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Miglitol increases the adiponectin level and decreases urinary albumin excretion in patients with type 2 diabetes mellitus

Hiroki Yokoyama[a,*], Sakiko Kannno[a], Ikue Ishimura[a], Koichi Node[b]

[a]*Jiyugaoka Medical Clinic, Internal Medicine, Obihiro 080-0848, Japan*
[b]*Department of Cardiovascular and renal medicine, Saga university faculty of medicine*

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Abstract

Postprandial hyperglycemia is associated with increased cardiovascular mortality; therefore, lowering postprandial hyperglycemia seems crucial in type 2 diabetes mellitus. We assessed the effect of 2 different postprandial glucose-lowering agents, the α-glucosidase inhibitor miglitol and the meglitinide analogue mitiglinide, on metabolic profile and atherosclerosis-related markers. Glucose levels, insulin levels, lipid profile, serum adiponectin, pulse wave velocity (PWV), and urinary albumin excretion rate (AER) were assessed before and after 3 months in 28 patients with type 2 diabetes mellitus randomly allocated to either miglitol 150 mg/d or mitiglinide 30 mg/d. Both agents improved postprandial glucose levels but exhibited different patterns of insulin levels. Body mass index (BMI) tended to decrease with miglitol ($P = .06$), and homeostasis model assessment of insulin resistance and AER significantly decreased ($P < .05$ and $P < .001$, respectively) with miglitol; these changes were not obtained with mitiglinide. Pulse wave velocity did not change. The 3-month changes in 1,5-anhydroglucitol levels were significantly more with miglitol than with mitiglinide ($P = .007$). Adiponectin levels were significantly increased only with miglitol ($P < .01$), and the 3-month changes were significantly more with miglitol than with mitiglinide ($P = .048$). The significant increase in adiponectin by miglitol was inversely correlated with the ratio of the 60-minute change in blood glucose at 3 months divided by the change at baseline ($r = -0.59$, $P = .020$), which was independent of the effect of age, sex, changes in hemoglobin A_{1c} and BMI, and the baseline concentration of adiponectin. The present comparative study indicated favorable effects of miglitol on BMI, homeostasis model assessment of insulin resistance, adiponectin, and AER, which are markers related to insulin resistance and atherosclerosis. Future studies are needed to elucidate the long-term effect.

1. Introduction

Epidemiological or other large-scale studies have shown that postchallenge hyperglycemia is associated with increased cardiovascular mortality in type 2 diabetes mellitus [1-3]. Postprandial hyperglycemia is a prominent and early defect in type 2 diabetes mellitus. Postprandial hyperglycemia and/or concomitant hypertriglyceridemia may induce endothelial dysfunction and inflammation and play an important role in the progression of unstable plaque and atherosclerotic disease [4]. However, the mechanism is presently unknown. Reduction in adiponectin seems to be closely associated with insulin resistance and obesity as compared with other adipokines [5]; and moreover, it plays a protective role in the vascular inflammation and development of atherosclerosis [6]. It can be hypothesized that postprandial hyperglycemia might affect adiponectin because lifestyle changes have been reported to affect adiponectin levels [5,7,8], but this remains at present hypothetical.

The importance of postprandial hyperglycemia has attracted considerable attention for the possibility of developing antidiabetic treatments designed to limit postprandial glucose excursions. Two different antidiabetic agents that lower postprandial blood glucose excursions have been available. One is an α-glucosidase inhibitor, which reduces or delays carbohydrate digestion by competitive enzyme inhibition at the ciliated border of the small intestine [9]. The other is a meglitinide analogue, which is a rapid-onset and rapidly reversible insulinotropic agent that restores early postprandial insulin secretion in a glucose-dependent manner [10]. Miglitol [9,11] and mitiglinide

* Corresponding author. Tel.: +81 155 58 5855; fax: +81 155 58 5856.
E-mail address: hiroki@m2.octv.ne.jp (H. Yokoyama).

