Original

Effect of Miglitol, an α-Glucosidase Inhibitor, on Postprandial Glucose and Lipid Metabolism in Patients with Type 2 Diabetes

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Abstract : Objective : The effects of miglitol on postprandial glucose and lipid metabolism were investigated in patients with type 2 diabetes mellitus (T2DM) treated with diet alone. Subjects and Methods : A meal tolerance test (MTT) was performed in 26 diabetic patients before and 2 weeks after 150 mg / day miglitol treatment, with the second MTT performed in patients after they had taken a dose of 50 mg miglitol. Results : Miglitol treatment decreased postprandial blood glucose and serum insulin levels 30 and 60 min after meal loading, but there was no change in blood glucose levels at 120 min. In addition, there were no significant decreases in the area under the curve (AUC) of blood glucose and serum insulin levels. However, the AUC of postprandial serum triglycerides and incremental triglycerides decreased significantly, as did the AUC of postprandial incremental remnant-like particle cholesterol. There were no significant changes in total cholesterol, high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol. Conclusions : Miglitol treatment improves postprandial hyperlipidemia, as well as postprandial hyperglycemia, in patients with T2DM. In T2DM patients treated with α-glucosidase inhibitors alone, measuring blood glucose levels 120 min after a meal may not be the best way to monitor postprandial glucose metabolism.

Key words : type 2 diabetes mellitus, postprandial dysmetabolism, miglitol

Introduction

Large prospective observational studies consistently show that 1 to 2-h post-glucose challenge levels are better predictors of the risk of coronary heart disease (CHD) than fasting glucose[1-3]. In Japan, the Funagata Diabetes study reported that impaired glucose tolerance (IGT), but not impaired fasting glucose (IFG), is a risk factor for cardiovascular disease[4]. Transient increases in blood glucose induce and accelerate endothelial dysfunction, oxidant stress[5], and hypercoagulability, and suppress nitric oxide (NO) production[6]. In addition, postprandial hypertriglyceridemia has been reported to independently increase the incidence

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Table 1. Baseline characteristics of the study subjects

	Diabetic subjects	Healthy volunteers
Number（male / female）	26（13 / 13）	6（5 / 1）
Age（years）	57.5 ± 3.6（29–74）	37.5 ± 8.0（26–49）
Body mass index（kg / m^2）	26.7 ± 1.3	21.9 ± 1.8
Glycosylated A1c（%）	6.89 ± 0.22	

（Mean±SD）

of myocardial infarction[7–11]. Postprandial hyperlipidemia is often associated with elevated plasma levels of the remnant lipoprotein fraction, the appearance of small, dense low-density lipoprotein（LDL）, and a decrease in high-density lipoprotein-cholesterol（HDL-C）. The postprandial state characterized by abnormally increased glucose and lipid levels has been referred to as "postprandial dysmetabolism"[12]. α-Glucosidase inhibitors have been reported to treat postprandial hyperglycemia and hypertension, as well as to suppress the incidence of cardiovascular events[13]. In a previous study we showed that acarbose, an α-glucosidase inhibitor, suppresses plasma levels of the remnant fraction in the fasting state[14]. Thus, the aim of the present study was to determine whether miglitol, one of the new α-glucosidase inhibitors[15, 16], can improve postprandial hyperglycemia and hyperlipidemia simultaneously in patients with type 2 diabetes mellitus（T2DM）treated by diet alone. To assess postprandial glucose and lipid metabolism simultaneously we used "Test meal A", which was designed by the Japan Diabetes Society Test Meal Development Working Group[17].

