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# The α-glucosidase inhibitor miglitol decreases glucose fluctuations and inflammatory cytokine gene expression in peripheral leukocytes of Japanese patients with type 2 diabetes mellitus

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**Abstract**

In this study, we examined the effects of switching from acarbose or voglibose to miglitol in type 2 diabetes mellitus patients for 3 months on gene expression of inflammatory cytokines/cytokine-like factors in peripheral leukocytes and on glucose fluctuations. We enrolled 47 Japanese patients with type 2 diabetes mellitus, aged 26 to 81 years, with hemoglobin $A_{1c}$ levels ranging from 6.5% to 7.9% and who were treated with the highest approved dose of acarbose (100 mg per meal) or voglibose (0.3 mg per meal) in combination with insulin or sulfonylurea. Their prior α-glucosidase inhibitors were switched to a medium dose of miglitol (50 mg per meal), and the new treatments were maintained for 3 months. Forty-three patients completed the 3-month study and were analyzed. The switch to miglitol for 3 months did not affect hemoglobin $A_{1c}$, fasting glucose, triglycerides, total cholesterol, or C-reactive protein levels, or adverse events other than hypoglycemia symptoms. Hypoglycemia symptoms and glucose fluctuations were significantly improved by the switch. The expression of interleukin-1*β*, tumor necrosis factor-α, and S100a4/6/9/10/11/12 genes in peripheral leukocytes, and the serum tumor necrosis factor-α protein levels were suppressed by switching to miglitol. Miglitol reduces glucose fluctuations and gene expression of inflammatory cytokines/cytokine-like factors in peripheral leukocytes of type 2 diabetes mellitus patients more than other α-glucosidase inhibitors and with fewer adverse effects.


## 1. Introduction

Many patients with type 2 diabetes mellitus are treated with α-glucosidase inhibitors, which inhibit the activity of disaccharidases in the brush border membrane of the small intestine, often in combination with other drugs such as insulin and sulfonylureas. Compared with other oral glucose-lowering drugs, α-glucosidase inhibitors reduce glucose fluctuations by inhibiting postprandial hyperglycemia and are associated with less frequent hypoglycemia. Acarbose, a pseudotetrasaccharide, is a competitive inhibitor of sucrase, glucoamylase, and isomaltase [1-4]. Voglibose, an *N*-substituted valiolamine derivative, has been reported to have stronger α-glucosidase inhibitory activity against maltase and sucrase [5]. Studies in animal models of type 2 diabetes mellitus have demonstrated that treatment with these α-glucosidase inhibitors decreased *β*-cell apoptosis and inhibited the attachment of macrophages to the vascular endothelium [6-8]. Furthermore, the epidemiologic studies Meta-analysis of Risk Improvement under Acarbose (MeRIA7) and Study TO Prevent Non-insulin-dependent diabetes mellitus (STOP-NIDDM) revealed that inhibition of postprandial hyperglycemia by acarbose in patients with type 2 diabetes mellitus or impaired glucose tolerance helped prevent the development and progression of type 2 diabetes mellitus and complications such as cardiovascular disease [9-13]. These findings indicate that treating type 2 diabetes mellitus patients with α-glucosidase inhibitors helps to prevent or delay the development and progression of type 2 diabetes mellitus and complications such as atherosclerosis. Miglitol, a 1-deoxynojirimycin derivative that was recently

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approved in Japan, is another antihyperglycemic agent [14]. Miglitol is a strong inhibitor of glucoamylase, sucrase, and isomaltase, and is absorbed from the small intestine, unlike other α-glucosidase inhibitors [15]. Using animal models of type 2 diabetes mellitus, it has been reported that miglitol decreased β-cell apoptosis and inhibited the attachment of macrophages to the vascular endothelium [16,17]. Miglitol elicits greater reductions in the 1-hour postprandial glucose level and glucose fluctuations than other α-glucosidase inhibitors because it can be given to patients at relatively high doses with a low incidence of digestive symptoms such as diarrhea [16]. Therefore, it is expected that miglitol will reduce the development and progression of type 2 diabetes mellitus and its complications by achieving greater reductions in glucose fluctuations than other α-glucosidase inhibitors.

