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Miglitol suppresses the postprandial increase in interleukin 6 and enhances active glucagon-like peptide 1 secretion in viscerally obese subjects

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Abstract

Visceral obesity and insulin resistance are regarded as risk factors for atherosclerosis. Epidemiologic studies have demonstrated long-term anti-atherosclerotic effects with administration of α-glucosidase inhibitors. α-Glucosidase inhibitors also have been reported to enhance glucagon-like peptide 1 (GLP-1) secretion. We compared the postprandial effects of a single administration of miglitol and acarbose on glucose and lipid metabolism, on insulin requirement, on GLP-1 secretion, and on inflammatory and endothelial markers in viscerally obese subjects. Twenty-four viscerally obese subjects with relative insulin resistance participated in this study. Subjects were given a single dose of miglitol (50 mg), acarbose (100 mg), or placebo blindly and randomly before a meal in a crossover design. The meal loads after drug administration were tested 3 times within 2 weeks. We measured glucose, insulin, lipids, lipoprotein lipase, interleukin 6, intracellular adhesion molecule 1, vascular cell adhesion molecule 1, and active GLP-1 at before and various minutes after the meal. Single administration of both α-glucosidase inhibitors had several beneficial effects in improving postprandial hyperglycemia and reducing postprandial insulin requirement approximately 25% of placebo without adversely affecting lipid profiles. Although lipoprotein lipase levels within 2 hours after the meal did not show differences among miglitol, acarbose, and placebo administrations, miglitol significantly suppressed the increases in triglycerides, remnant-like particle triglycerides, and remnant-like particle cholesterol compared to acarbose and placebo in the early phase. Miglitol also significantly enhanced active GLP-1 secretion to a greater extent than acarbose ($P < .01$) and placebo ($P < .001$), and significantly suppressed the postprandial increase in interleukin 6 compared to placebo ($P < .01$). The results point to the potential suitability of miglitol as an anti-atherosclerotic effect in viscerally obese subjects, in preference to acarbose. Further studies are needed to elucidate the long-term effects on enhanced GLP-1 secretion and anti-atherosclerosis.

1. Introduction

Visceral obesity, quantified by waist circumference, has been identified as an independent risk factor for insulin resistance (IR) [1] and cardiovascular disease (CVD) [2]. Insulin resistance is often assessed clinically according to the homeostasis model assessment of IR [3] and is predictive of CVD [4]. Visceral obesity and IR usually coexist, leading to the metabolic syndrome (hypertension, hypertriglyceridemia, low high-density lipoprotein [HDL] cholesterolemia, and hyperglycemia). The implementation of healthy behaviors with subsequent weight loss as well as drug-induced weight loss has been shown in several studies to improve metabolic parameters and lessen CVD risk factors [5,6].

α-Glucosidase inhibitors such as acarbose have shown long-term beneficial and protective effects against atherosclerosis. In the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial, acarbose reduced the risk of diabetes mellitus [7], cardiovascular events, and hypertension with weight loss [8] in subjects with impaired glucose tolerance (IGT). In addition, acarbose reduced the risk of myocardial infarction in the Meta-analysis of Risk Improvement Under Acarbose 7 (MeRIA[7]) study of patients with type 2 diabetes mellitus [9]. The efficacy of α-glucosidase inhibitors in reducing CVD risk is attributed largely to improvement of postprandial hyperglycemia. Reducing postprandial insulin requirements [10-12] and

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improving postprandial hypertriglyceridemia [11,13] might also affect the results, whereas the effects of α-glucosidase inhibitors on postprandial lipid profiles are still unclear.

Miglitol, another α-glucosidase inhibitor, has unique pharmacokinetics [14]. After oral administration of miglitol, it is rapidly and completely absorbed even at a high dose (<50 mg in humans) from small intestine [14], although other α-glucosidase inhibitors are scarcely absorbed there. These pharmcokinetics enable consequent strong and early-phase suppression of postprandial glucose elevation with decrease in severity of gastrointestinal complication even at high dose because absorption of carbohydrate in the lower small intestine where miglitol concentration is very low decreases flow of carbohydrate into colon.

We compared the postprandial effects of a single administration of miglitol and acarbose on glucose and lipid metabolisms, on insulin requirement, and on inflammatory and endothelial markers in viscerally obese subjects. We also examined active GLP-1, based on reports of α-glucosidase inhibitors increasing total GLP-1 [10,12].

