78	3.28 ± 0.84	2.67 ± 0.50	NS
HDL cholesterol (mmol/L)	1.39 ± 0.29	1.37 ± 0.25	1.39 ± 0.36	1.23 ± 0.30	NS
TG (mmol/L)	1.57 ± 0.75	1.42 ± 0.44	1.57 ± 0.99	1.41 ± 0.63	NS
Concomitant medications, *n* (%)					
Oral hypoglycemic agents	19 (86.4)	12 (66.7)	15 (68.2)	16 (84.2)	NS
Sulfonylurea	6 (27.3)	8 (44.4)	8 (36.4)	8 (42.1)	NS
Glinide	8 (36.4)	2 (11.1)	4 (18.2)	3 (15.8)	NS
DPP-4 inhibitor	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	NS
Thiazolidinedione	3 (13.6)	3 (16.7)	1 (4.6)	3 (15.8)	NS
Metformin	11 (50.0)	5 (27.8)	11 (50.0)	8 (42.1)	NS
Hypotensive agents	18 (81.8)	14 (77.8)	11 (50.0)	15 (79.0)	NS
Hypolipidemic agents	11 (50.0)	4 (22.2)	8 (36.4)	10 (52.6)	NS

Data are expressed as mean ± standard deviation. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program; TG, triacylglycerols; DPP-4, dipeptidyl peptidase 4. NS, not significant ($P \geq 0.05$).

quently, BMI was decreased from baseline only in the miglitol group at 4, 8 and 12 weeks (Table 2 and Figure 2c). However, no significant differences were observed in the changes from baseline in bodyweight (ΔBW) or BMI (ΔBMI) among the four groups (Figure 2b,c).

There were significant correlations between ΔHbA1c and ΔBW at 12 weeks in the miglitol ($r = 0.759$, $P < 0.001$) and voglibose ($r = 0.667$, $P = 0.002$) groups (Figure 3b,d). A similar correlation was observed between ΔHbA1c and ΔBW at 12 weeks in all participants ($r = 0.476$, $P < 0.001$; Figure 3e). No significant correlations were observed in the control and acarbose groups (Figure 3a,c).

Secondary End-points

Over the study period, neither FPG nor serum insulin was changed significantly in any groups. In addition, no significant

Table 2 | Changes in glycated hemoglobin, bodyweight and body mass index during the study period (primary end-points)

	Baseline	4 weeks	8 weeks	12 weeks
HbA1c (%)				
Control	7.24 ± 0.81	7.21 ± 0.69	7.34 ± 0.78	7.47 ± 0.78*
Miglitol	7.08 ± 0.61	6.89 ± 0.64*	6.77 ± 0.59***	6.73 ± 0.58*** †
Acarbose	7.12 ± 0.68	7.04 ± 0.61	7.04 ± 0.67	7.06 ± 0.72
Voglibose	7.14 ± 0.59	7.03 ± 0.57	6.97 ± 0.70	6.94 ± 0.80*
Bodyweight (kg)				
Control	69.9 ± 14.7	69.6 ± 14.8	69.8 ± 14.9	69.6 ± 15.2
Miglitol	69.0 ± 11.1	68.5 ± 11.1*	68.2 ± 11.4***	67.8 ± 11.2***
Acarbose	72.1 ± 11.4	72.0 ± 11.7	72.2 ± 11.5	71.9 ± 12.0
Voglibose	70.8 ± 11.3	70.5 ± 11.3	70.4 ± 11.1	70.2 ± 11.0
BMI (kg/m^2)				
Control	28.6 ± 3.1	28.5 ± 3.1	28.6 ± 3.2	28.5 ± 3.3
Miglitol	28.2 ± 3.1	28.0 ± 3.1*	27.8 ± 3.2***	27.7 ± 3.1***
Acarbose	28.7 ± 2.7	28.6 ± 2.9	28.7 ± 2.9	28.6 ± 2.9
Voglibose	28.9 ± 5.3	28.8 ± 5.2	28.8 ± 5.1	28.6 ± 4.9

Data are expressed as mean ± standard deviation. BMI, body mass index; HbA1c, glycated hemoglobin. *P < 0.05, ***P < 0.001 vs baseline. †P < 0.05 vs control group.

changes were observed in serum lipid profiles or adipocytokines at any time-point in any groups (Table 3).

