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Original

The Effect of Switching from Either Mitiglinide or Glimepiride to Repaglinide on Both Glycemic Control and Oxidative Stress in Patients with Type 2 Diabetes

Kohzo Takebayashi, Tomoko Terasawa, Rika Naruse, Kenji Hara, Mariko Suetsugu, Takafumi Tuchiya, and Toshihiko Inukai

Department of Internal Medicine, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Japan

ABSTRACT

Aims : The goal of this study was to investigate the effect of switching from either the low dose sulfonylurea glimepiride (1 mg once daily) or the glinide mitiglinide (10 mg three times daily) to repaglinide (0.5 mg three times daily) on both glycemic control and oxidative stress in patients with type 2 diabetes.

Patients and Methods : Finally 17 patients (patients treated with either glimepiride : n = 11 or mitiglinide : n = 6) completed the study. The type and dose of all drugs, including the anti-diabetic treatments, were not changed for at least 1 month prior to the study.

Results : Both groups showed a significant decrease in HbA1c levels. FPG showed a tendency (not significant) toward a decrease in the mitiglinide-treated group, while no change was found in the glimepiride-treated group. A significant decrease in 8-iso-PGF2α levels was found only in the glimepiride-treated group. There was a significant correlation between the difference in 8-iso-PGF2α levels and that in either FPG or HbA1c before and after the switch only in the mitiglinide-treated group.

Conclusions : Repaglinide may have an anti-oxidative effect probably due to the strong postprandial glucose lowering observed in patients with type 2 diabetes.

Key word : repaglinide, oxidative stress, type 2 diabetes

INTRODUCTION

Recent evidence suggests that postprandial plasma glucose (PPPG) or postchallenge plasma glucose as measured by a glucose-tolerance test may be more strongly related to cardiovascular events than fasting plasma glucose (FPG) levels in non-diabetic subjects and in patients with type 2 diabetes[1~6]. The detailed mechanisms for the possible atherogenic effect of postprandial hyperglycemia are unknown. However, increased oxidative stress due to glucose fluctuations[7] may be at least partially involved, because it is shown that oxidative stress has a critical role in the progression of diabetic complications[8,9]. Interestingly, variability in glycemic control due to alternating repetition of high and low glucose concentrations is more deleterious to endothelial cells than a constant high glucose concentration as demonstrated in an *in-vitro* study[10]. These findings support the hypothesis that treatment that inhibits postprandial hyperglycemia using short-acting antidiabetic drugs is more benefi-

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Reprint requests to : Kohzo Takebayashi MD.
Department of Internal Medicine, Dokkyo Medical University Koshigaya Hospital, 2-1-50, Minami-Koshigaya, Koshigaya, 343-8555, Japan.

cial for the inhibition of the progression of cardiovascular disease compared to that which decreases the overall glucose concentration (including FPG) using long-acting antidiabetic drugs. This is due to the expected decrease of oxidative stress by short-acting anti-diabetic drugs even if the overall glucose-lowering effect [as evaluated by hemoglobin (HbA1c)] of these drugs is similar.

The glinides, oral hypoglycemic agents that stimulate insulin secretion by pancreatic beta cells by reversibly blocking ATP-sensitive potassium channels, have similar activity to sulfonylureas. However, because the effect is short-acting compared to that of sulfonylureas, glinides are categorized as short-acting hypoglycemic agents for mainly postprandial hyperglycemia. Therefore, it is speculated that glinides may decrease oxidative stress and may inhibit the progression of atherosclerosis in patients with type 2 diabetes. In fact, in both an animal study and a clinical study with a small number of patients, the anti-oxidative effect of glinides was reported[11~13]. Furthermore, it was reported that improvement of postprandial hyperglycemia was associated with regression of carotid intima-media thickness (IMT) by the administration of glinides (but not by administration of sulfonylureas)[14].

Repaglinide, a glinide, has been suggested to have a stronger overall glucose-lowering effect compared with that of other glinides, such as nateglinide[15]. The strength of the glucose-lowering effect is equal to that of a normal dose of sulfonylureas[14]. Thus, the switch from either low dose-sulfonylureas or other glinides to repaglinide may more effectively improve glycemic control, and may decrease the oxidative stress by more significantly reducing postprandial glucose levels.