2. Methods

2.1. Subjects

This study recruited 24 viscerally obese Japanese patients (waist circumference, ≧85 cm in male and ≧90 cm in female matched with the Japanese Society of Internal Medicine criteria [15]). Subjects underwent a 75-g oral glucose tolerance test (OGTT) before the study to evaluate IR and glucose tolerance status according to World Health Organization criteria.

Patients were excluded by the following criteria: presence of concomitant chronic disease, including anemia, kidney, liver, and CVD; recent acute illness; previous treatment with antidiabetic drugs and/or with insulin sensitizers; or previous treatment with insulin. Subjects on lipid-lowering drugs stopped their prescription from 7 days before this study to completion. All subjects were instructed not to change their usual dietary habits for the duration of the study.

The study protocol was approved by the Ethic Commission of the Juntendo University Hospital, and written informed consent was obtained from all subjects. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964, amended in Edinburgh in 2000.

2.2. Study design

This was a single-center, single-blind, placebo-controlled, crossover study. The subjects attended the diabetes unit at 9:00 AM after a 12-hour fast (from 9:00 PM on the day before each test) and were administered either 50 mg of miglitol, 100 mg of acarbose, or placebo blindly and randomly just before an oral standard-meal load (coordinated by the Japan Diabetes Society [16]). The order of drugs taken was determined by a draw on the first patient visit and remained unknown. The total energy content of the standard meal was 1924.64 kJ (460 kcal), with 56.5 g of carbohydrate, 18.0 g of fat, and 18.0 g of protein; a total of 51.4 energy % (E%) from carbohydrate, 33.3 E% from fat, and 15.3 E% from protein. The meal had to be eaten within 15 minutes after receiving the drug. The subjects were at rest and sitting throughout testing.

An intravenous line was inserted into one forearm vein before drug administration and kept patent using 0.9% NaCl for repeated blood sampling. Blood was drawn at 0, 30, 60, 120, 180, and 240 minutes after the meal. Time zero corresponds to immediately before drug administration. We measured glucose, insulin, lipids (triglycerides [TG], free fatty acids [FFAs], remnant-like particle [RLP] TG, RLP cholesterol, low-density lipoprotein [LDL] cholesterol, very low-density lipoprotein [VLDL] cholesterol, HDL cholesterol, and total cholesterol), and lipoprotein lipase (LPL) at 0, 30, 60, 120, 180, and 240 minutes; chylomicrons, small-dense LDL at 0, 120, and 240 minutes; active glucagon-like peptide 1 (GLP-1) at 0, 60, and 120 minutes; interleukin 6 (IL-6), intracellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule (VCAM-1) at 0 and 240 minutes.

Testing of 3 meal loads with each drug was accomplished within 2 weeks. The study was conducted from November 2006 to April 2007.

2.3. Laboratory determinations

We outsourced the testing of all parameters as follows: LPL (as pre-heparin LPL mass) to Kishimoto Clinical Laboratories (Hokkaido, Japan); chylomicrons and small-dense LDL to Skylight Biotech Inc (Akita, Japan); IL-6, ICAM-1, and VCAM-1 to BML Inc (Tokyo, Japan); and the remainder of testing to SRL Inc (Tokyo, Japan).

The parameters described below were analyzed by a commercially available enzyme-linked immunosorbent assay kit [pre-heparin LPL mass, Sekisui Medical (Tokyo, Japan); Active GLP-1[GLP-1-(7-36) amide and GLP-1-(7-37)], Linco Research (St. Louis, MO); IL-6, Quantikine HS IL-6 and VCAM-1, Quantikine; VCAM-1, R&D Systems (Minneapolis, MN); ICAM-1, Human Soluble ICAM-1, Endogen, Pierce, Rockford, IL. Chylomicrons and small-dense LDL were analyzed by an upgraded high-performance lipid chromatography analysis, as described previously [17]. Other parameters (glucose, insulin, TG, FFAs, RLP-TG, RLP cholesterol, LDL cholesterol, VLDL cholesterol, and HDL cholesterol) were analyzed by standard methods.

2.4. Evaluation of IR/sensitivity

The homeostasis model assessment of IR (HOMA-IR) was used to calculate an index from the product of the fasting concentrations of plasma insulin (μIU/mL) and plasma glucose (mg/dL) divided by 405 [3]. The quantitative insulin sensitivity check index (QUICKI) proposed by Katz et al [18] was calculated as follows: 1/[log (fasting plasma insulin) +

(fasting plasma glucose)]. The whole-body insulin sensitivity index (WBISI) proposed by Matsuda and DeFronzo [19] was calculated as follows: 10000/square root of [(mean plasma insulin × mean plasma glucose during OGTT) × (fasting plasma insulin × fasting plasma glucose)].