Several recent studies have suggested that the major molecular mechanisms involved in the development/progression of type 2 diabetes mellitus and its complications include oxidative stress, viral/bacterial infection, and activation of leukocytes such as monocytes and macrophages. Collectively, these responses are referred to as *inflammation* [9]. Indeed, hyperglycemia directly induces inflammation by enhancing inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, IL-12, and IL-18, which are mainly expressed by leukocytes, including macrophages, monocytes, and neutrophils, and by many peripheral tissues [18-20]. In addition, several studies have demonstrated that the S100 family of proteins, including S100a4, S100a6, S100a8, S100a9, and S100a12, are not only putative inflammatory cytokines that are predominantly expressed in monocytes and neutrophils, but also useful diagnostic inflammatory markers for type 1 and 2 diabetes mellitus [21-23]. The S100a8-9 heterodimer induces the expression of other cytokines such as IL-1β and IL-6 in leukocytes by activating G-protein-coupled receptor/tyrosine receptor through binding to the advanced glycation end-product receptor [24]. Thus, decreasing the expression of these cytokines/cytokine-like factors and decreasing leukocyte activation may reduce the development and progression of type 2 diabetes mellitus and its complications. A recent study in obese Japanese subjects showed that a single dose of miglitol at mealtime suppressed postprandial elevations of glucose and plasma IL-6 levels more effectively than acarbose [25]. However, the long-term effects of α-glucosidase inhibitors, including miglitol, on plasma cytokines/cytokine-like factors have not yet been studied. Using hyperglycemic rats, we recently demonstrated that dietary supplementation with miglitol for 3 weeks reduced glucose fluctuations and the gene expression of IL-1β, TNFα, and S100 proteins such as S100a4/a6/a8/a9 in peripheral leukocytes [26,27]. However, whether the expression of these genes in peripheral leukocytes is down-regulated by reducing glucose fluctuations with miglitol in patients with type 2 diabetes mellitus has not been determined.

In this study, we enrolled patients with type 2 diabetes mellitus with hemoglobin $A_{1c}$ ($HbA_{1c}$) values ranging from 6.5% to 7.9% who were being treated with a high dose of the α-glucosidase inhibitors acarbose or voglibose in combination with insulin or a sulfonylurea. Their prior α-glucosidase inhibitors were switched to a medium-strength dose of miglitol, which was administered for 3 months. We hypothesized that switching from acarbose or voglibose to miglitol in type 2 diabetes mellitus patients would reduce glucose fluctuations and the gene expression of inflammatory cytokines/cytokines-like factors in peripheral leukocytes.

## 2. Participants and methods

### 2.1. Study population

This study was an exploratory trial conducted in a hospital setting (Naka Memorial Clinic, Ibaragi) in Japan. We first reviewed the clinical records of potential subjects and identified those that met the inclusion criteria, namely, male and female patients with type 2 diabetes mellitus, $HbA_{1c}$ ranging from 6.5% to 7.9%, and treatment with the highest approved dose of α-glucosidase inhibitors (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. Overall, 47 patients were enrolled and 4 patients dropped out during the trial. The patients had been undergoing stable treatment for at least 3 months before entering the study. We excluded patients who were pregnant, possibly pregnant, or planning to become pregnant; patients with severe nephropathy (serum creatinine ≥2 mg/100 mL); patients younger than 20 years; and patients otherwise considered inappropriate for inclusion in the study. We also excluded patients with severe clinical conditions, such as hepatic disorders, cardiovascular disease, impaired pulmonary function, pancreatopathy, cancer, infectious diseases, external injury, and type 2 diabetes mellitus complications, as well as perioperative patients. Their prior α-glucosidase inhibitors were switched to miglitol at a dose of 50 mg per meal, which was continued for 3 months. Anthropometric data were measured and blood samples were collected for each patient before and 3 months after the switch to miglitol. Before and 3 months after the switch, the subjects were questioned regarding abdominal distension, flatulence, and abnormalities of bowel function by questionnaire, using a visual analog scale 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 palpitation, had occurred at least once or never during each 1-month period. Overall, 43 patients completed the study; and their clinical data were analyzed. All participants in the study provided informed consent for the use of their personal information in our analyses. 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, body height and weight were measured; and fasting plasma glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol levels were measured in blood samples obtained in the morning after an overnight fast. 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 just before and 1 hour after each meal (6 values per day) using a Glutest Neo SMBG device (Sanwa Kagaku Kenkyusho, Nagoya, Japan). M-values were determined from the SMBG values using the formula $[10 \times \log(\text{blood glucose level}/120)]^3$ + (blood glucose level$^{max}$ − blood glucose level$^{min}$)/20 [28]. Blood samples for RNA extraction were also obtained, and each sample was immediately mixed in a PAXgene RNA tube with a fixation solution to fix leukocytes without altering the messenger RNA (mRNA) levels in these cells (Qiagen/BD, Tokyo, Japan). The blood samples plus fixation solution were incubated at room temperature for 1 day and then stored at −70°C in accordance with the manufacturer's instructions.