Methods

Study subjects

Twenty-six T2DM patients treated with diet alone and without a history of cardiovascular complications, hepatic disorders, thyroidal dysfunction, and renal failure were enrolled in the present study. None of the patients had taken any hypoglycemic or antihyperlipidemic agents, or had had insulin injections. All of the diabetic patients were Japanese and all were outpatients of Toho University Omori Medical Center and Makita General Hospital. In addition, six non-diabetic healthy volunteers were enrolled in the study. All subjects provided written informed consent prior to participating in the study. None of the subjects received any compensation for participating in the study. The baseline characteristics of the subjects are given in Table 1. The mean ± SD age of the T2DM patients and healthy volunteers was 57.5 ± 3.6（range 29–74）and 37.5 ± 8.0 years, respectively ; their mean ± SD body mass index was 26.7 ± 1.3 and 21.9 ± 1.8 kg / m^2, respectively ; and the mean ± SD glycosylated hemoglobin（HbA1c）of the T2DM patients was 6.89 ± 0.22%. Two diabetic patients had simple retinopathy, whereas microalbuminuria was detected in another two. None of the patients had any sensory disturbance.
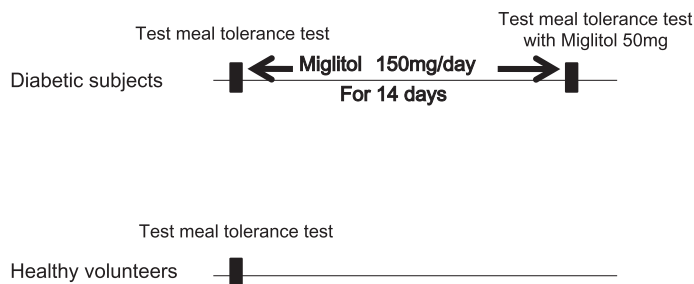
Fig. 1. Protocol for the meal tolerance test.

Methodology

The study protocol was approved by the Ethics Committee of the Toho University Omori Medical Center and Makita General Hospital. In the present study, we used "JANEFF48" (Kewpie, Tokyo, Japan) as the test meal, which is produced according to the menu of "Test meal A" designed by the Japanese Diabetes Society Test Meal Development Working Group[17]. The meal contains a soft pudding, cracker, and cream chicken stew, with 460 kcal total energy (carbohydrates 51.4%, lipids 33.3%, and proteins 5.3%). On the first day of the study, diabetic patients and healthy volunteers visited our hospital after 12 h fasting and underwent blood tests. They were then given the test meal with 100 mL water to consume in 15 min. They then underwent further blood testing at 30, 60, 90, 120, and 180 min after meal loading. Thereafter, only the diabetic patients were started on 50 mg miglitol (Sanwa Kagaku Kenkyusho, Tokyo, Japan), to be taken before each meal, three times a day, for 2 weeks. The second meal tolerance test was performed with only diabetic patients in the same manner, with taking 50 mg miglitol before consuming the test meal (Fig. 1).

Biochemical measurements

In the present study, HbA1c values (%) were estimated as Japan Diabetes Society [JDS] equivalent values (%) calculated using the formula HbA1c (%) = HbA1c (National Glyco-hemoglobin Standardization Program [NGSP]) (%) − 0.4 (%), based on previous determinations of the relationship between HbA1c (JDS) (%), as measured by Japanese standard substance and measurement methods, and HbA1c (NGSP)[18]. Blood glucose levels were measured using the glucose-oxidase method, whereas serum insulin levels were determined as the Chemiluminescent Immuno Assay (CLIA). Serum lipid levels were measured using an autoanalyzer and serum remnant-like particle cholesterol (RLP-C) levels were determined using an immunoaffinity column[19].

Statistical analysis

Data were checked for normal distribution. Data during the meal tests were analyzed by repeated-measures analysis of variance (ANOVA). Data were also analyzed using Steel's

multiple comparison test for multiple related samples. All analyses were performed using SPSS software package (IBM Corp.), and significance was set at 0.05. In case of correspondence, data were analyzed using Student's *t*-test and paired *t*-test. The area under the curve (AUC) was estimated by calculating the sum of the area between each sampling point. Comparisons of AUCs were made using paired *t*-tests.

Results

The most common adverse gastrointestinal tract events associated with α-glucosidase inhibitors are flatulence, diarrhea, and abdominal pain. In the present study, all diabetic patients tolerated miglitol well and no adverse events were observed.