2.5. Statistical analysis

Results are expressed as mean ± SD, unless otherwise indicated. Multiple comparison tests were made with 2-way analysis of variance, followed by post hoc analysis (Bonferroni test) to locate the significant differences identified by ANOVA. Linear regression analysis was used as appropriate. The area under the curve (AUC) was calculated by the trapezoidal method. A value of $P < .05$ was considered statistically significant.

3. Results

All subjects completed the study. Demographic data and other baseline characteristics are described in Table 1. The mean waist circumference was 100.9 ± 15.1 cm. HOMA-IR, QUICKI, and WBISI were 2.78 ± 1.44, 0.335 ± 0.022, and 3.75 ± 1.63, respectively. These indices demonstrated relative IR in all subjects compared to previous reports [20,21]. Most of the subjects also had several metabolic abnormalities (hypertension, hypertriglyceridemia, low HDL cholesterolemia, and hyperglycemia, matched with Japanese metabolic syndrome criteria [15]). Of 24 subjects, 15 had 2 to 3 abnormalities, 7 had 1 abnormality, and 2 had none. These data indicated that the subjects were at high risk of CVD. Glycated albumin was examined at every meal load, with no significant difference among tests (data not shown), indicating little change in glucose tolerance during the study period.

Table 1
Baseline characteristics of the subjects

N	24
Sex (female)	9
Age (y)	49.0 ± 11.1
BMI (kg/m^2)	28.9 ± 7.7
Waist circumference (cm)	100.9 ± 15.1
Glucose tolerance (n)[a]	
Normal	12
IGT/IFG	7
Diabetes	5
HbA_{1C} (%)	5.4 ± 0.5
Fasting plasma glucose (mmol/L)	6.02 ± 0.77
Fasting plasma insulin (pmol/L)	61.8 ± 28.8
HOMA-IR	2.78 ± 1.44
QUICKI	0.334 ± 0.022
WBISI	3.75 ± 1.63
Systolic blood pressure (mm Hg)	138.4 ± 19.4
Diastolic blood pressure (mm Hg)	87.5 ± 12.8
Medication (n)[b]	
ARB	1
CCB	2
ARB + CCB	2
CCB + α-blocker	1

Data are expressed as mean ± SD. Two subjects were on statins and stopped 7 days before this study. BMI indicates body mass index; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IFG, impaired fasting glucose.

[a] Glucose tolerance was determined by 75-g OGTT according to the World Health Organization before this study.

[b] None of the subjects took diabetes medication.

3.1. Glucose and insulin

Fig. 1 shows changes in glucose (A), AUCs of glucose (B), and glucose swings (C) that represent the difference between maximum and minimum glucose, excluding baseline levels. Miglitol and acarbose both caused significantly lower glucose levels at 30 and 60 minutes than placebo administration (Fig. 1A). Moreover, glucose levels at 30 and 60 minutes were significantly lower after miglitol administration than at the same times after acarbose. In contrast, glucose levels remained slightly but significantly higher with both α-glucosidase inhibitors than with placebo at 120 (only miglitol), 180, and 240 minutes. There was no significant difference in the AUCs of glucose from 0 to 240 minutes among α-glucosidase inhibitors and placebo, whereas the glucose AUC decreased significantly from 0 to 120 minutes with both miglitol and acarbose compared to placebo (Fig. 1B). Moreover, the AUC of glucose was significantly lower from 0 to 120 minutes with miglitol compared to that with acarbose. Glucose swings (Fig. 1C) with both α-glucosidase inhibitors were significantly lower than those with placebo, whereas again the levels were lower with miglitol than with acarbose. These results indicated that α-glucosidase inhibitors improve postprandial hyperglycemia without changing the AUCs of glucose and that 50 mg of miglitol has a stronger effect than 100 mg of acarbose after a single dose administration.

Fig. 2 shows changes in insulin (A) and AUCs of insulin (B). As for glucose, both α-glucosidase inhibitors significantly reduced insulin levels at 30 and 60 minutes compared to placebo. Moreover, insulin at 60 minutes after miglitol was significantly lower than levels after acarbose. In contrast, insulin levels were significantly higher with miglitol administration compared to acarbose at 120 minutes and compared to both acarbose and placebo at 180 minutes. The AUCs of insulin from 0 to 120 minutes after miglitol and acarbose were reduced by 55.0% and 68.0%, respectively, compared to placebo (Fig. 2B), whereas from 0 to 240 minutes, the AUCs with both inhibitors decreased to approximately 25% of placebo. There was no significant difference in the AUC of insulin between the 2 α-glucosidase inhibitors.