Table 1
Primer sequences

| Gene | Sequence | TaqMan probe |
|---|---|---|
| IL-1β | 5′-ctgtcctgcgtgttgaaaga-3′ | #78 |
| | 5′-ttgggtaatttttgggatctaca-3′ | |
| IL-2 | 5′-aagttttacatgcccaagaagg-3′ | #65 |
| | 5′-aagtgaaagtttttgctttgagcta-3′ | |
| IL-4 | 5′-caccgagttgaccgtaacag-3′ | #16 |
| | 5′-gccctgcagaaggtttcc-3′ | |
| IL-10 | 5′-tgggggagaacctgaagac-3′ | #30 |
| | 5′-ccttgctcttgttttcacagg-3′ | |
| IL-12A | 5′-cactcccaaaacctgctgag-3′ | #50 |
| | 5′-tctcttcagaagtgcaagggta-3′ | |
| IL-18 | 5′-caacaaactatttgtcgcagga-3′ | #46 |
| | 5′-tgccacaaagttgatgcaat-3′ | |
| IFNγ | 5′-ggcattttgaagaattggaaaag-3′ | #21 |
| | 5′-tttggatgctctggtcatctt-3′ | |
| TNFα | 5′-cagcctcttctccttcctgat-3′ | #29 |
| | 5′-gccagagggctgattagaga-3′ | |
| S100a4 | 5′-gggattcttcccctctctaca-3′ | #73 |
| | 5′-catgacagcagtcaggatcaa-3′ | |
| S100a6 | 5′-gctcaccattggctcgaa-3′ | #79 |
| | 5′-ggaaggtgacatactcctgga-3′ | |
| S100a8 | 5′-caagtccgtgggcatcat-3′ | #78 |
| | 5′-gacgtcgatgatagagttcaagg-3′ | |
| S100a9 | 5′-gtgcgaaaagatctgcaaaa-3′ | #85 |
| | 5′-tcagctgcttgtctgcattt-3′ | |
| S100a10 | 5′-gagttccctggatttttggaa-3′ | #76 |
| | 5′-cactggtccaggtccttcat-3′ | |
| S100a11 | 5′-tctccaagacagagttcctaagc-3′ | #8 |
| | 5′-atcatgcggtcaaggacac-3′ | |
| S100a12 | 5′-cacattcctgtgcattgagg-3′ | #31 |
| | 5′-ggtgtcaaaatgccccttc-3′ | |
| 18S rRNA | 5′-cgattggatggtttagtgagg-3′ | #81 |
| | 5′-agttcgaccgtcttctcagc-3′ | |
| TFIIB | 5′-ggagatttgtctaccatgattgg-3′ | #17 |
| | 5′-aattgccaaattcgtcaaaact-3′ | |

Table 2
Baseline patient characteristics

| | |
|---|---|
| Sex (male/female) | 22/21 |
| Age (y) | 64.2 ± 11.0 |
| BMI (kg/m$^2$) | 22.3 ± 2.8 |
| Duration of diabetes (y) | 19.2 ± 11.4 |
| Diabetic complications | 30 |
| Hyperlipidemia | 30 |
| Prescription of statins | 25 |
| Hypertension | 21 |
| Prescription of angiotensin receptor blockers | 11 |
| Assigned calorie intake (kcal) | 1509 ± 150 |
| Combined drugs | |
| Insulin | 27 |
| Sulfonylurea | 16 |
| Prior α-glucosidase inhibitor | |
| Acarbose (100 mg) | 37 |
| Voglibose (0.3 mg) | 6 |

Means ± SD or number.

