Switching α-Glucosidase Inhibitors to Miglitol Reduced Glucose Fluctuations and Circulating Cardiovascular Disease Risk Factors in Type 2 Diabetic Japanese Patients

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Abstract

Background and Objectives In this study we examined the effects of switching α-glucosidase inhibitors (α-GI) from acarbose or voglibose to miglitol on glucose fluctuations and circulating concentrations of cardiovascular disease risk factors, such as soluble adhesion molecules (sE-selectin, sICAM-1 and sVCAM-1), a chemokine monocyte chemoattractant protein (MCP)-1, plasminogen activator inhibitor-1, and fatty acid-binding protein 4, in type 2 diabetic patients for 3 months.

Methods We enrolled 47 Japanese patients with type 2 diabetes, with HbA1c levels with 7.26 ± 0.5 % (mean ± standard deviation), and who were treated with the highest approved dose of acarbose (100 mg/meal) or voglibose (0.3 mg/meal) in combination with insulin or sulfonylurea. Patients’ prior α-GIs were switched to a medium dose of miglitol (50 mg/meal), and the new treatments were maintained for 3 months. Thirty-five patients who completed the 3-month study and provided serum samples were analyzed.

Results The switch to miglitol for 3 months did not affect HbA1c, fasting glucose, triglycerides, total-cholesterol or C-reactive protein levels, or result in any adverse events. Glucose fluctuations were significantly improved by the change in treatment (M-value: 10.54 ± 4.32 to 8.36 ± 2.54), while serum protein concentrations of MCP-1 (525.04 ± 288.06–428.11 ± 163.78 pg/mL) and sE-selectin (18.65 ± 9.77–14.50 ± 6.26 ng/mL) were suppressed.

Conclusion Our results suggest that switching from acarbose or voglibose to miglitol for 3 months suppressed glucose fluctuations and serum protein levels of MCP-1 and sE-selectin in type 2 diabetic Japanese patients, with fewer adverse effects.

Key Points

Switching α-glucosidase inhibitors to miglitol reduced glucose fluctuations and circulating cardiovascular disease (CVD) risk factors in type 2 diabetic Japanese patients

Reducing glucose fluctuations may reduce the development of CVD in type 2 diabetic patients

1 Introduction

Large-scale cohort studies such as Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe
(DECODE) and FUNAGATA have shown that impaired glucose tolerance (IGT) is strongly associated with subsequent incidence of cardiovascular disease (CVD) [1–3]. The Study TO Prevent Non-insulin-dependent diabetes mellitus (STOP-NIDDM) and Meta-analysis of Risk Improvement under Acarbose (MeRIA7) trials have demonstrated that inhibition of postprandial hyperglycemia by the α-glucosidase inhibitor (α-GI) acarbose reduces pronounced CVD events in subjects with IGT and type 2 diabetes [4, 5]. These results suggest that inhibition of postprandial hyperglycemia, rather than the total rise of glucose throughout the day, is important for preventing CVD development.

Recent studies have suggested that adhesion molecules such as E-selectin, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1, which are expressed in the vascular endothelium and induce leukocyte attachment to the blood vessels, are involved in the development of arteriosclerosis-related diabetic complications, including CVD. In addition, the chemokine monocyte chemoattractant protein (MCP)-1 is a key mediator of the arteriosclerosis-related diabetic complications via monocyte/macrophage trafficking to the vascular endothelium in diabetic conditions [6]. It has been reported in cell studies that hyperglycemia induces expression of ICAM-1, VCAM-1, E-selectin, and MCP-1 in vascular endothelial cells [7–9]. Previous longitudinal and cross-sectional studies including Japanese populations have demonstrated that serum concentrations of soluble (s) sE-selectin in particular, as well as sICAM-1 and sVCAM-1, are positively associated with arteriosclerosis-related clinical parameters and the subsequent incidence of CVD in type 2 diabetic patients [10–13]. Moreover, many longitudinal and cross-sectional studies have demonstrated that circulating MCP-1 concentrations are strongly and positively associated with atherosclerosis-associated clinical parameters in healthy subjects, subjects with obesity, or subjects with type 2 diabetes [14–16].