3.2. Lipids and LPL

As shown in Table 2, TG, RLP-TG, RLP cholesterol, VLDL cholesterol, and chylomicrons increased after the meal load in all groups. Miglitol significantly suppressed the

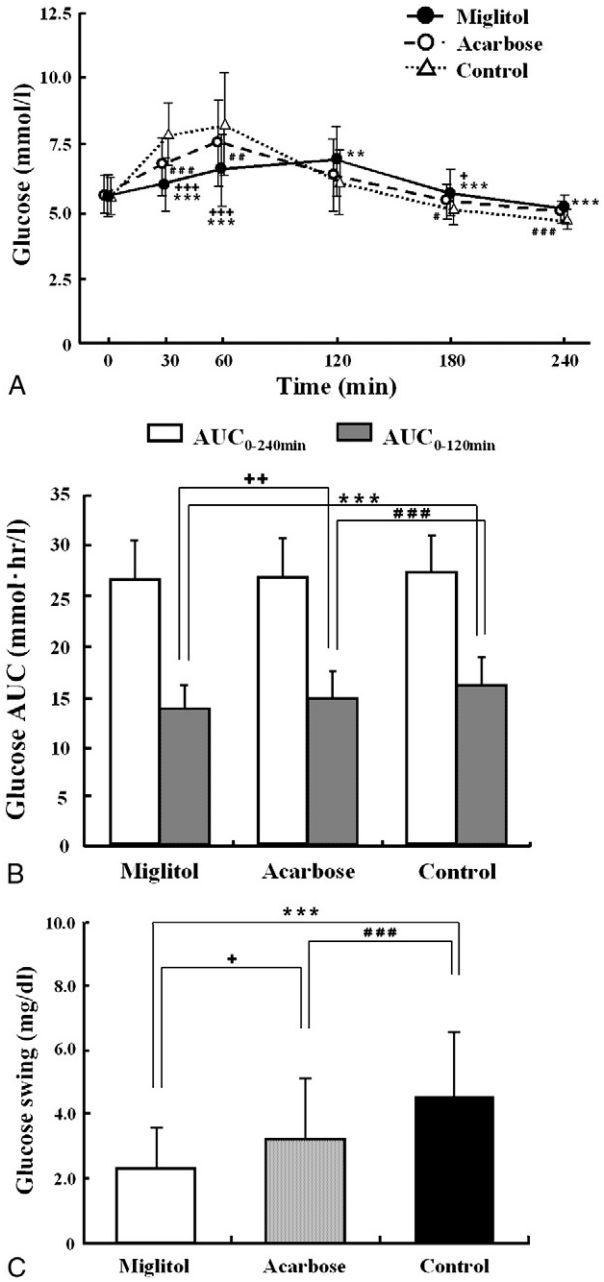

Fig. 1. Time course of glucose, AUCs of glucose, and glucose swings before and after meal load with α-glucosidase inhibitors or placebo. Time course of glucose (A), AUCs of glucose (B), and glucose swings (C) before (baseline) and after meal load with miglitol (50 mg), acarbose (100 mg), or placebo were indicated. Two-way ANOVA followed by a Bonferroni post hoc test for multiple comparisons was used for continuous variables. $^{+}P < .05$, $^{++}P < .01$, $^{+++}P < .001$, miglitol vs acarbose; $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$, miglitol vs placebo; $^{\#}P < .05$, $^{\#\#}P < .01$, $^{\#\#\#}P < .001$, acarbose vs placebo.

increases in TG, RLP-TG, and RLP cholesterol at 60 and/or 30 minutes compared to acarbose and placebo. Decreases in FFAs were significantly less at 60 minutes after miglitol compared to placebo and more than placebo at 240 minutes. Miglitol also suppressed the meal load–induced decrease in HDL cholesterol at 30 and 60 minutes. No significant differences were observed in chylomicrons or small-dense LDL among α-glucosidase inhibitors and placebo. Miglitol significantly decreased LPL at 180 minutes compared to acarbose and placebo.

3.3. Active GLP-1

Both α-glucosidase inhibitors significantly increased active GLP-1, whereas subjects given placebo showed only a slight increase (Table 2). Moreover, active GLP-1 levels were significantly higher after miglitol than after acarbose at 60 and 120 minutes.