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[10,12] are now the most newly available agents of α-glucosidase inhibitor and meglitinide analogue, respectively. The aim of this study was to investigate prospectively the short-term effect of the 2 different agents, miglitol and mitiglinide, on the metabolic profile and whether this effect leads to differences in atherosclerosis-related markers. Adiponectin seems to be protective against atherogenesis [6]. Slightly increased urinary albumin excretion rate (AER) seems to be a marker of cardiovascular disease not only in diabetic subjects but also in the general population [13,14]. Aortic pulse wave velocity (PWV), which reflects arterial stiffness, is a marker of both the severity of vascular damage and the prognosis of atherosclerotic vascular disease in patients with hypertension and diabetes [15,16] and in the general population [17]. We assessed adiponectin, AER, and PWV as atherosclerosis-related markers. If the different metabolic profile were associated with differences in these markers, this would provide a clue to preventing the atherosclerotic disease process at an early stage.

2. Research design and methods

Patients with type 2 diabetes mellitus were recruited from the outpatient clinic of Jiyugaoka Internal Medicine. Type 2 diabetes mellitus was diagnosed according to the Japan Diabetes Society criteria. Inclusion criteria included age older than 35 years, never treated with antidiabetic agents, treated by diet and exercise for more than 3 months but still having a glycosylated hemoglobin A_{1C} level (A1c) between 6.0% and 9.0%. Subjects with impaired hepatic, renal, or cardiac function were excluded. A total of 30 patients participated in the study and were randomly assigned to either miglitol, at a standard dose of 50 mg, or mitiglinide, at a standard dose of 10 mg, before each meal. The study was carried out in accordance with the Helsinki Declaration II and approved by the ethical committee, with written informed consent given by all participants.

At baseline and 3 months, meal tolerance test was performed after an overnight fast (more than 12 hours). Each test was performed without the medication at baseline and with the medication at 3 months. The same prespecified breakfast was prepared, containing 63.8 g carbohydrate, 24.6 g protein, 11.0 g fat, 1.2 g sodium, and a total of 466 calories. Blood samples were drawn before and after 30, 60, and 120 minutes. During the follow-up, 2 patients discontinued visits, leaving a total of 28 subjects. Six and 3 patients had been treated with antihypertensive and antihyperlipidemic agents, respectively, which were not changed during the study. The plasma glucose concentration was measured by the glucose oxidase method. The A1c was measured by high-performance liquid chromatography (ADAMS A_{1C} HA8160; Arkray, Kyoto, Japan; reference range, 4.3%-5.8%). This method was standardized by the Japan Diabetes Society and was calibrated every 2 weeks using GlycoHB (Kokusai Shiyaku, Kobe, Japan) as a control. Serum concentrations of 1,5-anhydroglucitol (AG) was measured by enzymatic method (Determina-L 1.5 AG; Kyowa Medics, Japan; normal >14.0 μg/mL). 1,5-Anhydroglucitol is a more sensitive indicator of glucose excursions than A1c and is useful in conjunction with A1c to assess glycemic control in patients with moderate or good control [18]. Adiponectin was measured by enzyme-linked immunosorbent assay (human adiponectin enzyme-linked immunosorbent assay kit; Otsuka, Tokyo, Japan). Serum insulin was measured by immunoradiometric assay (Insulin RIA BEADS II; Yamasa Shoyu, Tokyo, Japan). The urinary albumin concentration was determined by turbidimetric immunoassay with the use of a Superior-Microalbumin kit (DPC, Tokyo, Japan) and was corrected for urinary creatinine concentration, which was measured by the enzymatic reaction. The interassay variation coefficients were 5% to 8% for all assays.

Brachial-ankle PWV was measured using a volume-plethynographic apparatus (form PWV/ABI version-112; Colin, Komaki, Japan). This instrument records PWV, ankle brachial index, blood pressure, electrocardiogram, and heart sounds simultaneously and automatically. Details of the method have been described elsewhere [16]. The normal values of PWV (in centimeters per second) in healthy subjects were 1376 ± 373 (mean ± SD) in men and 1352 ± 222 in women (n = 598; aged 45 to 75 years; mean age, 61 ± 6; 376 men, 222 women) [16].