Blood glucose levels of diabetic patients were significantly higher at every sampling point than those in healthy volunteers, with a peak at 60 min after the test meal in T2DM patients (Fig. 2a). Serum insulin peaked at 90 min after the test meal in diabetic patients, compared with a peak at 30 min in healthy volunteers (Fig. 2b).

After miglitol treatment, fasting blood glucose level did not change, but the peak in postprandial blood glucose levels shifted from 60 to 90 min, but did not change at all at 120 min. In addition, miglitol treatment significantly decreased postprandial blood glucose levels ($P < 0.01$, repeated-measures ANOVA ; Fig. 2a). Following miglitol treatment, postprandial blood glucose at 30 and 60 min decreased from 170.9 ± 5.4 to 142.7 ± 6.2 mg / dL and from 188.7 ± 7.2 to 170.2 ± 7.5 mg / dL, respectively ($P < 0.001$ and $P < 0.05$, paired *t*-test, respectively). There was a tendency for the AUC of blood glucose (0–3 h) to decrease from 475.2 ± 17.1 to 444.3 ± 14.9 mg·h / dL after miglitol treatment, but the difference failed to reach statistical significance. In contrast, there was a significant decrease in the AUC of incremental blood glucose (0–3 h) from 114.3 ± 26.9 to 80.4 ± 23.3 mg·h / dL after miglitol treatment ($P < 0.05$, paired *t*-test ; Table 2).

Miglitol treatment of diabetic patients significantly decreased postprandial serum insulin levels ($P < 0.01$, repeated-measures ANOVA ; Fig. 2b). Specifically, significant decreases were seen after miglitol treatment in serum insulin levels at 30 min (from 26.4 ± 5.0 to 16.6 ± 2.8 μU / mL ; $P < 0.001$, paired *t*-test), 60 min (from 36.0 ± 6.7 to 21.6 ± 2.8 μU / mL ; $P < 0.05$, paired *t*-test), and at 90 min after the test meal (from 37.0 ± 6.6 to 24.9 ± 2.5 μU / mL ; $P < 0.05$, paired *t*-test). Although there was a tendency for the AUC of serum insulin (0–3 h) to decrease after miglitol treatment (from 87.3 ± 14.7 to 64.9 ± 8.2 U·h / dL), the difference failed to reach statistical significance. However, miglitol treatment significantly decreased the AUC of incremental serum insulin (0–3 h) from 70.0 ± 18.8 to 44.3 ± 12.4 U·h / dL ($P < 0.05$, paired *t*-test ; Table 2). Miglitol treatment also decreased the homeostasis model assessment for insulin resistance (HOMA-R) from 2.56 ± 3.02 to 2.24 ± 1.88 ($P = 0.0756$).

After miglitol treatment, there was a tendency for postprandial serum triglyceride and incremental triglyceride to decrease, but the differences were not significant ($P > 0.05$,

a. Blood Glucose

(mg/dl)

b. Serum insulin

(μU/ml)

c. Serum Triglyceride

(mg/dl)

d. Incremental triglyceride

(mg/dl)