Based on this information, we investigated in the current study the effect of switching from a low dose of the sulfonylurea glimepiride (1 mg once daily) or the glinide mitiglinide (10 mg three times daily) to repaglinide (0.5 mg three times daily) on glycemic control and oxidative stress. We evaluated this switch based on urinary 8-iso-prostaglandin (PG) F2α levels, which is one of the representative markers of systemic oxidative stress[16]. We hypothesized that the switch to repaglinide from these drugs may result in an improvement in both oxidative stress and glycemic control.

PATIENTS AND METHODS

Patients

This was a prospective single-arm study. Patients with type 2 diabetes who had been treated with either glimepiride 1 mg once daily after breakfast or with mitiglinide 10 mg three times daily before each meal, were switched to repaglinide 0.5 mg three times daily before each meal.

The target number of patients was initially set as 20, and the 20 patients were consecutively enrolled from February 2014 to May 2014 (except 1 patient enrolled on December 2012) in our hospital. Finally 17 patients (patients treated with either glimepiride : n = 11 or mitiglinide : n = 6) completed the study. In the mitiglinide group, 1 patient discontinued within 3 months after enrollment. In the glimepiride group, 2 patients discontinued taking repaglinide because 1 patient felt occasional nausea and the other patient felt mild leg cramps after switching to the drug.

Key inclusion criteria were 1) patients aged 20 or over, 2) patients diagnosed as type 2 diabetes according to the Japan Diabetic Society Criteria[17], 3) outpatient status, 4) patients with 6.5% and higher HbA1c levels, 5) patients with 0.5% or less variation in their HbA1c levels 2 month prior to the study, 6) patients in whom the type and dose of all drugs, including anti-diabetic ones, did not change during at least 1 month prior to the study, and 7) patients giving consent in writing for participation in this study. Key exclusion criteria were 1) patients with severe ketosis, diabetic coma, or type 1 diabetes, 2) patients with severe infectious disease, within 1 month after surgery, or having a severe traumatic injury, and 3) patients otherwise judged as unacceptable for participation in this study by our medical doctor.

Clinical and laboratory tests showed no evidence of either liver dysfunction or autoimmune disease in any patients. The characteristics at baseline of the patients treated with glimepiride and with mitiglinide before the switch to repaglinide are shown in Table 1. We previously measured fasting urinary 8-iso-PGF2α levels in non-diabetic healthy subjects (9 men and 1 woman) as a control. Their mean age, body mass

Table 1 Clinical characteristics at baseline of the patients changed from glimepiride or mitiglinide to repaglinide

	Glimepiride	Mitiglinide	P
No. (male/female)	11 (2/9)	6 (4/2)	—
Age (year)	72.3±10.5	72.8±7.5	0.9098
BMI (kg/m^2)	22.9±3.2	24.0±4.3	0.5653
FPG (mg/dL)	138.5±33.1	199.0±46.0	0.0067*
HbA1c (%)	7.4±0.4	7.5±0.9	0.8131
Urinary 8-iso PGF2α (pg/g.Cr)	365.1±263.9	171.5±93.6	0.1064
Diabetic therapy			
DPP4-I	3	1	—
Metformin	1	1	—
AGI	2	1	—
DPP4-I, AGI	2	1	—
DPP4-I, metformin, pioglitazone	1	0	—
Diet alone	2	2	—

Data are expressed as mean±standard deviation (SD), Comparison in variables between two groups were made by use of an unpaired *t* test. P : p value, P<0.05 are defined as statistical significance (*). BMI : body mass index, FPG fasting plasma glucose, HbA1c : hemoglobin A1c, 8-iso-PGFα : 8-iso-plostaglandin F2α, DPP4-I : dipeptidyl peptidase (DPP)-4 inhibitors, AGI : α-glucosidase inhibitors.

index (BMI), and 8-iso-PGF2α were 40.8±8.7 years, 23.2±3.12 kg/m^2, and 152.8±66.7 pg/g.Cr, respectively.