Our previous study demonstrated that switching α-GI from acarbose or voglibose to miglitol, which has a greater effect on reducing 1 h postprandial glucose levels than other α-GIs [17], in type 2 diabetic patients reduced glucose fluctuations and messenger RNA (mRNA) levels of inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, which are known to induce attachment of activated leukocytes to blood vessels [18], in peripheral leukocytes and circulating TNF-α protein levels [19]. However, whether circulating levels of soluble adhesion molecules and MCP-1 are suppressed by miglitol treatment in type 2 diabetic patients has not been determined.

In this study, we examined whether switching from acarbose or voglibose to miglitol in type 2 diabetic patients reduced glucose fluctuations and circulating levels of soluble adhesion molecules such as sE-selectin, sICAM-1, sVCAM-1, and MCP-1.

2 Methods

2.1 Study Population

This study was a prospective exploratory trial conducted in a hospital setting (Naka Kinen Clinic, Ibaraki) in Japan. We first reviewed the clinical records of potential subjects and identified those that met the criteria of inclusion and exclusion. Inclusion criteria were male and female patients with type 2 diabetes, HbA1c values ranging from 6.9 to 8.3 %, and treatment with the highest approved doses of α-GIs (100 mg acarbose or 0.3 mg voglibose at each meal) in combination with insulin or a sulfonylurea for at least 6 months, who visited the hospital between May 2007 and April 2008. The number of patients compliant with the inclusion criteria was 196 type 2 diabetic patients who visited the clinic during the study period (n = 1,136). Among these patients, we excluded from the study patients considered inappropriate, e.g. pregnant, possibly pregnant, or young (patients younger than 20 years of age). Four patients with severe nephropathy (serum creatinine ≥2 mg/100 mL) were excluded. We also excluded patients with severe clinical conditions, such as hepatic disorders, CVD, impaired pulmonary function, pancreatopathy, cancer, infectious diseases, external injury, and perioperative patients. We selected 47 patients matching the above criteria and all patients were enrolled as previously reported [19]. The patients had been undergoing stable treatment for at least 3 months before entering the study. Subjects’ prior α-GIs were switched to miglitol at a dose of 50 mg/meal, and continued for 3 months. Anthropometric data were measured and blood samples collected from each patient before and 3 months after the switch to miglitol. Before and 3 months after the switch, subjects were questioned regarding abdominal distension, flatulence, and abnormalities of bowel function using a questionnaire consisting of a visual analog scale (VAS) from 1 to 10, with 1 indicating no problems in daily life and 10 indicating an inability to perform activities of daily living. Before and 3 months after the switch, each patient was asked by medical staff whether symptoms consistent with hypoglycemia, such as hand and foot trepidations and palpitations, had occurred at least once or never during each 1-month period. The prescriptions for medications other than α-GIs including insulin units for patients were not changed during the trial. Among the subjects, four patients dropped out during the trial. Overall, 43 patients completed the trial and were included in the analysis of the relationship between glucose fluctuation and inflammatory cytokine mRNA levels in
peripheral leukocytes, as previously reported [19]. Among the subjects who completed the trial, we reanalyzed 35 patients because serum samples were missing from eight patients. All patients in the study provided informed consent for use of their personal and health information in our analysis. The study protocol was approved by the Ethics Committee of the University of Shizuoka, Shizuoka, Japan.