e. Serum RLP-cholesterol

(mg/dl)
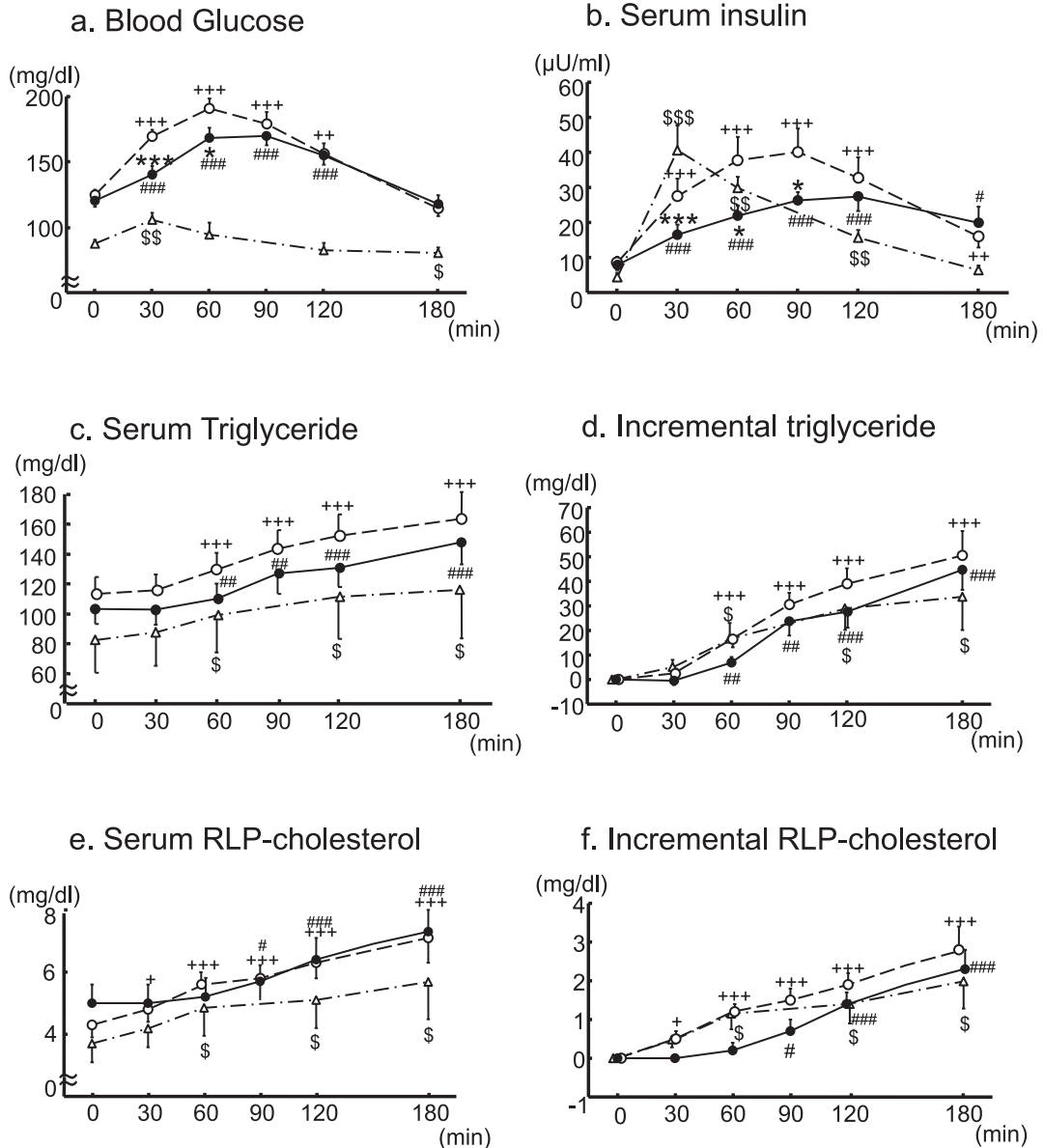
f. Incremental RLP-cholesterol

(mg/dl)

Fig. 2. (a) Blood glucose, (b) serum insulin, (c) serum triglyceride, (d) incremental triglyceride, (e) serum remnant-like particle cholesterol (RLP-C), and (f) incremental RLP-C levels in diabetic patients and healthy volunteers during the meal tolerance test. Open and closed circles represent values obtained from diabetic patients (n = 26) before and after miglitol treatment, respectively. Open triangles represent values obtained from healthy volunteers (n = 6). Data are expressed as the mean ± SD. Statistical significance was analyzed by repeated-measures ANOVA, and Student's t-test and paired t-test in case of correspondence. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ compared with before miglitol treatment; $^{†}P < 0.05$, $^{††}P < 0.01$, $^{†††}P < 0.001$ compared with the 0 min time point before miglitol treatment; $^{‡}P < 0.05$, $^{‡‡}P < 0.01$, $^{‡‡‡}P < 0.001$ compared with the 0 min time point after miglitol treatment; $^{§}P < 0.05$, $^{§§}P < 0.01$, $^{§§§}P < 0.001$ compared with the 0 min time point in healthy volunteers.