METHODS

The primary outcomes of this study for each group were HbA1c levels, fasting plasma glucose (FPG) levels, and urinary 8-iso-PGF2α levels 3 months after starting the study. Key secondary outcomes for each group were fasting plasma insulin levels, HOMA-IR, HOMA-β, serum lipids, and urinary albumin excretion (UAE) levels 3 months after starting the study.

Blood and urine were collected in the outpatient department from 8 : 30 to 9 : 30 a.m. after overnight fasting for at least 10 hr. The collected blood was immediately placed into specific test tubes for different assays, and then rapidly centrifuged at 1,500 rpm for 5 minutes to separate the serum or plasma from the clot-containing blood cells. The samples for 8-iso-PGF2α (urine) and insulin (plasma) analyses were stored frozen at −70° C until analysis.

Measurement of plasma glucose, hemoglobin (Hb) A1c, and serum lipids. Fasting plasma glucose (FPG) was evaluated immediately after blood collection using an automated glucose oxidase method (Glucose Auto Stat GA1160® ; Arkray, Kyoto, Japan). HbA1c was also measured immediately after blood collection in a test tube containing EDTA-2K using high-performance lipid chromatography (HPLC ; Hi-Auto A1c®, HA8150® ; Arkray). Only HbA1c is detected with this method, and the normal range is 4.5% to 6.2% [NGSP : national glycohemoglobin standardization program]. Serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum triglyceride (TG) were measured using enzymatic assays. The Determiner L TC II® and Determiner L TG® reagents (Kyowa Medics, Tokyo, Japan) were used for measurements of TC and TG, respectively. HDL-C was measured directly by a method based on selective solubilization of different lipoproteins by proprietary detergents using Cholestest N HDL-C® (Daiichi Pure Chemicals, Tokyo, Japan). LDL-C was also measured directly using Cholestest LDL® (Daiichi Pure Chemicals), rather than indirectly using the Friedwald equation. Plasma insulin was measured by a chemiluminescent enzyme immunoassay (CLEIA) using the lumipulse Presto Insulin Kit® (Fujirebio, Tokyo, Japan).

Urinary 8-iso-PGF2α assay. Urinary 8-iso-PGF2α

Table 2 Changes during 3 months in various variables by changing fro glimepiride or mitiglinide to repaglinide

	Glimepiride (n=11)			Mitiglinide (n=6)		
	Baseline	3 months	P	Baseline	3 months	P
FPG (mg/dL)	138.5±33.0	141.5±33.1	0.7974	199.0±46.0	144.0±24.3	0.0910
HbA1c (%)	7.4±0.4	6.7±0.5	0.0004*	7.5±0.9	6.7±0.8	0.0034*
TC (mg/dL)	184.3±15.3	181.8±33.4	0.7564	198.3±41.2	195.3±30.5	0.8358
TG (mg/dL)	117.7±65.5	118.5±61.2	0.9657	168.3±102.7	144.7±60.2	0.5655
HDL-C (mg/dL)	54.5±13.2	48.7±12.8	0.0392*	46.3±14.6	50.5±15.9	0.2299
LDL-C (mg/dL)	112.7±65.5	118.5±61.2	0.9657	113.3±26.3	109.3±18.7	0.5460
SBP (mmHg)	129.0±10.9	131.0±8.7	0.6364	125.3±8.5	118.3±26.2	0.5465
DBP (mmHg)	α72.7±6.7	72.4± 6.1	0.9082	79.2±19.6	70.7±2.4	0.3492
Insulin (μU/mL)	13.3±11.5	9.3±4.0	0.2637	20.9±18.2	9.4±5.7	0.3299
UAE (mg/g.Cr)	246.6±375.9	242.1±471.3	0.9245 (0.3980[A])	789.7±540.2	736.7±477.9	0.8379 (1.000[A])
HOMA-IR	4.9±5.0	3.2±1.6	0.3227	10.9±10.2	3.7±2.9	0.2977
HOMA-β	66.5±39.0	47.6±19.7	0.1034	55.2±43.2	38.2±10.1	0.5164
8-iso-PGF2α (pg/g.Cr)	365.1±263.9	323.6±239.5	0.0495* (0.0454[A])	171.5±93.6	159.8±48.6	0.8348 (0.7532[A])