2.2 Measurements

Before and 3 months after the switch to miglitol, basic parameters in the morning following an overnight fast state were measured. Body heights and weights were measured using instruments (body heights: AD-6225A; body weight: AD6207A; A&D Co., Ltd, Tokyo, Japan). Triglycerides (TGL), total cholesterol (T-cho), high-density lipoprotein (HDL), and C-reactive protein (CRP) were measured in blood samples with an auto-analyzer (7180; Hitachi High-Technologies Co., Ltd, Tokyo, Japan). Fasting plasma glucose and HbA1c were measured using instruments (fasting plasma glucose: GA-1171; HbA1c: HA8181; ARKRAY, Inc., Kyoto, Japan). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Self-monitoring of blood glucose (SMBG) was performed over 5 days within 1 month before the switch (baseline) and within 1 month before the end of the trial (after the switch). SMBG was performed just before and 1 h after each meal (six time points per day) using a Glutest Neo SMBG device (Sanwa Kagaku Kenkyusho, Nagoya, Japan). The SMBG data over 5 days within 1 month before the switch to miglitol. Serum protein concentrations of MCP-1 were measured using a Milliplex Human Cytokine/Chemokine Immunoassay Kit (Millipore, Billerica, MA, USA), and adhesion molecules (sE-selectin, sICAM-1 and sVCAM-1) and total plasminogen activator inhibitor (tPAI)-1 were measured using a Milliplex CVD Panel 1 Immunoassay kit (Millipore). Serum fatty acid-binding protein (FABP) 4 concentrations were measured using human adipocyte FABP enzyme-linked immunosorbent assay (BioVendor Inc., Brno, Czech Republic). The mean intra-assay coefficients of variation for MCP-1, sE-selectin, sICAM-1, sVCAM-1, tPAI-1, and FABP4 reported by the manufacturers were 6.1, 11.2, 7.9, 4.5, 11.8, and 2.5 %, respectively. The inter-assay coefficients of variation for MCP-1, sE-selectin, sICAM-1, sVCAM-1, tPAI-1, and FABP4 were 12.0, 13.4, 9.7, 8.5, 12.5, and 3.9 %, respectively.

2.3 Statistical Analysis

Values are presented as mean ± standard deviation (SD). All statistical analyses were performed using Excel 2007 for Windows (Microsoft Corporation, Redmond, WA, USA). Significant differences between two groups were determined by paired Student’s t tests. Values of p < 0.05 were considered significant.

3 Results

Baseline patient characteristics are shown in Table 1. We obtained data from 35 type 2 diabetic patients whose mean HbA1c values were 7.26 ± 0.51 % at baseline. Among these patients, 25 had any one or more diabetic complications such as neuropathy and nephropathy. The mean age, BMI, and duration of type 2 diabetes were 65.8 ± 9.5 years, 21.8 ± 2.8 kg/m², and 20.5 ± 11.3 years, respectively.

Table 1 shows the clinical characteristics just before and 3 months after switching from acarbose or voglibose to

| Table 1 Baseline patient characteristics |
|-----------------------------------------|
| Sex (male/female) 17/18 |
| Age (years) 65.8 ± 9.5 |
| BMI (kg/m²) 21.8 ± 2.8 |
| HbA1c (%) 7.26 ± 0.51 |
| Duration of diabetes (years) 20.5 ± 11.3 |
| Diabetic complications |
| Retinopathy 21 |
| Neuropathy 15 |
| Nephropathy 0 |
| Any one or more of these complications 25 |
| Hyperlipidemia 22 |
| Prescription of statins 18 |
| Hypertension 19 |
| Prescription of angiotensin receptor blockers 10 |
| Assigned caloric intake (kcal) 1,495 ± 151 |
| Combined drugs |
| Insulin 21 |
| Intermediate-acting 16 |
| Long-acting 4 |
| Pre-mixed (intermediate-acting and rapid-acting) 1 |
| Sulfonylurea 14 |
| Prior α-glucosidase inhibitor |
| Acarbose (100 mg three times daily) 30 |
| Voglibose (0.3 mg three times daily) 5 |

Data are expressed as mean ± SD, or frequency

BMI body mass index

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miglitol. Switching to miglitol did not affect VAS values for digestive symptoms such as abdominal distention, flatulence, and abnormalities of bowel function. The α-GI switch had no effects on levels of HbA1c, fasting glucose, T-cho, and CRP. The results indicate that the switch from acarbose or voglibose to miglitol did not affect basic clinical parameters.

Figure 1 shows blood glucose concentrations pre- and post-meals compared with periods just before and after the α-GI switch. Blood glucose concentrations were significantly higher just before lunch (p = 0.018), significantly lower 1 h after lunch (p = 0.012), significantly higher just before dinner (p < 0.001), and significantly lower 1 h after dinner (p = 0.045) after the switch compared with before the switch. M-values were significantly reduced by the switch to miglitol (p = 0.010). Glucose fluctuations were improved by the switch without changing the total rise of glucose (HbA1c).