Total RNA was extracted from blood using the PAXgene kit (PreAnalytix, Qiagen/BD). Total RNA samples (50 ng) were converted to complementary DNA by reverse transcription using SuperScript III RT (Invitrogen, Tokyo, Japan) in accordance with the manufacturer's instructions. To estimate the mRNA levels of the selected genes, polymerase chain reaction (PCR) amplification using a universal TaqMan probe was performed on a Light-Cycler instrument (Roche Molecular Biochemicals, Tokyo, Japan), as previously described [27]. The PCR primer sequences and universal TaqMan probe numbers are listed in Table 1. The cycle threshold (CT) values for each gene and transcription factor IIB (TFIIB) detected by real-time reverse transcriptase PCR were converted to signal intensities by the Δ-Δ method [29], which calculates the difference of one CT value as a 2-fold difference between the signal for each gene and the signal for a gene for normalization (TFIIB). The formula used was $[2^{(\text{CT each gene} - \text{CT TFIIB})}]$. Serum TNFα levels were measured using a Milliplex Human cytokine Immunoassay Kit (Millipore, Tokyo, Japan).

### 2.3. Statistical analysis

Values are presented as mean ± SD. All statistical analyses were performed using Excel 2003 for Windows (Microsoft, Redmond, WA). The significance of differences between 2 groups was determined by paired Student $t$ tests or $\chi^2$ tests, as appropriate. Values of $P < .05$ were considered significant.

## 3. Results

We examined data obtained from 22 men and 21 women with type 2 diabetes mellitus and $HbA_{1c}$ values ranging from 6.5% to 7.9%. The characteristics of the subjects are shown in Table 2. The mean age, BMI, and duration of type 2 diabetes mellitus were 64.2 ± 11.0 years, 22.3 ± 2.8 kg/m$^2$, and 19.2 ± 11.4 years, respectively. Table 3 shows the clinical parameters before and 3 months after switching

Table 3
Clinical characteristics at baseline and at 3 months after switching to miglitol

| | n | Baseline | 3 mo | *P* value |
|---|---|---|---|---|
| $HbA_{1c}$ (%) | 43 | 6.80 ± 0.49 | 6.82 ± 0.58 | .725 |
| Fasting glucose (mg/100 mL) | 42 | 132 ± 27.6 | 128 ± 28.2 | .452 |
| Triglycerides (mg/100 mL) | 42 | 81.1 ± 42.7 | 81.6 ± 45.0 | .907 |
| Total cholesterol (mg/100 mL) | 41 | 184.5 ± 29.0 | 187.1 ± 27.0 | .416 |
| C-reactive protein (mg/100 mL) | 41 | 0.101 ± 0.16 | 0.086 ± 0.17 | .636 |
| Hypoglycemia symptoms (n) | 43 | 19 | 8 | .011* |
| Abdominal distention (score 1-10) | 35 | 2.78 ± 2.09 | 2.85 ± 2.15 | .869 |
| Flatulence (score 1-10) | 35 | 4.26 ± 2.60 | 3.24 ± 2.04 | .064 |
| Abnormalities of bowel function (score 1-10) | 34 | 1.78 ± 1.29 | 2.14 ± 1.48 | .232 |

Mean ± SD or number. Statistical analyses were performed using 2-sided paired Student *t* test or $\chi^2$ test for hypoglycemia.
* $P < .05$ by $\chi^2$ test.

from the highest approved doses of acarbose or voglibose to a medium dose of miglitol. The frequency of hypoglycemia symptoms was significantly decreased by the switch ($P = .011$), whereas flatulence tended to be reduced ($P = .064$). Other clinical parameters were not affected by switching to miglitol. Blood glucose concentrations determined by SMBG tended to be lower after breakfast ($P = .056$), higher before lunch ($P = .053$), significantly lower 1 hour after lunch ($P = .0049$), significantly higher before dinner ($P = .000047$), and significantly lower 1 hour after dinner ($P = .000047$) at 3 months after the switch than before starting miglitol. The M-values in subjects at 3 months after the switch (7.80 ± 2.78) were significantly lower than those before the switch (10.29 ± 4.32, $P = .00092$) (Fig. 1).