2.1. Statistical analysis

Results are given as the mean ± SD unless otherwise stated. Differences between relevant groups were tested by means of unpaired Student *t* test for continuous variables and the χ^2 test for discrete variables. The influences of various variables on changes in adiponectin were explored by simple (Pearson coefficient correlations) and multiple (with conditional backward selection) linear regression analysis. Two-tailed unpaired Student *t* test or 1-way factorial analysis of variance (ANOVA), followed by Bonferroni post hoc intragroup comparisons, was used to compare intergroup or intragroup means. Comparisons of time curves during meal tolerance test were analyzed by 2-factor repeated-measures ANOVA, followed by Bonferroni post hoc intragroup comparisons. The distributions of AER, triglyceride, and adiponectin were normalized by logarithmic transformation before statistical analysis. *P* values of less than 5% (2-tailed) were considered to be significant.

3. Results

Overall, the mean age was 58 years; sex distribution, 82:18 (male-female); body mass index (BMI), 25.7; mean duration of diabetes, 3 years; A1c, 7.4%; and systemic blood pressure, 123/71 mm Hg. As shown in Table 1, all variables at baseline were quite similar between the groups except for a slightly higher triglyceride level in the miglitol group. After 3 months, glycemic control was improved more with

Table 1
Clinical variables at baseline and the changes after miglitol or mitiglinide treatment in patients with type 2 diabetes mellitus

	Miglitol	Mitiglinide	*P*
Male-female	13:2	10:3	.860
Age (y)	57 ± 9	60 ± 10	.537
Duration of diabetes (y)	4 ± 4	3 ± 3	.902
BMI			
Baseline	25.7 ± 3.1	25.6 ± 2.9	.898
Change from baseline	−0.58 ± 1.24	0.28 ± 1.08	.064
Systolic blood pressure (mm Hg)			
Baseline	125 ± 7	120 ± 17	.366
Change from baseline	−2 ± 11	1 ± 12	.576
Diastolic blood pressure (mm Hg)			
Baseline	72 ± 6	70 ± 10	.513
Change from baseline	−2 ± 7	2 ± 3	.112
A1c %			
Baseline	7.4 ± 0.8	7.4 ± 0.6	.988
Change from baseline	−0.9 ± 0.7 **	−0.5 ± 0.8 ****	.170
1,5-AG (μg/mL)			
Baseline	5.04 ± 4.88	4.93 ± 1.54	.939
Change from baseline	7.64 ± 5.36 *	2.90 ± 2.59 ***	.007
Fasting TG (mg/dL) [a]			
Baseline	197 (116 to 306)	127 (97 to 159)	.049
Change from baseline	−51 (−90 to −51)	−17 (−37 to 22)	.471
2-h postprandial TG (mg/dL) [a]			
Baseline	211 (130 to 289)	167 (120 to 194)	.112
Change from baseline	−12 (−107 to 13)	−25 (−42 to 18)	.650
TC (mg/dL)			
Baseline	221 ± 64	197 ± 31	.228
Change from baseline	−12 ± 34	−8 ± 29	.768
HDL (mg/dL)			
Baseline	49 ± 8	52 ± 9	.340
Change from baseline	0 ± 8	1 ± 9	.721
Adiponectin (μg/mL) [a]			
Baseline	4.20 (3.64 to 4.70)	5.42 (4.27 to 6.60)	.087
Change from baseline	0.83 (0.26 to 0.94) ***	0.13 (−0.48 to 1.01)	.048
AER (mg/g Cr) [a]			
Baseline	18.7 (12.1 to 28.1)	6.6 (6.5 to 52.2)	.432
Change from baseline	−4.75 (−6.8 to −1.5) **	−0.60 (−5.25 to 0.63)	.165
PWV (cm/s)			
Baseline	1602 ± 235	1608 ± 372	.956
Change from baseline	−19 ± 193	−18 ± 204	.989
HOMA-IR			
Baseline	4.82 ± 4.45	4.26 ± 2.78	.697
Change from baseline	−2.12 ± 3.88 ****	−0.15 ± 2.72	.069
Meal tolerance at baseline			
Plasma glucose (mg/dL)			
0 min	174 ± 37	172 ± 35	.870
30-min change from 0 min	69 ± 23	71 ± 19	.781
60-min change from 0 min	99 ± 32	107 ± 27	.442
120-min change from 0 min	65 ± 58	78 ± 32	.491
$AUC_{0\text{-}120min}$ (mg·h/dL)	489 ± 81	498 ± 80	.758
Serum insulin (μmol/mL)			
0 min	10.4 ± 7.5	10.0 ± 6.4	.893
30-min change from 0 min	12.9 ± 16.1	15.0 ± 6.6	.668
60-min change from 0 min	26.6 ± 25.0	34.3 ± 21.3	.390
120-min change from 0 min	32.4 ± 39.7	40.3 ± 33.9	.576
$AUC_{0\text{-}120min}$ (μmol·h/mL)	63.4 ± 46.1	73.5 ± 46.1	.568
Meal tolerance after 3 mo			
Plasma glucose (mg/dL)			
0 min	145 ± 18 ***	158 ± 28 ****	.164
30-min change from 0 min	22 ± 14 *	59 ± 27 ****	.000
60-min change from 0 min	50 ± 27 *	62 ± 31 **	.283
120-min change from 0 min	66 ± 34	28 ± 24 *	.002
$AUC_{0\text{-}120min}$ (mg·h/dL)	372 ± 59 *	406 ± 64 **	.160
Serum insulin (μmol/mL)			
0 min	7.5 ± 4.2	10.3 ± 9.0	.300
30-min change from 0 min	4.1 ± 6.3 ****	45.2 ± 28.2 **	.000
60-min change from 0 min	11.3 ± 9.7 ****	53.2 ± 34.3 ***	.000
120-min change from 0 min	25.7 ± 21.2	39.9 ± 44.0	.277
$AUC_{0\text{-}120min}$ (μmol·h/mL)	38.4 ± 23.2 ***	103.0 ± 72.3 ***	.003