Questionnaire

The questionnaire data on digestive symptoms showed that the participants in the three αGI-treated groups experienced some digestive symptoms. Participants in the acarbose group in particular reported increased incidences of persistent borborygmus, abdominal distension and flatulence (Table S1). No distinct differences were observed among the groups with respect to drug compliance or appetite.

DISCUSSION

In the present study, we evaluated the effects of three αGIs on glycemic control and bodyweight reduction in Japanese patients with obese type 2 diabetes. Miglitol and voglibose lowered HbA1c, whereas only miglitol reduced bodyweight and BMI.

αGIs retard carbohydrate digestion and absorption, and thus reduce postprandial hyperglycemia. Among the three αGIs, miglitol differs from acarbose and voglibose with respect to pharmacokinetics. After oral administration, acarbose and voglibose are practically not absorbed[10,11]. In contrast, miglitol presents at a high concentration in the upper small intestine and is subsequently absorbed[12]. Such differences in pharmacokinetics could contribute to the superior therapeutic benefit of miglitol; that is, it can suppress the postprandial blood glucose elevation most effectively. Indeed, recent studies with continuous glucose monitoring showed that miglitol strongly reduces postprandial blood glucose levels in type 2 diabetes[13,14]. Although there were no concurrent changes in fasting plasma glucose or insulin levels, adequate suppression of postprandial hyperglycemia could con-