Gene expressions of IL-1$\beta$ ($P = .00544$), TNF$\alpha$ ($P = .00046$), S100a4 ($P = .02330$), S100a6 ($P = .01440$), S100a9 ($P = .03970$), S100a10 ($P = .00405$), S100a11 ($P = .00377$), and S100a12 ($P = .03110$) were significantly lower in subjects at 3 months after the switch to miglitol compared with the expression levels before the switch. Serum TNF$\alpha$ protein levels were significantly lower ($P = .01915$) in subjects at 3 months after the switch to miglitol compared with the levels before the switch (Table 4).

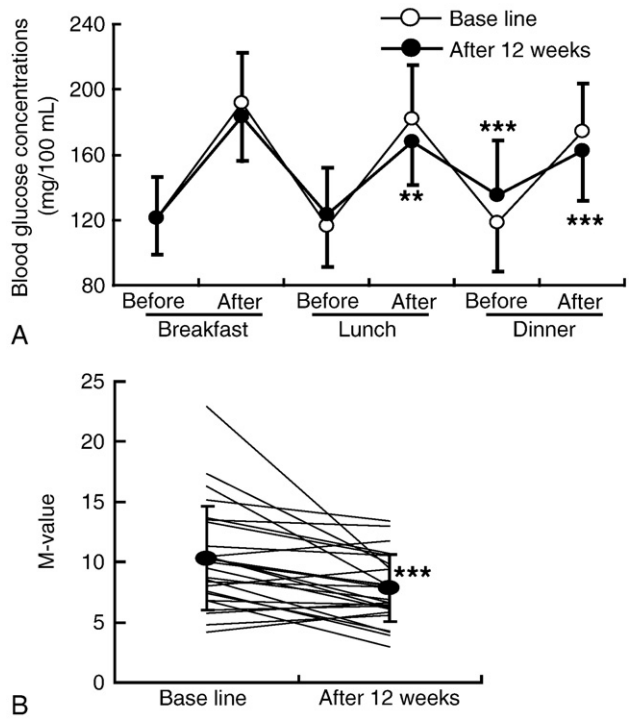


Fig. 1. Effects of switching from the highest approved doses of the α-glucosidase inhibitors acarbose or voglibose to a medium dose of miglitol in patients with type 2 diabetes mellitus on glucose fluctuations. A, Glucose concentrations determined by SMBG. B, M-values. Values are mean ± SEM. Asterisks denote significant differences (Student's *t* test) compared with the value before switching to miglitol (**$P < .01$, and ***$P < .001$).

## 4. Discussion

In this study of type 2 diabetes mellitus patients with $HbA_{1c}$ levels ranging from 6.5% to 7.9% and who were previously treated with the highest approved doses of α-glucosidase inhibitors (acarbose or voglibose) in combination with insulin or sulfonylureas, the α-glucosidase inhibitors were switched to a medium dose of miglitol without changes in insulin or sulfonylurea doses. As shown in Table 3, switching from acarbose or voglibose to miglitol for 3 months did not affect $HbA_{1c}$ or fasting glucose levels. These findings indicate that medium doses of miglitol have effects on long-term glycemic control similar to those of the highest doses of acarbose or voglibose. In addition, the incidence of adverse effects was not increased by this switch. Interestingly, glucose concentrations at 1 hour after lunch and dinner were significantly decreased, whereas that just before dinner was elevated, after switching to miglitol. In addition, the M-value, a marker of glucose fluctuations [28], was reduced by switching to miglitol (Fig. 1). The mean insulin dose did not differ between before (12.4 ± 5.1 U/d) and after (12.0 ± 4.6 U/d) the switch to miglitol, although 4 patients reduced their insulin dose after the switch. These findings suggest that replacing high doses of acarbose or voglibose with a medium dose of miglitol reduces postprandial hyperglycemia and inhibits the decreases in glucose concentrations between meals. Indeed, the incidence of hypoglycemia