Data are expressed as means±SD. P : p value for change before and after therapy by paired *t* test.
P<0.05 are defined as statistically significant (*). A : P value calculated by Wilcoxon signed rank test.
FPG : fasting plasma glucose ; HbA1c : hemoglobin A1c ; TC : total cholesterol ; TG : triglyceride ; HDL-C : high-density lipoprotein cholesterol ; LDL-C : low-density lipoprotein cholesterol ; SBP : systolic blood pressure ; DBP : diastolic blood pressure ; UAE : urinary albumin excretion, HOMA-IR : homeostasis assessment insulin resistance, HOMA-β : homeostasis assessment β, 8-iso-PGF2α : 8-iso-prostaglandin F2α. The number of patients in TC, insulin, UAE was respective 9, 9, 7 in glimepiride-treated group and respective 6, 4, 3 in mitiglinide-treated group.

was measured on the first urine of the morning with an enzyme immunoassay (EIA) kit (ACE® EIA ; Cayman Chemical Company, Ann Arbor, MI) with intra- and interassay CVs of less than 10% , based on actual values. This assay has been reported to show no differences between measurements of morning urine samples and urine samples stored for 24 hours[18]. Data were adjusted by urine creatinine concentrations. It has been reported that urinary 8-iso-PGF2α levels can change during short-term treatment, such as 1-2 hours[19].

Homeostasis model assessment-insulin resistance (HOMA-IR), and Homeostasis model assessment β (HOMA-β). HOMA-IR was used as an indicator of insulin resistance and was calculated as follows : HOMA-IR=FPG (mg/dL)× fasting immunoreactive insulin (μU/mL)/405. HOMA-β was used as an indicator of insulin secretion activity and was calculated as follows : HOMA-β=360×fasting immunoreactive insulin (μU/mL)/fasting plasma glucose (mg/dL)-63.

Ethical considerations. All subjects gave informed consent for inclusion in the study. The study was approved by the Local Ethics Committee in Dokkyo Medical University Koshigaya Hospital and was performed according to the guidelines of the Declaration of Helsinki.

Statistical methods. The two time points for each parameter for an individual were compared using a paired t-test. For 8-iso-PGF2α and UAE, a Wilcoxon signed rank test was also used as a non-parametric test due to its skewed distributions. Comparisons between the two groups were made using an unpaired t-test for normally distributed data (confirmed by a χ^2 test). A Student t-test or a Welch t-test was chosen based on the homogeneity of variance calculated by an F-test. For multiple comparisons, the Bartlett test showed that there were no significant differences in variance among the three groups. A parametric comparison was performed by one-way analysis of variance (ANOVA). The ANOVA was significant. Therefore, the significance of the individual differences was assessed using the Bonferroni test. A *P* value of less than 0.05 was accepted as indicating statistical significance (two-sided).