Table 2. The area under the curve（AUC 0–3hr）of study parameters in healthy volunteers, and diabetic subjects before and after miglitol treatment.

| | AUC 0–3hr | | | |
| | Healthy subjects（6） | Diabetic subjects（26） | | |
		before treatment	2 weeks after Miglitol treatment	p value
Blood Glucose（mg·hr / dl）	268.0 ± 16.6	475.2 ± 17.1	444.3 ± 14.9	0.0501
Incremental Blood Glucose（mg·hr / dl）	33.0 ± 13.5	114.3 ± 26.9	80.4 ± 23.3	0.0226
Serum Insulin（μU·hr / dl）	62.6 ± 7.0	87.3 ± 14.7	64.9 ± 8.2	0.0504
Incremental Serum Insulin（μU·hr / dl）	49.36 ± 7.4	70.0 ± 18.8	44.3 ± 12.4	0.0164
Triglyceride（mg·hr / dl）	308.4 ± 79.7	418.4 ± 39.0	367.5 ± 33.9	0.0359
Incremental triglyceride（mg·hr / dl）	60.9 ± 21.0	79.2 ± 12.8	58.1 ± 10.0	0.0489
RLP-cholesterol（mg·hr / dl）	14.6 ± 2.6	17.4 ± 1.4	17.7 ± 1.9	0.8468
Incremental RLP-cholesterol（mg·hr / dl）	3.5 ± 1.2	4.4 ± 0.8	2.6 ± 0.6	0.0050

All data are expressed as the mean ± SD. The number in parenthesis indicates the subject number. Significant differences between before and after treatment in diabetic subjects are indicated by p values（paired *t*-test was employed）.

repeated-measures ANOVA ; Fig. 2c, d）. However, miglitol treatment produced significant decreases in the AUC（0–3 h）of serum triglyceride from 418.4 ± 39.0 to 367.5 ± 33.9 mg·h / dL（$P < 0.05$, paired *t*-test ; Table 2）and incremental triglyceride from 79.2 ± 12.8 to 58.1 ± 10.0 mg·h / dL（$P < 0.05$, paired *t*-test ; Table 2）.

Serum RLP-C and incremental RLP-C levels increased gradually after test meal loading in diabetic patients（repeated-measures ANOVA ; Fig. 2e, f）. Miglitol treatment significantly decreased the AUC of incremental serum RLP-C（0–3 h）from 4.4 ± 0.8 to 2.6 ± 0.6 mg·h / dL（$P = 0.005$, paired *t*-test ; Table 2）. Miglitol treatment had no effect on postprandial levels of total cholesterol, HDL-C, and LDL-C.

Discussion

To assess postprandial glucose and lipid metabolism simultaneously, we used the "JANEF F48" meal（Kewpie）, which was produced according to the formula of "Test Meal A". To characterize glucose and lipid excursions after test meal loading in diabetic patients, we also performed test meal loading in non-diabetic healthy subjects. Blood glucose levels of diabetic patients at every sampling point were significantly higher than those in the healthy volunteers, with the peak shifted from 30 to 60 min. The serum insulin peak was shifted in diabetic patients from 30 to 90 min. Thus, this test meal loading is suitable for the investigation of blood glucose and insulin responses in patients with mild diabetes.

In diabetic patients, possibly because of a suppressed blood glucose response caused by miglitol, postprandial serum insulin levels decreased significantly（Fig. 2b）. Thus, miglitol treatment may have favorable effects in diabetic patients from the viewpoint of insulin resistance. In support of this, average HOMA-R decreased to below 2.5, which is the lower

limit for the presence of insulin resistance according to the recommendations of the Japanese Diabetes Society[20].