Serum protein concentrations of CVD risk factors are shown in Fig. 2. Serum MCP-1 and sE-selectin concentrations decreased at levels of 82 % (p < 0.001) and 78 % (p = 0.014), respectively, and serum sVCAM-1 concentrations increased at levels of 107 % (p = 0.014) 3 months after the switch compared with baseline. Serum protein concentrations of sICAM-1, tPAI-1, and FABP4 were unchanged by the switch. These results indicate the switch from acarbose or voglibose to miglitol reduced circulating protein concentrations of CVD risk factors such as MCP-1 and sE-selectin.

4 Discussion

In large-scale cohort studies, such as DECODE and FUNAGATA, it has been reported that postprandial hyperglycemia, rather than HbA1c, is closely associated with subsequent incidence of CVD [1–3]. Additionally, the STOP-NIDDM and MeRIA7 trials have demonstrated that inhibition of postprandial hyperglycemia by the α-GI acarbose greatly reduces CVD events in subjects with IGT and type 2 diabetes [4, 5]. Thus, reduction of glucose fluctuations by miglitol may reduce CVD incidence in type 2 diabetic patients. In addition, we previously reported in 43 type 2 diabetic patients from the same sample that mRNA levels of inflammatory cytokines, such as IL-1β and TNF-α, in peripheral leukocytes and circulating TNF-α proteins were reduced by the switch to miglitol [19]. In this study we reanalyzed serum samples of 35 patients from the same sample and found that serum protein concentrations of MCP-1 and sE-selectin were reduced by the switch. MCP-1 induces migration of leukocytes to blood vessels and E-selectin facilitates leukocytes rolling onto the endothelium, resulting in the induction of the adhesion of leukocytes to blood vessels [21, 22]. Together, the results of this study and our previous study indicate that the switching from an α-GI (acarbose or voglibose) to miglitol suppresses glucose fluctuations, inflammatory cytokine expression in peripheral leukocytes, and circulating protein concentrations of MCP-1, sE-selectin, and TNF-α in type 2 diabetic patients in a clinical setting in Japan.

Serum protein concentrations of sICAM-1, tPAI-1, and FABP4 were not altered and sVCAM-1 was slightly increased by the switch to miglitol. sICAM-1 and sVCAM-1 participate in inducing leukocyte attachment to blood vessels after leukocyte migration and rolling of leukocytes around blood vessels [23]. PAI-1 expressed from adipose tissues promotes atherogenesis by forming blocked blood vessels by inducing blood coagulation [24], and FABP4 expressed from adipose tissues and macrophages enhances atherogenesis by tracking cholesterol in atheromatosis [25]. These steps are later steps in the attachment of leukocytes to blood vessels. Thus, α-GIs, including miglitol, may inhibit CVD development by repressing the initial step of atheromatosis, i.e. inhibition of circulating MCP-1 and sE-

| Table 2 | Clinical characteristics at baseline and 3 months after switching to miglitol |
|---------|---------------------------------|
|         | n  | Baseline       | 3 months       | p-Value |
| HbA1c (%) | 35 | 7.26 ± 0.51 | 7.27 ± 0.61 | 0.817 |
| Fasting glucose (mg/100 mL) | 35 | 130.6 ± 29.6 | 129.0 ± 30.2 | 0.771 |
| Triglycerides (mg/100 mL) | 35 | 73.9 ± 35.9 | 77.8 ± 34.4 | 0.501 |
| Total cholesterol (mg/100 mL) | 33 | 179.9 ± 28.4 | 183.8 ± 27.4 | 0.340 |
| CRP (mg/100 mL) | 35 | 0.09 ± 0.16 | 0.08 ± 0.18 | 0.815 |
| Abdominal distention (score 1–10) | 35 | 2.6 ± 2.1 | 2.8 ± 2.1 | 0.546 |
| Flatulence (score 1–10) | 35 | 4.2 ± 2.7 | 3.1 ± 2.0 | 0.161 |
| Abnormalities of bowel function (score 1–10) | 29 | 1.7 ± 1.2 | 2.1 ± 1.5 | 0.206 |