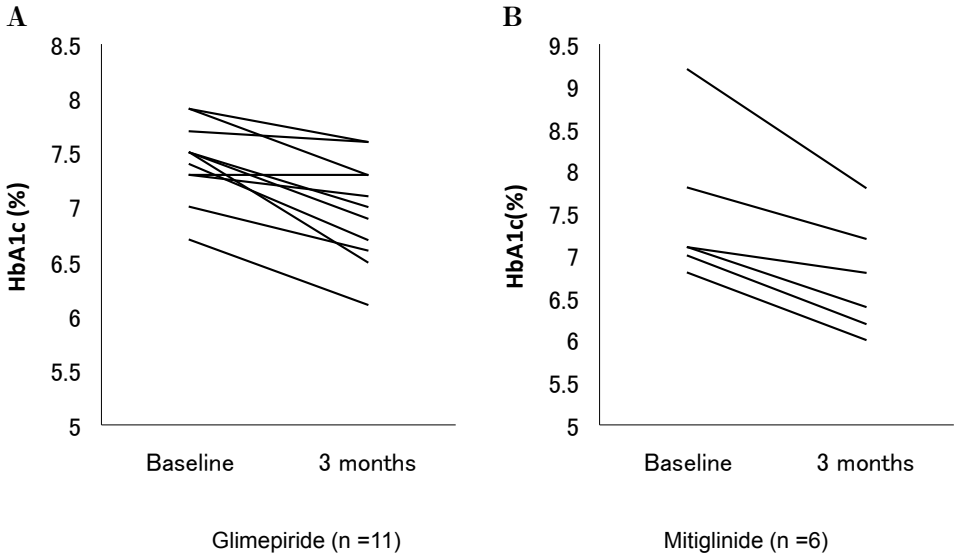

Fig. 1A, B The changes in HbA1c by therapy changing from glimepiride (**A**) or mitiglinide (**B**) to repaglinide

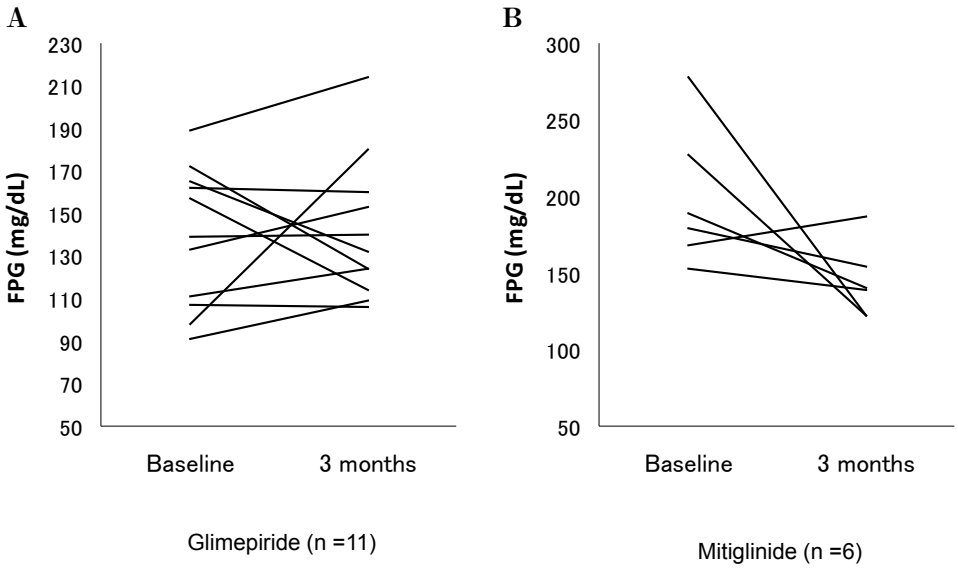

Fig. 2A, B The changes in FPG by therapy changing from glimepiride (**A**) or mitiglinide (**B**) to repaglinide

RESULTS

Although patients with 0.5% or less variation of HbA1c levels in the 2 months prior to the study were intended to be included in this study as described in the inclusion criteria, 2 patients in the glimepiride-treated group showed equal to or more than a 0.6% variation of HbA1c levels. We decided to include these patients because of the relative small number of patients in this study. In these patients, The HbA1c levels at 2 months before the switch, at baseline and at 3 months after the switch were 6.8-7.9-7.6% and 6.9-7.5-6.5% , respectively. Their 8-iso-PGF2α levels at baseline and at 3 months after the switch were 380-383 pg/g.Cr and 205-199 pg/g.Cr, respectively.

Changes in certain variables at baseline and at 3 months in patient-groups treated with either glimepiride or mitiglinide before the switch to repaglinide are presented in Table 2. A significant decrease was obtained in HbA1c levels in both groups (Fig. 1). FPG showed a tendency (no significance) toward a decrease in the mitiglinide-treated group,