Miglitol treatment shifted the peak of postprandial blood glucose levels from 60 to 90 min in diabetic patients (Fig. 2a). However, as indicated in Table 2, miglitol did not decrease the AUC of blood glucose (0–3 h). It has been suggested that the effect of miglitol is only to delay carbohydrate absorption[21]. Most of the carbohydrates in the small intestine may be digested within 3 h, despite miglitol treatment.

In diabetic patients, the peak of postprandial glucose shifted from 60 to 90 min after meal, whereas levels at 120 min did not change at all after miglitol treatment (Fig. 2a). The International Diabetes Federation (IDF) Guidelines for the Management of Postmeal Glucose[22] recommend monitoring 2-h postprandial glucose levels for the prevention of cardiovascular events. However, it may be inappropriate to monitor 2-h glucose levels during treatment with α-glucosidase inhibitors alone because of a shift in the timing of the blood glucose peak. On the basis of the results of the present study, we recommend monitoring 1-h postprandial glucose levels during treatment with α-glucosidase inhibitors.

Although it is known that 2-h postprandial hyperglycemia is related to chronic complications of diabetes and is currently used in international guidelines to drive therapy[22], Esposito *et al* have reported that incremental glucose peaks (IGP) in the everyday life of patients with T2DM occur for most patients (95%) within 1 h after a meal[23]. Furthermore, they suggested that there is a good correlation between IGP and carotid intima-media thickness, and that the timing of the IGP is not influenced by treatment (diet or drugs). These findings support our proposal to monitor 1-h post-meal glucose levels.

After miglitol treatment, the AUC of serum triglycerides decreased significantly in diabetic subjects (Table 2). It is possible that slowing of monosaccharide absorption by miglitol may result in the suppression of triglyceride production in the small intestine. In diabetic patients, serum RLP-C levels after test meal loading did not change with miglitol treatment (Fig. 2d). However, if we estimate the incremental RLP-C from Time 0, the RLP-C increment was suppressed at 30, 60, 90, and 120 min following treatment (Fig. 2f). It is of interest that miglitol suppressed the post-meal RLP-C levels in diabetic patients. Because a single dose of acarbose, another α-glucosidase inhibitor, cannot suppress postprandial triglyceride levels in diabetic patients[24] and insulin-resistant states are known to induce overproduction of chylomicron from the small intestine[25], it is speculated that improvement of the insulin resistant state following 2 weeks treatment with miglitol may result in suppression of post-meal increases in RLP-C levels.

The postprandial state characterized by abnormally increased levels of glucose and lipids (also referred to as postprandial dysmetabolism) is now proposed to be an independent predictor of future cardiovascular events[12]. Yokoyama *et al* reported that miglitol treatment increased adiponectin levels and decreased the urinary albumin excretion rate in T2DM patients[26]. Suppression of the postprandial glucose spike may protect diabetic patients

against the development of early stage renal damage and may also increase adiponectin secretion from adipocytes. These possibilities warrant further investigation.

Large swings in glucose concentrations in the culture medium of human umbilical vein cells have been reported to stimulate cell apoptosis[27]. Furthermore, Mita *et al* reported that the area of the arteriosclerotic lesion in ApoE-deficient mice decreased after miglitol treatment[28]. It is possible that in ApoE-deficient mice miglitol treatment minimized the glucose swing, thereby decreasing the area of arteriosclerotic lesions.

In conclusion, miglitol treatment improved not only postprandial glucose, but also triglyceride and remnant lipoprotein metabolism in T2DM patients who were not able to optimize glucose control by diet alone. The findings of the present study suggest that miglitol may have a beneficial effect in preventing atherogenesis in T2DM by improving postprandial dysmetabolism. Furthermore, it is of noteworthy that monitoring 2-h post-meal glucose levels is not suitable in diabetic patients being treated with α-glucosidase inhibitors alone. In these patients, it is recommended that 1-h post-meal glucose levels are monitored instead of 2-h levels.

Disclosure

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