Data are expressed as mean ± SD, or frequency
Statistical analyses were performed using two-sided, paired Student’s t test
CRP C-reactive protein

△ Adis
Glucose Fluctuations and CVD Risk

selectin proteins via inhibition of postprandial hyperglycemia and glucose fluctuations. However, the associations between glucose fluctuations and the concentrations of circulating CVD risk factors in type 2 diabetic patients, as well as in subjects with IGT and healthy subjects, remain unclear. Thus, there is a need to examine the associations between glucose fluctuations and the concentrations of circulating CVD risk factors in subjects with type 2 diabetes or IGT and healthy subjects in cross-sectional studies. Additionally, whether subjects with higher circulating concentrations of CVD risk factors accompanied by glucose fluctuations had higher subsequent incidence of CVD should be explored in cohort studies. In addition, randomized, double-blind, placebo-controlled (RCT) trials are needed to examine whether repression of circulating CVD risk factor concentrations by miglitol, but less so by other α-GIs, reduces the subsequent incidence of CVD in type 2 diabetic patients.

tPAI-1 and FABP4 are expressed from adipose tissues and related to lipid metabolism. Thus, switching α-GIs from acarbose or voglibose to miglitol may not reduce lipid abnormalities related to atherogenesis risk. It has been reported from an RCT conducted in Germany that drugs improving lipid metabolism (insulin resistance) such as metformin and pioglitazone and their combination reduced tPAI-1 concentrations in type 2 diabetic patients receiving stable basal insulin therapy [26], although it is still unclear whether circulating FABP4 concentrations are reduced by these drugs. The combination of miglitol with these drugs for improving insulin resistance may reduce CVD development by decreasing circulating concentrations of tPAI-1, MCP-1, and sE-selectin. This hypothesis should be examined in intervention trials.

Switching from acarbose or voglibose to miglitol for 3 months has been found to reduce hypoglycemic symptoms and blood glucose concentrations between meals [19]. It has been shown that hypoglycemia is strongly and positively associated with subsequent CVD incidence [27]. Thus, reducing hypoglycemia using miglitol may reduce CVD risk; however, hypoglycemic symptoms in our trials were self-reported. The self-reported hypoglycemic symptoms were limited because they may be underreported by patients to medical staff. A previous study has demonstrated that postprandial hyperglycemia within 1 h after a standard meal loading was higher, and that over 1 h was lower, in viscerally obese Japanese subjects treated with miglitol compared with those treated with acarbose [17]. In addition, it was reported that treatment with miglitol, but not with acarbose or voglibose, in Japanese women who had undergone a total gastrectomy reduced reactive hypoglycemia [28]. Combining our results with those of previous studies, treatment with miglitol could be a lower risk of hypoglycemia rather than other α-GIs. Further large-scale studies should examine whether miglitol treatment of type 2 diabetic patients reduces hypoglycemia assessed by SMBG and hypoglycemic symptoms, such as hypoglycemia-induced lethargy, compared with other α-GIs. Additionally, whether slight and severe degrees of hypoglycemia induce circulating protein concentrations of MCP-1 and sE-selectin, and whether the reduction of hypoglycemia by miglitol reduces circulating protein concentrations of MCP-1 and sE-selectin and CVD incidence in type 2 diabetic patients, should be examined.

In addition, it should be noted that we analyzed samples from 35 of the 43 patients who completed the study because serum samples were not obtained from eight patients. Our previous study using the same sample demonstrated that glucose fluctuations in 43 type 2 diabetic Japanese patients were reduced by switching from acarbose or voglibose to miglitol for 3 months. In this study, we obtained the same result in 35 patients. Thus, missing data from the eight patients would be less likely to affect the results of this study.