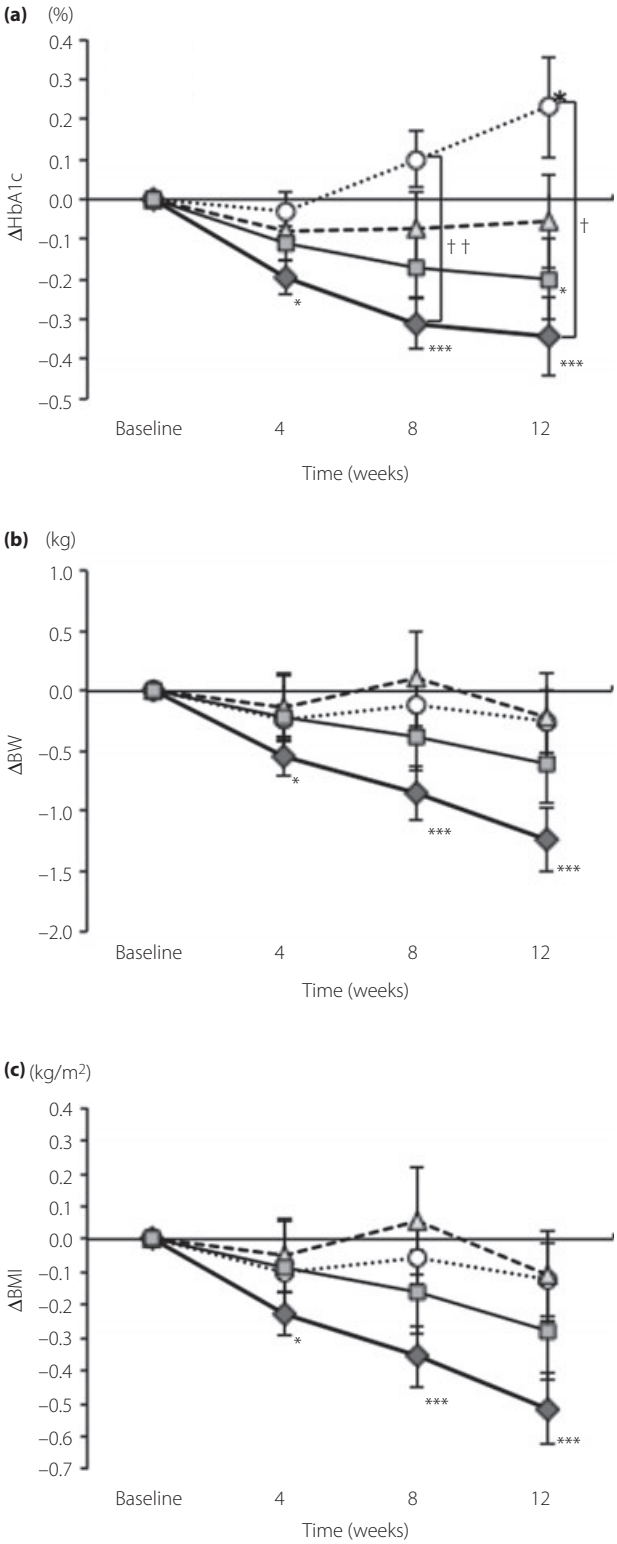

Figure 2 | Changes in (a) glycated hemoglobin (ΔHbA1c), (b) bodyweight (ΔBW) and (c) body mass index (ΔBMI) from baseline. Data are expressed as mean ± standard error of the mean. *P < 0.05, ***P < 0.001 vs baseline. †P < 0.05, ††P < 0.01 vs control group. ○, Control; ♦, miglitol; ▲, acarbose; ■, voglibose.

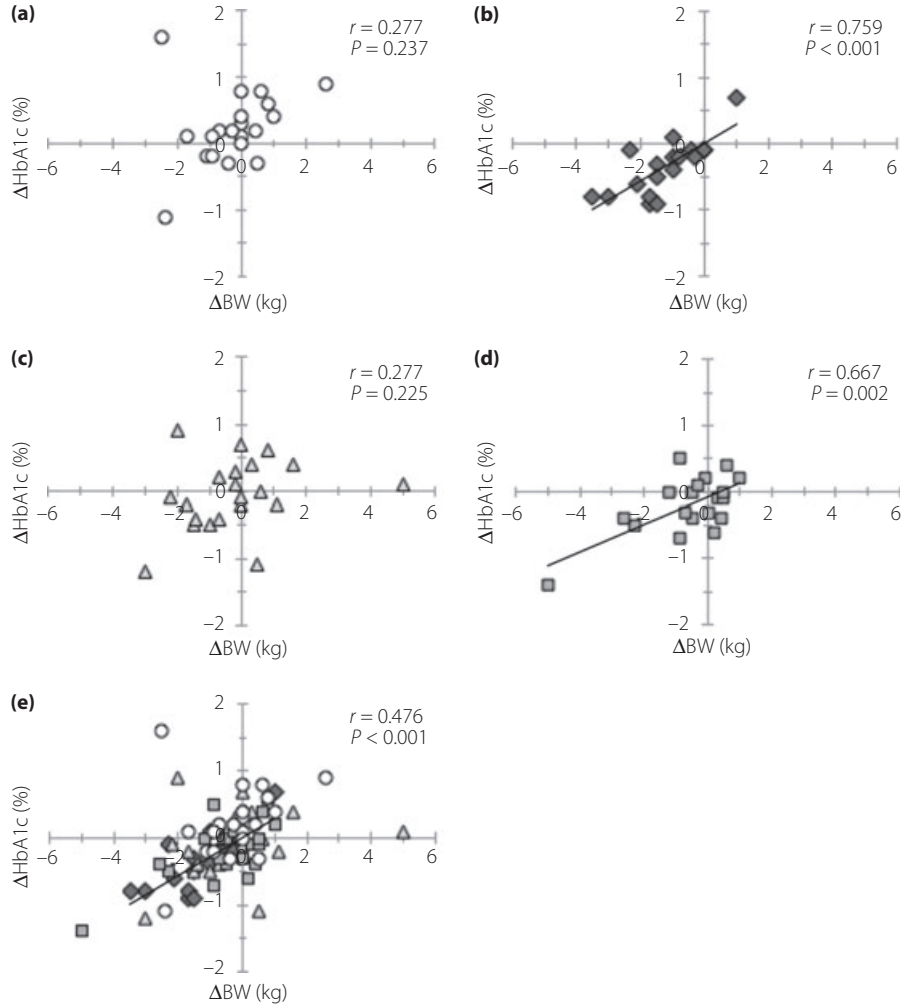

Figure 3 | Correlations between changes in glycated hemoglobin (ΔHbA1c) and bodyweight (ΔBW) over 12 weeks. (a) Control, (b) miglitol, (c) acarbose, (d) voglibose group and (e) total participants. ○, Control; ♦, miglitol; ▲, acarbose; ■, voglibose.

tribute to the rapid and persistent reduction of HbA1c in the miglitol group. Meanwhile, in the present study, HbA1c did not show a significant decrease in the acarbose group. Most of the previous intervention studies with acarbose were carried out for much longer durations, and reported that acarbose treatment significantly reduced HbA1c[7]. Therefore, the relatively short study period (12 weeks) might obscure the blood glucose-lowering effect of acarbose.