Meal tolerance test was performed at baseline and 3 months after each treatment, and the changes in plasma glucose and serum insulin during the test are shown. TG indicates triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; Cr, creatinine.

[a] Median and interquartile range are given.

* $P < .0001$ from baseline.

** $P < .001$ from baseline.

*** $P < .01$ from baseline.

**** $P < .05$ from baseline.

miglitol than with mitiglinide in terms of changes in 1,5-AG. Changes in serum concentration of the lipid profiles were not different between the groups. Serum concentration of adiponectin at 3 months was increased significantly only with miglitol ($P = .001$), and the change between the groups was significantly different ($P = .048$) even after correction for body weight ($P = .017$). The AER and homeostasis model assessment of insulin resistance (HOMA-IR) were significantly decreased after miglitol treatment ($P < .001$ and $P < .05$, respectively), which was not obtained by mitiglinide. The BMI tended to decrease with miglitol ($P = .06$), but the changes between the groups were not different. In terms of adverse events, flatulence/diarrhea was observed in 7/5 patients with miglitol and in 0/1 patient with mitiglinide, where the symptoms were transient and acceptable without the need to discontinue the agent.

During meal tolerance test at baseline, changes in plasma glucose and insulin were similar between the groups (Table 1, Fig. 1). After 3 months, plasma glucose was decreased significantly more with miglitol than with mitiglinide at 30 minutes ($P < .0001$) and vice versa at 120 minutes ($P = .002$). The serum concentration of insulin was significantly decreased at 60 minutes after miglitol treatment ($P < .05$), whereas it was significantly increased at 30 and 60 minutes after mitiglinide treatment ($P < .01$); therefore, it was markedly different at 30 and 60 minutes between the groups ($P < .001$). Intergroup comparison revealed that, after 3 months, the curve differences between miglitol and mitiglinide by 2-way repeated-measures ANOVA were significant for glucose and insulin levels ($P < .0001$, respectively).