3.4. Interleukin 6, ICAM-1, and VCAM-1

Postprandial increase in IL-6 was suppressed significantly only with miglitol compared to placebo (Table 3). Postprandial decrease in ICAM-1 was enhanced only with miglitol compared to placebo, but the difference was not

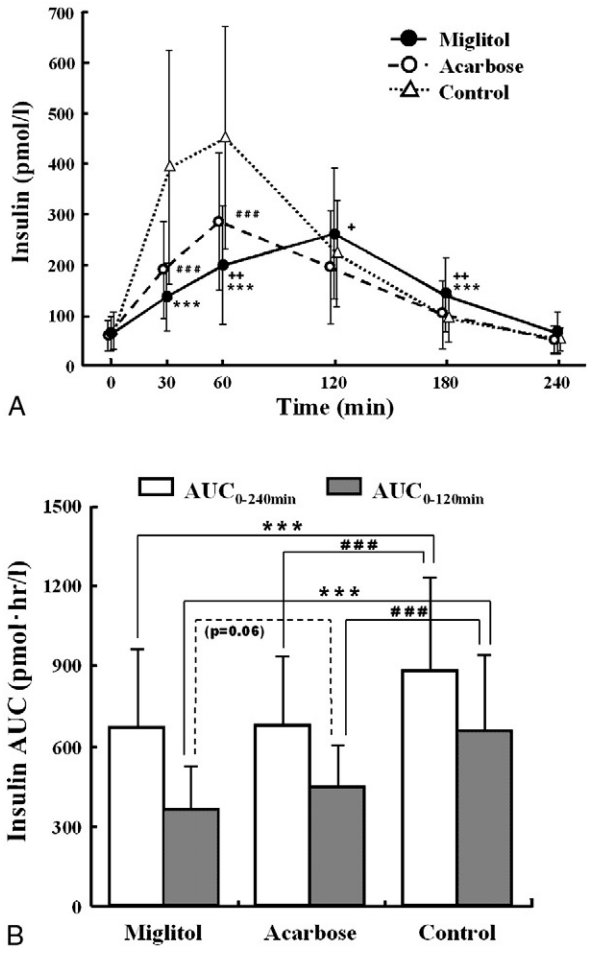

Fig. 2. Time course of insulin and AUCs of insulin before and after meal load with α-glucosidase inhibitors or placebo. Time course of insulin (A) and AUCs of insulin (B) before (baseline) and after meal load with miglitol (50 mg), acarbose (100 mg), or placebo were indicated. Two-way ANOVA followed by a Bonferroni post hoc test for multiple comparisons was used for continuous variables. $^{+}P < .05$, $^{++}P < .01$, $^{+++}P < .001$, miglitol vs acarbose; $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$, miglitol vs placebo; $^{\#}P < .05$, $^{\#\#}P < .01$, $^{\#\#\#}P < .001$, acarbose vs placebo.

Table 2
α-glucosidase inhibitors or placebo for lipids, preheparin LPL mass, and active GLP-1