Intensive diabetic therapies with insulin and its secretagogues increase the risk of weight gain in type 2 diabetes[15,16]. Weight gain and obesity could induce insulin resistance and increase the risk of cardiovascular diseases in such patients. In the present study, a weight-lowering effect was observed only in the miglitol group. The effects of miglitol on incretins might be one of the reasons for this result. Recent studies suggest that miglitol enhances the release of GLP-1 whilst it suppresses the release of glucose-dependent insulinotropic polypeptide (GIP) by increasing glucose absorption from the lower small intestine[17,18]. Indeed, elevated GLP-1 contributes to appetite control by inhibiting gastrointestinal motility[19] and inducing satiety[20] through the central nervous system. In fact, Arakawa *et al.*[21] report that miglitol affects postprandial GLP-1 secretion more strongly than acarbose in patients with visceral obesity, and several reports suggest that miglitol increases GLP-1 and decreases GIP to greater extents than voglibose after a single[22] or long-term[6] administration in type 2 diabetes. Further analysis for the modulation of postprandial incretin levels with αGIs could explain the differences in the weight-lowering effects among αGIs.

We did not find any changes in fasting plasma lipid profiles in the present study. However, a meta-analysis of acarbose showed a small tendency towards decreased fasting TG levels[7]. In addition, some studies showed that postprandial TG decreased significantly in accordance with decreased insulin levels with acute[23,24] or long-term[24] acarbose treatment in type 2 diabetes. These data suggest that the improvement of insulin resistance by αGIs might suppress postprandial TG elevation. Hence, postprandial insulin and TG levels should be assessed to further understand the lipid-lowering effect of each αGI.

Table 3 | Changes in fasting plasma glucose, serum insulin, serum lipids and adipocytokines during the study period (secondary end-points)

	Baseline	4 weeks	8 weeks	12 weeks
FPG (mmol/L)				
Control	7.43 ± 1.47	7.47 ± 1.04	7.60 ± 1.29	7.50 ± 1.37
Miglitol	7.22 ± 1.05	7.12 ± 0.96	7.16 ± 1.10	7.11 ± 1.46
Acarbose	7.41 ± 1.59	7.39 ± 1.13	7.36 ± 1.51	7.10 ± 1.00
Voglibose	6.65 ± 1.24	6.94 ± 1.32	6.80 ± 1.40	6.67 ± 1.54
Serum insulin (pmol/L)				
Control	80.2 ± 47.4	87.3 ± 75.6	87.7 ± 66.1	70.2 ± 33.9
Miglitol	63.4 ± 49.2	60.8 ± 45.5	54.8 ± 41.7	61.6 ± 49.3
Acarbose	80.9 ± 54.3	101 ± 58.1	161 ± 191	68.0 ± 38.1
Voglibose	75.3 ± 38.6	96.7 ± 86.2	69.4 ± 36.4	79.3 ± 41.2
Total cholesterol (mmol/L)				
Control	4.78 ± 0.61	4.96 ± 0.61	4.94 ± 0.65	5.01 ± 0.55
Miglitol	5.12 ± 0.90	5.23 ± 1.03	5.62 ± 1.21	5.43 ± 1.29
Acarbose	5.30 ± 1.44	5.53 ± 1.23	5.48 ± 1.39	5.42 ± 1.76
Voglibose	4.88 ± 0.66	4.79 ± 0.49	4.58 ± 0.69	4.81 ± 0.57
LDL cholesterol (mmol/L)				
Control	3.00 ± 0.96	2.94 ± 0.81	2.86 ± 0.67	3.00 ± 0.75
Miglitol	3.04 ± 0.85	3.15 ± 0.82	3.08 ± 0.87	2.87 ± 0.79
Acarbose	3.24 ± 0.73	3.23 ± 0.73	3.32 ± 0.91	3.07 ± 1.12
Voglibose	2.64 ± 0.56	2.67 ± 0.66	2.82 ± 0.54	2.80 ± 0.59
HDL cholesterol (mmol/L)				
Control	1.37 ± 0.28	1.32 ± 0.27	1.35 ± 0.27	1.31 ± 0.28
Miglitol	1.39 ± 0.28	1.40 ± 0.26	1.39 ± 0.28	1.38 ± 0.31
Acarbose	1.36 ± 0.26	1.39 ± 0.22	1.35 ± 0.30	1.33 ± 0.18
Voglibose	1.27 ± 0.29	1.23 ± 0.31	1.23 ± 0.24	1.22 ± 0.25
TG (mmol/L)				
Control	1.52 ± 0.69	1.71 ± 1.27	1.63 ± 0.81	1.68 ± 0.81
Miglitol	1.56 ± 0.37	1.48 ± 0.69	1.34 ± 0.50	1.56 ± 1.20
Acarbose	1.66 ± 1.14	1.48 ± 1.02	1.95 ± 1.85	1.59 ± 0.94
Voglibose	1.39 ± 0.68	1.62 ± 1.45	1.35 ± 0.67	1.37 ± 0.37
Adiponectin (μg/mL)				
Control	9.98 ± 6.06	10.1 ± 7.59	10.1 ± 6.53	9.97 ± 5.87
Miglitol	9.96 ± 4.05	9.88 ± 4.84	10.3 ± 5.81	10.3 ± 5.80
Acarbose	8.91 ± 3.78	8.26 ± 2.89	8.66 ± 2.94	8.27 ± 2.03
Voglibose	13.0 ± 13.6	11.2 ± 11.6	12.9 ± 15.8	12.3 ± 11.5
Leptin (ng/mL)				
Control	11.3 ± 6.42	12.1 ± 8.88	11.6 ± 6.63	11.8 ± 7.80
Miglitol	6.98 ± 3.95	6.73 ± 3.56	7.08 ± 4.87	7.41 ± 4.17
Acarbose	11.7 ± 8.35	12.0 ± 7.35	12.5 ± 8.49	10.0 ± 7.41
Voglibose	11.1 ± 7.68	10.1 ± 7.02	11.1 ± 7.91	10.7 ± 8.42