The increase in adiponectin observed with miglitol was significant if corrected for body weight ($P = .002$) and had no univariate correlations with changes in A1c, 1,5-AG, insulin

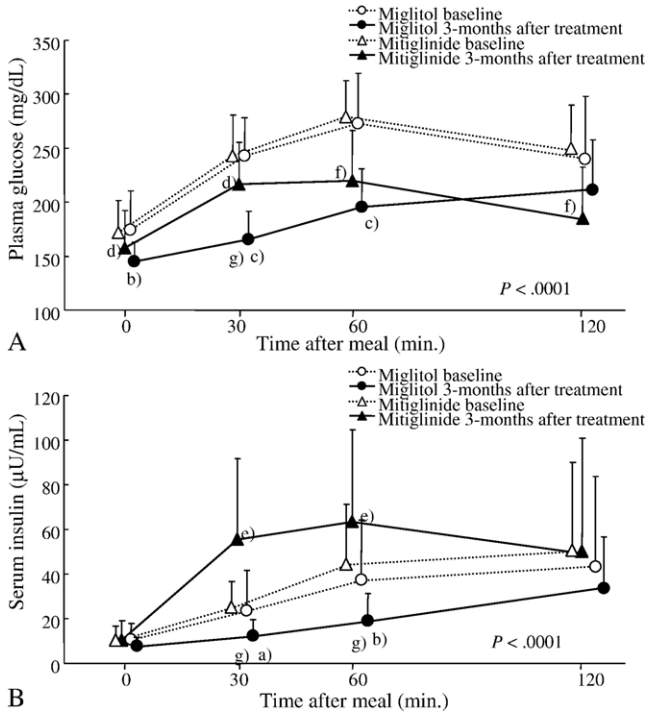

Fig. 1. Plasma glucose levels (A) and serum insulin levels (B) during meal tolerance test at baseline and 3 months after miglitol or mitiglinide treatment in patients with type 2 diabetes mellitus. Data are expressed as mean ± SD. The *P* values for curve difference by 2-factor repeated-measures ANOVA, followed by Bonferroni post hoc intragroup comparisons, are shown. $^{a}P < .05$, $^{b}P < .01$, $^{c}P < .001$ vs miglitol baseline. $^{d}P < .05$, $^{e}P < .01$, $^{f}P < .001$ vs mitiglinide baseline. $^{g}P < .001$ miglitol vs mitiglinide.

levels, and BMI. Interestingly, it was most significantly correlated with the ratio of the 60-minute change in blood glucose at 3 months divided by the change at baseline ($R = -0.59$, $P = .02$), whereas the ratio of 30 and 120 minutes showed less correlations (Table 2). It was significantly correlated with HOMA-IR at 3 months ($R = -0.54$, $P = .04$), but not significantly with the area under the curve (AUC) of plasma glucose or insulin during meal tolerance test at 3 months. The association of the ratio of the 60-minute change in blood glucose with the increase in adiponectin remained significant after adjustment for age, sex, changes in A1c and BMI, and the baseline concentration of adiponectin. Multiple linear regression analysis including these factors, the ratio of 60-minute change, and treatment differences in all patients indicated that only miglitol treatment remained as a determinant of the increase in adiponectin (standardized correlation coefficient, 0.352; $P = .06$).

4. Discussion

This head-to-head prospective comparative study between miglitol and mitiglinide treatment for 3 months revealed different patterns of insulin levels during the meal tolerance test. This is expected because miglitol slows carbohydrate digestion and inhibits the increase in postprandial glucose, whereas mitiglinide stimulates postprandial insulin secretion. Both improved blood glucose control; and miglitol was more potent than mitiglinide in terms of 1,5-AG, whereas no treatment difference was seen in A1c. Although the study only observed the short-term effect in 28 subjects with type 2 diabetes mellitus, insulin resistance indexes such as BMI and HOMA-IR decreased with miglitol as compared with mitiglinide with borderline treatment differences ($P = .06$); and 3-month changes in 1,5-AG and adiponectin levels were significantly different. Only miglitol treatment decreased AER and HOMA-IR significantly, although treatment differences were not found.