It should be noted that our study is relatively small in scale. It has been reported that an increase of the

△ Adis
The postprandial incremental area under the curve of blood glucose in a single oral meal test in eight type 2 diabetic patients was reduced by miglitol treatment at doses of 50, 75, 100, and 200 mg [29]. An RCT of 36 type 2 diabetic patients found that postprandial blood glucose levels were reduced by 50% in patients treated with miglitol compared with those treated with placebo [30]. A double-blind, crossover design in 15 type 2 diabetic patients found that treatment with miglitol (300 mg/day) effectively reduced postprandial blood glucose levels over 8 weeks [31]. In addition, a previous study reported that treatment with miglitol in 24 viscerally obese subjects reduced glucose fluctuations and circulating IL-6 concentrations versus acarbose treatment [17]. From these studies, we considered that our sample of 35 type 2 diabetic Japanese patients is comparable; however, a large-scale RCT is needed to examine whether miglitol reduces glucose fluctuations and circulating concentrations of CVD risk factors in type 2 diabetic patients compared with other α-GIs.

We assessed glucose fluctuations by SMBG. Recent studies have suggested that blood glucose profiles monitored by SMBG are not always correlated with continuous glucose monitoring (CGM), particularly given that measurement of blood glucose concentrations by SMBG often omit hypoglycemic events entirely [32, 33]. A study of ten type 2 diabetic patients hospitalized for 4 days found that glucose fluctuations, which were monitored by CGM, in a standard meal loading were reduced effectively by treatment with miglitol (50 mg) compared with acarbose (100 mg) [34]. In addition, in this study we demonstrated that switching α-GIs from acarbose or voglibose to miglitol in type 2 diabetic Japanese patients reduced glucose fluctuations, which were assessed by the averages at just before and 1 h after each meal measured over 5 days by SMBG. Combining our results with the results from CGM in a previous study, miglitol could reduce glucose fluctuations and hypoglycemic symptoms more effectively than other α-GIs. However, it is still unclear whether glucose fluctuations were lower in type 2 diabetic patients who were treated longer with miglitol than in those who were treated longer with other α-GIs. Although CGM during the treatment of α-GIs were performed under oral meal loading tests at breakfast, lunch, and dinner in patients hospitalized for 4 days in the previous study [34], the diet during days when SMBG was performed in our trials was dependent on each patient. RCT trials, in which dietary habits are well controlled, should examine whether glucose fluctuations by

![Graph of serum protein levels](image-url)

**Fig. 2** Serum protein levels of CVD risk factors at baseline and 3 months after switching to miglitol. Values are means ± SD. Statistical analyses were performed using two-sided paired Student’s *t* test. Asterisks denote significant differences compared with the value before switching to miglitol (*p < 0.05 and **p < 0.01). CVD cardiovascular disease, SD standard deviation, MCP monocyte chemotactant protein, VCAM vascular cell adhesion molecule, ICAM intercellular adhesion molecule, tPAI total plasminogen activator inhibitor, FABP4 fatty acid binding protein, s soluble
long-term CGM are lower in type 2 diabetic patients treated with miglitol than in those treated with acarbose or voglibose.

It should be noted that our trial is a prospective exploratory trial that is not an RCT, which introduces some confounding factors and bias in our trial. It has been reported that blood glucose control is affected by seasonal changes. Indeed, it has been reported that HbA1c has a duration across the year that is highly detected during spring and gradually decreases by autumn in Japan [35]. One of the other possibilities is that lifestyles such as dietary and exercise habits in patients were changed during the trial. In this trial, the doctor assigned caloric intake and the suggestion was not changed during the trial. However, it is possible that the lifestyles of patients were changed by themselves. In addition, miglitol treatment may reduce a patient’s appetite because the change of α-GI to miglitol treatment inhibits symptoms of hypoglycemia and reduction of blood glucose levels during a meal; however, our results indicate that the change of α-GI to miglitol reduced glucose fluctuation but not HbA1c. Thus, the effect is most likely a result of the effects of miglitol because changes in dietary and exercise habits may alter HbA1c levels. Whether miglitol treatment reduces circulating CVD risk factors including MCP-1 and sE-selectin in type 2 diabetic Japanese patients needs to be examined in an RCT.

5 Conclusion

The results of this study indicate that switching from acarbose or voglibose to miglitol for 3 months suppressed glucose fluctuations and serum protein concentrations of MCP-1 and sE-selectin more effectively than the prior α-GI.

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Conflict of interest Mr. Fuchigami is an employee of Sanwa Kagaku Kenkyusho Co., LTD, Nagoya, Japan.

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