	Baseline	30 min	60 min	120 min	180 min	240 min
TG (mmol/L)						
Miglitol	1.68 ± 0.78	−0.06 ± 0.15	−0.04 ± 0.12 **	0.36 ± 0.29	0.36 ± 0.35	0.51 ± 0.43
Acarbose	1.59 ± 0.63	−0.10 ± 0.26	0.05 ± 0.39	0.31 ± 0.49	0.51 ± 0.65	0.52 ± 0.62
Placebo	1.55 ± 0.91	0.00 ± 0.13	0.21 ± 0.20	0.48 ± 0.21	0.60 ± 0.28	0.65 ± 0.32
FFAs (mmol/L)						
Miglitol	0.62 ± 0.27	−0.10 ± 0.11	−0.21 ± 0.19 *	−0.35 ± 0.24	−0.33 ± 0.27	−0.23 ± 0.28 *
Acarbose	0.62 ± 0.23	−0.10 ± 0.13	−0.26 ± 0.18	−0.38 ± 0.22	−0.31 ± 0.24	−0.12 ± 0.25
Placebo	0.59 ± 0.21	−0.10 ± 0.11	−0.31 ± 0.18	−0.39 ± 0.21	−0.28 ± 0.23	−0.07 ± 0.21
RLP-TG (mmol/L)						
Miglitol	0.28 ± 0.21	0.00 ± 0.07 **	0.02 ± 0.08 †††,***	0.31 ± 0.18	0.43 ± 0.22	0.36 ± 0.22
Acarbose	0.24 ± 0.11	0.02 ± 0.04 $^{\#}$	0.14 ± 0.12	0.28 ± 0.16	0.43 ± 0.29	0.41 ± 0.29
Placebo	0.28 ± 0.29	0.08 ± 0.10	0.20 ± 0.12	0.26 ± 0.14	0.35 ± 0.27	0.35 ± 0.28
RLP cholesterol (mmol/L)						
Miglitol	0.14 ± 0.06	−0.01 ± 0.02	−0.01 ± 0.03 ***	0.06 ± 0.05	0.10 ± 0.06	0.09 ± 0.06
Acarbose	0.14 ± 0.06	−0.01 ± 0.03	0.01 ± 0.05 $^{\#}$	0.05 ± 0.06	0.09 ± 0.09	0.09 ± 0.09
Placebo	0.14 ± 0.08	0.01 ± 0.02	0.04 ± 0.03	0.05 ± 0.04	0.08 ± 0.06	0.09 ± 0.07
LDL cholesterol (mmol/L)						
Miglitol	3.57 ± 0.63	−0.12 ± 0.14	−0.18 ± 0.13	−0.25 ± 0.21	−0.29 ± 0.19	−0.24 ± 0.24
Acarbose	3.61 ± 0.67	−0.19 ± 0.18	−0.21 ± 0.16	−0.24 ± 0.22	−0.29 ± 0.18	−0.21 ± 0.24
Placebo	3.50 ± 0.83	−0.19 ± 0.16	−0.27 ± 0.16	−0.25 ± 0.18	−0.22 ± 0.16	−0.13 ± 0.19
VLDL cholesterol (mmol/L)						
Miglitol	0.69 ± 0.42	−0.02 ± 0.14	0.04 ± 0.13	0.07 ± 0.24	0.14 ± 0.25	0.16 ± 0.24
Acarbose	0.68 ± 0.27	−0.04 ± 0.13	−0.06 ± 0.16	0.03 ± 0.19	0.12 ± 0.19	0.14 ± 0.20
Placebo	0.68 ± 0.39	−0.03 ± 0.12	0.02 ± 0.13	0.06 ± 0.17	0.04 ± 0.15	0.13 ± 0.16
HDL cholesterol (mmol/L)						
Miglitol	1.33 ± 0.30	−0.03 ± 0.05 *	−0.04 ± 0.05 ††,***	−0.09 ± 0.10	−0.11 ± 0.07	−0.09 ± 0.08
Acarbose	1.36 ± 0.29	−0.07 ± 0.05	−0.10 ± 0.06	−0.11 ± 0.07	−0.11 ± 0.09	−0.11 ± 0.08
Placebo	1.34 ± 0.28	−0.07 ± 0.06	−0.10 ± 0.06	−0.10 ± 0.07	−0.12 ± 0.09	−0.07 ± 0.11
Total cholesterol (mmol/L)						
Miglitol	5.61 ± 0.75	−0.18 ± 0.18 *	−0.19 ± 0.17	−0.29 ± 0.24	−0.28 ± 0.17	−0.19 ± 0.24
Acarbose	5.68 ± 0.76	−0.30 ± 0.19	−0.39 ± 0.20	−0.34 ± 0.26	−0.32 ± 0.26	−0.21 ± 0.23
Placebo	5.44 ± 1.07	−0.22 ± 0.33	−0.28 ± 0.38	−0.21 ± 0.41	−0.22 ± 0.36	0.00 ± 0.46
Chylomicrons (mg/dL)						
Miglitol	0.57 ± 0.68	–	–	2.63 ± 1.44	–	4.04 ± 3.41
Acarbose	0.75 ± 0.51	–	–	2.02 ± 1.69	–	4.32 ± 3.51
Placebo	0.57 ± 0.51	–	–	1.64 ± 0.95	–	3.01 ± 3.17
Small-dense LDL (mg/dL)						
Miglitol	30.23 ± 5.91	–	–	−2.63 ± 2.23	–	−2.45 ± 2.53
Acarbose	29.77 ± 5.85	–	–	−1.24 ± 1.27	–	−0.79 ± 1.58
Placebo	31.10 ± 6.65	–	–	−1.83 ± 1.54	–	−1.13 ± 2.56
Preheparin LPL mass (ng/mL)						
Miglitol	45.9 ± 10.6	−4.5 ± 4.4	−4.0 ± 5.0	−4.9 ± 5.7	−5.0 ± 5.3 †,*	−2.6 ± 6.2
Acarbose	42.8 ± 10.8	−5.0 ± 5.3	−5.4 ± 6.7	−2.9 ± 6.3	0.8 ± 9.2	1.1 ± 9.7
Placebo	45.0 ± 12.6	−4.6 ± 5.0	−5.4 ± 4.5	−1.6 ± 5.6	−0.1 ± 6.0	2.0 ± 7.4
Active GLP-1 (pmol/L)						
Miglitol	2.36 ± 0.58	–	4.83 ± 3.18 †,***	3.63 ± 2.60 ††,***	–	–
Acarbose	2.54 ± 0.77	–	2.75 ± 1.76	1.89 ± 1.84	–	–
Placebo	2.53 ± 0.77	–	1.04 ± 1.05	1.06 ± 1.15	–	–