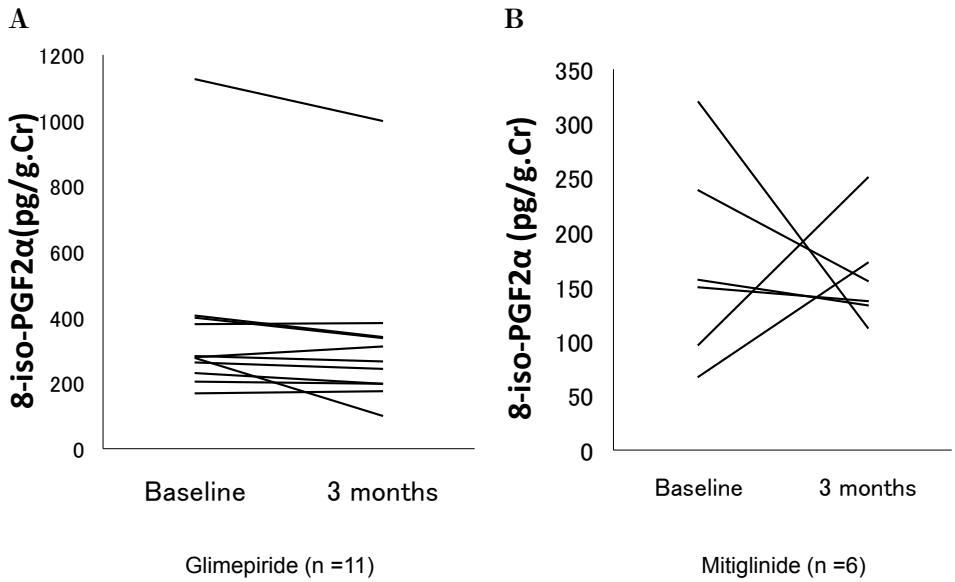

Fig. 3A, B The changes in 8-isoPGF2α by therapy changing from glimepiride (**A**) or mitiglinide (**B**) to repaglinide

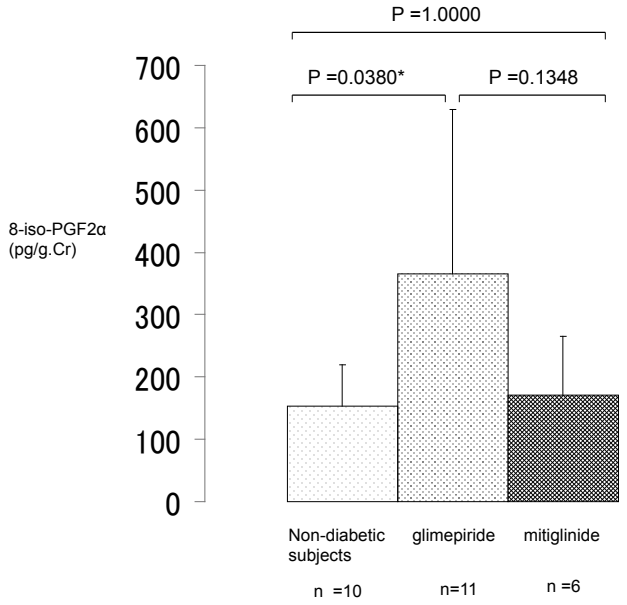

Fig. 4 Comparison in 8-isoPGF2α at baseline among non-diabetic subjects, patients with glimepiride, and patients with mitiglinide

while no change was found in the glimepiride-treated group (Fig. 2). A significant decrease in 8-iso-PGF2α was found in the glimepiride-treated group (Fig. 3).

There was no significant change in SBP, DBP, serum lipids, insulin, and HOMA-IR in both groups, except for a significant decrease in HDL-C in the glimepiride-treated group. There was a tendency toward a decrease in HOMA-β in the glimepiride-treated group.

There was a significant difference in the 8-iso-PGF2α levels between the glimepiride-treated group at baseline and the healthy control group (Fig. 4). The difference in 8-iso-PGF2α was also significant between the glimepiride-treated group 3 months after the switch to repaglinide and the healthy control group.

There was a tendency toward a positive correlation (no significance) between 8-iso-PGF2α and FPG at baseline in both groups, but no correlation between 8-iso-PGF2α and HbA1c at baseline in both groups was observed (Table 3).

There was significant positive correlation between the difference in 8-iso-PGF2α and that in both FPG and HbA1c before and after the switch only in the mitiglinide-treated group (Table 3).