Table 4
Relative mRNA levels in peripheral leukocytes and serum protein levels at baseline and at 3 months after switching to miglitol

| mRNA | Baseline | | 3 mo | | 3 mo/baseline | *P* value |
|---|---|---|---|---|---|---|
| | (n) | | (n) | | (%) | |
| IL-1$\beta$ | 42 | 0.477 ± 0.240 | 42 | 0.360 ± 0.215 | 75.4 | .00544$^{\dagger}$ |
| IL-2 | 41 | 0.00395 ± 0.00265 | 41 | 0.00356 ± 0.00194 | 90.7 | .49400 |
| IL-4 | 41 | 0.00102 ± 0.00770 | 41 | 0.00886 ± 0.00554 | 87.1 | .27800 |
| IL-10 | 40 | 0.00716 ± 0.00441 | 40 | 0.00662 ± 0.00422 | 92.4 | .45900 |
| IL-12A | 42 | 0.0135 ± 0.00774 | 42 | 0.0123 ± 0.00719 | 90.7 | .45800 |
| IL-18 | 42 | 0.108 ± 0.0370 | 42 | 0.102 ± 0.0416 | 93.9 | .38000 |
| IFN$\gamma$ | 42 | 0.0468 ± 0.0248 | 42 | 0.0391 ± 0.0177 | 83.4 | .06170 |
| TNF$\alpha$ | 42 | 0.186 ± 0.0717 | 42 | 0.141 ± 0.0458 | 76.2 | .00046$^{\ddagger}$ |
| S100a4 | 42 | 8.88 ± 3.64 | 42 | 7.41 ± 2.58 | 83.4 | .02330* |
| S100a6 | 42 | 12.26 ± 5.44 | 42 | 9.87 ± 4.04 | 80.4 | .01440* |
| S100a8 | 42 | 132 ± 71.1 | 42 | 110 ± 66.9 | 83 | .08090 |
| S100a9 | 42 | 9.64 ± 5.53 | 42 | 7.42 ± 4.98 | 77 | .03970* |
| S100a10 | 42 | 5.27 ± 2.21 | 42 | 4.29 ± 1.35 | 81.3 | .00405$^{\dagger}$ |
| S100a11 | 42 | 19.7 ± 9.75 | 42 | 14.7 ± 6.49 | 74.5 | .00377$^{\dagger}$ |
| S100a12 | 42 | 7.27 ± 4.35 | 42 | 5.55 ± 3.00 | 76.2 | .03110* |
| 18S rRNA | 42 | 1080 ± 478 | 42 | 1086 ± 498 | 101 | .95600 |
| TNF$\alpha$ protein (pg/mL) | 34 | 8.78 ± 2.74 | 34 | 7.95 ± 3.49 | 90.5 | .01915* |

Mean ± SD.
*$P < .05$, $^{\dagger}P < .01$, and $^{\ddagger}P < .001$ by 2-sided paired Student's *t* test.

symptoms was significantly reduced by switching to miglitol. Thus, miglitol suppressed glucose fluctuations more effectively than the other α-glucosidase inhibitors, with a lower incidence of hypoglycemia symptoms, consistent with the results obtained in animal models and in type 2 diabetes mellitus patients reported elsewhere [16,25].