Data are expressed as mean ± SD. Two-way ANOVA followed by Bonferroni post hoc test for multiple comparisons was used for continuous variables. Baseline values and changes from baseline at 30, 60, 120, 180, and 240 minutes after meal load with miglitol (50 mg), acarbose (100 mg), or placebo for lipids, pre-heparin LPL mass, and active GLP-1 were indicated.

$^{\#\#}P < .01$, acarbose vs placebo.

$^{\#\#\#}P < .001$, acarbose vs placebo.

† $P < .05$, miglitol vs acarbose.

†† $P < .01$, miglitol vs acarbose.

††† $P < .001$, miglitol vs acarbose.

* $P < .05$, miglitol vs placebo.

** $P < .01$, miglitol vs placebo.

*** $P < .001$, miglitol vs placebo.

$^{\#}$ $P < .05$, acarbose vs placebo.

Table 3
α-glucosidase inhibitors or placebo for IL-6 and adhesion molecules

	Baseline	240 min
IL-6 (pg/mL)		
Miglitol	2.34 ± 1.39	0.10 ± 0.36 [§]
Acarbose	2.11 ± 1.27	0.43 ± 0.50
Placebo	2.23 ± 0.95	0.78 ± 0.48
ICAM-1 (ng/mL)		
Miglitol	278.8 ± 35.7	−21.2 ± 19.4
Acarbose	274.5 ± 46.8	−12.9 ± 13.3
Placebo	270.4 ± 34.8	−5.43 ± 25.3
VCAM-1 (ng/mL)		
Miglitol	1016 ± 201 [¶, §]	−127 ± 100
Acarbose	896 ± 157	−50 ± 57
Placebo	897 ± 178	−65 ± 62

Data are expressed as mean ± SD. Two-way ANOVA followed by a Bonferroni post hoc test for multiple comparisons was used for continuous variables. Baseline values and changes from baseline at 240 minutes after meal load with miglitol (50 mg), acarbose (100 mg), or placebo for IL-6, ICAM-1, and VCAM-1 were indicated.

[¶] $P < .01$, miglitol vs acarbose.

[§] $P < .01$, miglitol vs placebo.

statistically significant ($P = .088$). There were no significant postprandial changes in VCAM-1 among meal loads after α-glucosidase inhibitors and placebo administrations.

4. Discussion

The present study showed that a single administration of miglitol has preferentially beneficial effects on postprandial hyperglycemia, postprandial insulin requirement, lipid parameters, active GLP-1, and IL-6 compared to acarbose in viscerally obese subjects with relative IR. To the best of our knowledge, this is the first demonstration that compared α-glucosidase inhibitors directly and that examined effects of the drugs on inflammatory and endothelial markers.

Early-phase postprandial glucose elevation was suppressed significantly by both α-glucosidase inhibitors tested compared to placebo. In contrast, latter-phase levels were slightly higher with both drugs than with placebo. Although the AUCs of glucose from 0 to 240 minutes did not differ among the drugs and placebo in this study, STOP-NIDDM [7,8] and MeRIA[7] [9] study patients showed a reduced risk of CVD after administration of acarbose, via improved postprandial hyperglycemia. The role of glucose swings may explain this discrepancy. We demonstrated previously that repetitive postprandial fluctuations in glucose concentration evoke higher levels of monocyte adhesion to endothelial cells than that induced by stable hyperglycemia in rats [22]. In addition, modulation of glucose swings with miglitol attenuated the progression of atherosclerosis in apolipoprotein E knockout mice [23]. In the present study, glucose swings were significantly lower in subjects given miglitol compared to those who received acarbose or placebo. Extrapolation of these results thus implicates a role for miglitol in the prevention of atherosclerosis in humans.