Data are expressed as mean ± standard deviation. FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triacylglycerols.

After the 12-week αGI treatment, a significant decrease in HbA1c was observed in the miglitol and voglibose groups, but not in the acarbose group. In addition, a significant correlation was observed between ΔHbA1c and ΔBW in the miglitol and voglibose groups. Thus, the improved glycemic control with these αGIs might be partly due to weight reduction. A few studies suggest that acarbose and miglitol increase plasma adiponectin levels[25,26]. Although reductions in bodyweight and body fat mass by αGIs are speculated to modulate adipocytokine levels, adiponectin and leptin levels did not change in any groups of the present study. Other pathways, such as those involving incretins, could contribute to both the better glycemic control and bodyweight reduction by αGIs. Miglitol[17] and voglibose[27] have been reported to increase postprandial incretin levels in patients with type 2 diabetes, whereas acarbose has not[28], in placebo-controlled studies. Further research into the underlying mechanisms of the different effects on glycemic control and bodyweight among αGIs is necessary for better understanding of the characteristics of these drugs.

The present study had several limitations. First, this study was an open-label study with a small sample size, though the participants were randomized and a control group was included. Second, we did not evaluate postprandial levels of plasma glucose, insulin and incretins. These postprandial measures would provide direct information on the effects of αGI. Third, we did not select the maximum dose permitted in Japan in the miglitol group. If the maximum dose was selected, it could be preferable to the present dose for both blood glucose and bodyweight control in the miglitol group. However, as the dose of αGI is increased, the side-effects such as abdominal symptoms might be likely to occur. It remains to be elucidated whether the maximum dose of miglitol would have superior efficacy with good tolerability. Fourth, we investigated only patients with obese type 2 diabetes. Whether similar effects of miglitol are observed in other types of diabetes or individuals with impaired glucose tolerance is of particular interest. Further investigation is required to better understand these characteristics of each αGI.

In conclusion, the present findings show that miglitol and voglibose lowered HbA1c in patients with obese type 2 diabetes. In addition, miglitol reduced bodyweight within a short period (4 weeks of treatment). These results suggest that miglitol is a preferable agent for improving glycemic control with promoting bodyweight reduction. Further studies on the characteristics of each αGI could provide better treatment options, not only for blood glucose control with bodyweight management, but also for preventing complications in type 2 diabetes.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Questionnaire survey data.