Previous epidemiologic studies such as STOP-NIDDM and MeRIA7 revealed that inhibiting postprandial hyperglycemia with acarbose in patients with type 2 diabetes mellitus or impaired glucose tolerance is important in preventing the development and progression of type 2 diabetes mellitus and complications such as cardiovascular disease [9-13]. One mechanism involved in the progression of type 2 diabetes mellitus and its complications is the activation of leukocytes and the resultant induction of inflammatory cytokines in the diabetic state [9,18-20]. Indeed, insulin resistance and hyperglycemia in type 2 diabetes mellitus patients are associated with elevated levels of circulating inflammatory cytokines such as TNFα, IL-6, IL-12, and IL-18 [30-32], as well as putative inflammatory cytokine-like factor S100 proteins such as S100a8, S100a9, and S100a12 [23,33,34]. Our recent studies have shown that hyperglycemia in animal models induced the gene expression of inflammatory cytokines such as IL-1$\beta$ and TNFα and of S100 proteins such as S100a4/a6/a8/a9 in peripheral leukocytes. Furthermore, the induction of these genes was suppressed by reducing glucose fluctuations with miglitol [26,27]. Interestingly, in the present study, we found that the gene expression of IL-1$\beta$, TNFα, and S100 proteins such as S100a4/a6/a9/a10/a11/a12 in peripheral leukocytes was reduced by switching from high doses of acarbose or voglibose to a medium dose of miglitol. In addition, the serum TNFα protein levels were significantly reduced by the switch (Table 4). This indicates that the decrease in TNFα mRNA levels in peripheral leukocytes induced by switching to miglitol was reflected by changes in serum TNFα protein levels. Of note, the prescription of drugs other than α-glucosidase inhibitors was not changed during the trial period. Thus, any changes in inflammatory cytokine expression in the peripheral leukocytes and serum TNFα protein levels would be due to the switch from the highest doses of acarbose or voglibose to a medium dose of miglitol. Future studies should assess whether other drugs for type 2 diabetes mellitus, hyperlipidemia, or hypertension affect the expression of inflammatory cytokine genes in peripheral leukocytes. Overall, our findings indicate that switching from the highest doses of acarbose or voglibose to a medium dose of miglitol reduces glucose fluctuations, which may reduce the risk of complications such as cardiovascular disease, nephropathy, insulin resistance, and impaired $\beta$-cell function by inhibiting the induction of leukocyte infiltration and cytokines/cytokine-like factors [18-20,24]. Nevertheless, the associations between changes in gene expression of inflammatory cytokines/cytokine-like factors in peripheral leukocytes and type 2 diabetes mellitus-related complications require further investigation.

It should be noted that the serum IL-1$\beta$ protein levels were undetectable in most patients in this study (data not shown). However, it is known that IL-1$\beta$ is highly unstable and is rapidly degraded in serum. It has been reported that the concentration of IL-1$\beta$ was more detectable when it is stabilized by injecting healthy subjects or patients with cryopyrin-associated periodic syndromes with an antibody against IL-1$\beta$ [35]. Thus, further studies are needed to investigate whether stabilized IL-1$\beta$ in serum is affected by the switch to miglitol using a more sensitive method for determining the serum IL-1$\beta$ concentration. Despite this limitation, we suggest that the mRNA levels of cytokine/

cytokine-like factors in peripheral leukocytes, rather than the serum protein levels, are a more sensitive and convenient biomarker for assessing inflammation in type 2 diabetes mellitus and the effectiveness of treatments for type 2 diabetes mellitus. This is because the mRNA levels of IL-1$\beta$ and other genes are easily detectable and the magnitude of the reduction in TNF$\alpha$ mRNA levels in peripheral leukocytes by the switch was greater than that of serum TNF$\alpha$ and C-reactive protein levels. This is supported by an animal study that showed that the magnitude of the hyperglycemia-induced increase in these mRNAs in peripheral leukocytes was greater than that for circulating C-reactive protein [26].

Clearly, cohort and interventional studies are needed to prospectively investigate the association between the gene expression of cytokines/cytokine-like factors in peripheral leukocytes and the progression of type 2 diabetes mellitus and related complications in patients with type 2 diabetes mellitus. In addition, randomized, double-blind, placebo-controlled studies and cohort studies with defined end points related to type 2 diabetes mellitus complications are needed to compare the effects of miglitol with other $\alpha$-glucosidase inhibitors on the expression of inflammatory cytokines in peripheral leukocytes.

It should be noted that we did not record dietary data during the trial. Thus, future studies should assess whether switching from the highest approved doses of acarbose or voglibose to the medium dose of miglitol in type 2 diabetes mellitus patients affects food intake using self-administered diet history questionnaire or weighed dietary records.

In conclusion, the results of this study indicate that switching from voglibose or acarbose to miglitol for 3 months suppressed glucose fluctuations and the gene expression of inflammatory cytokines/cytokine-like factors in peripheral leukocytes more effectively than the prior $\alpha$-glucosidase inhibitor, with fewer adverse effects.

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