α-Glucosidase inhibitors reduce insulin levels by suppressing postprandial glucose elevation. Interestingly, both inhibitors tested here reduced the AUCs of insulin from 0 to 240 minutes by approximately 25% compared to placebo, although no such difference was observed in the AUCs of glucose. This could implicate changing patterns of postprandial glucose elevation, especially the glucose peak and/or time of peak, in the "insulin-saving" mechanism.

Although the insulin response to acarbose mirrored that to placebo with less amount of insulin, the peak of insulin after miglitol was later than those after control or acarbose. Reason for the later peak of insulin after miglitol administration may be the following: miglitol was absorbed from the small intestine and the concentration of it in lower small intestine becomes very low [14]. It resulted in elevation of glucose at a later postprandial stage. Elevation of plasma glucose level increased insulin level at the same stage and produced its later peak.

Together with improving postprandial hyperglycemia, this insulin-saving mechanism would prevent the progression from IGT to diabetes and reduce the risk of CVD, as shown in the STOP-NIDDM trial [7,8].

As described above, reduced postprandial insulin secretion after administration of α-glucosidase inhibitors was of concern with respect to possible adverse effects on postprandial lipids. Postprandial insulin spikes have been known to induce LPL activity, preventing postprandial hypertriglyceridemia [24]; therefore, we also assessed lipid profiles and the relationship between insulin and LPL. TG, RLP-TG, RLP cholesterol, VLDL cholesterol, and chylomicrons increased after a meal load in all groups. The lipid increases were attributable mainly to exogenous lipids because the subjects had fasted for 12 hours. Miglitol significantly suppressed the early-phase increases in TG, RLP-TG, and RLP cholesterol, and the early-phase decrease in HDL cholesterol. No significant changes were observed in chylomicrons that are degraded immediately on absorption and small-dense LDL. We also examined active GLP-1, based on reports that α-glucosidase inhibitors increased total GLP-1 [10,12]. Miglitol enhanced active GLP-1 secretion significantly more than acarbose at 60 and 120 minutes. Deceleration of gastric emptying by intravenously administered exogenous GLP-1 reduced the postprandial glucose elevation, and this was associated with reduced postprandial insulin levels [25]. Based on this, we speculated that the oral stimulation of endogenous GLP-1 secretion in this study contributed to the reductions of glucose and insulin. We also propose that deceleration of gastric emptying contributed to the suppressed increases in postprandial exogenous lipids in the early phase. Interestingly, the miglitol-induced decrease in LPL was sustained, possible due to the slow absorption of exogenous lipids and consequently sufficient time for interactions between exogenous lipids and LPL. There was no association between LPL and insulin in this study. On the other hand, as it has been reported that the combination of an α-glucosidase inhibitor and a dipeptidyl peptidase-IV (DPP-IV) inhibitor

increased active GLP-1 and improved glucose tolerance additively in mice compared to DPP-IV inhibitor alone [26], the combination of miglitol and a DPP-IV inhibitor is expected to be an useful option for improving postprandial hyperglycemia in clinical practice.

Previous studies have demonstrated that IL-6, a predictive marker for CVD [27], increases after a meal [28,29], whereas postprandial changes in ICAM-1 and VCAM-1 are controversial [29,30]. Interleukin 6 increased in this study, whereas ICAM-1 and VCAM-1 decreased. The lack of fat quantity and fat ratio, the time of blood sampling, or other factors might contribute to these postprandial changes in ICAM-1 and VCAM-1. Only miglitol suppressed the increase in IL-6 significantly compared to placebo. Acute hyperglycemia has been reported to increase circulating IL-6 more than continuous hyperglycemia [31], and there was a significant correlation between glucose swing and IL-6 in this study ($r = 0.52$, $P < .01$). Suppressing hyperglycemia-induced increase in IL-6 with miglitol might prevent the progression of atherosclerosis. Miglitol also has been reported to have preferable effects on body mass index, HOMA-IR, adiponectin, and urinary albumin excretion rate, which are markers related atherosclerosis [32].

In conclusion, miglitol improved postprandial hyperglycemia and reduces postprandial insulin requirements without deteriorating lipid profiles. We showed the possibility that this drug has potential for anti-atherosclerotic effects through decrease of glucose swing and postprandial IL-6 level in viscerally obese subjects. We assessed only single-administration effects in this study. Further large-scale studies to assess long-term effects are therefore necessary, particularly concerning the effect of changes to glucose tolerance with insulin secretion, enhanced GLP-1 secretion, and cardiovascular event.

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