Why was an increase in adiponectin found with miglitol and not mitiglinide? Several factors seem to be associated. One is BMI, which tended to decrease with miglitol and increase with mitiglinide. The decrease in BMI with miglitol is consistent with previous studies [9,19] and could provide an advantage over sulfonylurea [19,20]. This is to our knowledge the first to report the favorable effect of α-glucosidase inhibitors on adiponectin, although an adverse effect of weight gain by glibenclamide on increasing leptin concentrations has been reported in comparison with acarbose [20]. The increase in BMI with mitiglinide is consistent with findings on the meglitinides [21]. Body mass index significantly correlates with adiponectin [8]. Three studies have indicated an association of modest weight loss with an enhancement of adiponectin in nondiabetic obese subjects; increases of adiponectin (in micrograms per milliliter) with concomitant BMI reduction were found to be +2.7 with a reduction of −5.2 (+0.52 per BMI) [8], +0.8 with a reduction of −2.6 (+0.31 per BMI) [7], and +2.1 with a reduction of −8.4 (+0.25 per BMI) [22]. The corresponding data of +0.83 with a reduction of −0.58 (+1.43 per BMI) in the present study were striking and might not be adequately accounted for by only the weight reduction. Actually, the increase in adiponectin was independent of body weight change in our study, although the short observation period should be acknowledged. Secondly, inhibition of the postprandial glucose increase from 30 to 60 minutes seemed to be associated with an adiponectin increase. This

Table 2
Possible variables that could enhance adiponectin levels observed in miglitol group

	R	*P*
Ratio of 30-min change in blood glucose at 3 mo divided by the change at baseline	−0.52	.06
Ratio of 60-min change in blood glucose at 3 mo divided by the change at baseline	−0.59	.02
Ratio of 120-min change in blood glucose at 3 mo divided by the change at baseline	−0.41	.13
AUC of plasma glucose during meal tolerance test at 3 mo	−0.25	.39
AUC of serum insulin during meal tolerance test at 3 mo	−0.49	.07
HOMA-IR at 3 mo	−0.54	.04

Correlation coefficients with change in adiponectin levels are shown.

association was weak when analyzed at 120 minutes. During the 30- to 60-minute period, not only plasma glucose but also the insulin levels were different between the two. The lower plasma glucose with lower insulin levels seen in miglitol treatment, which can be translated into improved insulin resistance, may be associated with an increase in adiponectin. Actually, we found that increase in adiponectin was significantly correlated with HOMA-IR. Inhibition of postprandial insulin secretion together with inhibition of postprandial plasma glucose excursions may have a beneficial effect on reduction in visceral fat or decrease in adipocyte size, an important organ to produce adiponectin [23]. Adiponectin is considered to be a marker of chronic insulin resistance in type 2 diabetes mellitus [5], and decreased adiponectin could play a causative role in the development of insulin resistance [24]. It can be suggested that inhibition of postprandial hyperglycemia within 60 minutes rather than 120 minutes might be more important as a target. Taken together, because an elevated circulating level of adiponectin is expected to have potential as a novel therapeutic tool for its antidiabetic and antiatherogenic effects [23], the above findings could be important for future studies that examine this possibility.

The reduction in AER was not explained by the treatment difference. However, the reduction in AER had a weak correlation with a reduction in systolic blood pressure (r = 0.35, P = .08) and in diastolic blood pressure (r = 0.36, P = .06) and a significant correlation with a reduction in PWV (r = 0.55, P = .002) when analyzed in all patients (data not shown). Although there were no changes of antihypertensive agents and no correlation between reductions in blood glucose and blood pressure, decreases in postprandial glucose might contribute to a reduction in blood pressure and arterial stiffening. Because association of microalbuminuria with insulin resistance has been suggested [25], improvement of insulin resistance by miglitol also might account for the reduction in AER. Finally, we should acknowledge the lack of placebo group, although both groups at baseline had no antidiabetic agents.

In conclusion, the present comparative study between miglitol and mitiglinide indicates favorable effects of miglitol on BMI, HOMA-IR, adiponectin, and AER, which are markers related to insulin resistance and atherosclerosis. Future large-scale clinical trials are needed to elucidate the long-term effect including cardiovascular event and mechanism of these agents.

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