DISCUSSION

In the current study, the switch from glimepiride 1 mg once daily to repaglinide 0.5 mg three times daily significantly decreased HbA1c levels during the 3 month observation-period. This result basically supports previous reports showing the strong glucose-lowering effect of repaglinide[14]. However, no significant change was observed in FPG. The result appears to be reasonable because repaglinide is short-acting when compared with glimepiride, and therefore main-

Table 3 Correlation between 8-iso-PGF2α and glycemic control markers at baseline, or between difference in 8-iso-PGF2α and that in glycemic control markers before and after the change to repaglinide

Glimepiride		
Baseline 8-isoPGF2α -FPG	0.5298	0.0936
Baseline 8-isoPGF2α- HbA1c	0.1722	0.6125
Δ8-isoPGF2α-ΔFPG	0.2881	0.3903
Δ8-isoPGF2α-ΔHbA1c	0.1182	0.7293
Mitiglinide		
Baseline 8-isoPGF2α- FPG	0.5937	0.2141
Baseline 8-isoPGF2α- HbA1c	0.3295	0.5235
Δ8-isoPGF2α-ΔFPG	0.9016	0.0141*
Δ8-isoPGF2α-ΔHbA1c	0.8695	0.0244*

Glimepiride : patients-group changed from glibenclamide to repaglinide,
Mitiglinide : patients-group changed from mitiglinide to repaglinide, FPG : fasting plasma glucose (mg/dL), HbA1c : hemoglobin A1c (%), 8-iso-PGFα : 8-iso-prostaglandin F2α (pg/g.Cr).

ly reduces postprandial plasma glucose (PPPG), although this agent can decrease FPG to some degree[15]. In the current study, the PPPG levels were not evaluated ; we chose FPG for our evaluation of glucose levels because we also intended to evaluate HOMA-IR and HOMA-β, which are calculated using FPG. However, given the fact that HbA1c levels were significantly decreased despite a similar effect for FPG by these drugs, it is speculated that PPPG was largely decreased by the switch to repaglinide. On the other hand, the switch from mitiglinide to repaglinide also significantly decreased the HbA1c levels as expected. There is a report written in Japanese demonstrating that repaglinide has an overall stronger glucose-lowering effect when compared with mitiglinide (reference is not shown). Interestingly this change led to the tendency toward a decrease of FPG despite the fact that both drugs are short-acting, and further supports the mild FPG-lowing effect of repaglinide[15].

As expected, the switch from glimepiride to repaglinide significantly decreased the 8-iso PGF2α levels (a marker of systemic oxidative stress). It is reported that 8-iso PGF2α levels positively correlate with the daily variation of plasma glucose levels evaluated by an index, such as mean amplitude of glycemic excursions (MAGE)[7]. Therefore, it may be possible that the results in this study were based on the speculated larger decrease of PPPG and consequently the greater reduction in variation of plasma glucose levels by repaglinide compared with that of glimepiride. However, since the switch to repaglinide showed not only the speculated improvement in the glucose variation but also a decrease in HbA1c levels, the overall improvement of glycemic control by repaglinide may have been partially due to the decrease in the 8-iso PGF2α levels. It should also be noted that 8-iso PGF2α levels are also influenced by the glucose level itself[19]. In the current study, a tendency toward a positive correlation between 8-iso PGF2α and FPG in both groups was also found. Recently, Yamazaki et al, reported that the switch from glimepiride to repaglinide showed no difference in the HbA1c levels, and the 8-iso PGF2α levels were also not changed, although urinary 8-hydroxydeoxyguanosine (8-OHGd) (another marker of systemic oxidative stress) was significantly reduced[12]. It is difficult to interpret this result accurately. However, the baseline HbA1c levels and the 8-iso PGF2α levels were higher in our study. In addition, in the study by Yamazaki et al., glimepiride 1 mg once daily was switched to repaglinide 0.25 mg three times daily. These differences may partially explain the positive result in the current study. On the other hand, the switch from mitiglinide to repaglinide did not change the 8-iso PGF2α levels despite the stronger effect on overall glycemic control by repaglinide compared with that by mitiglinide. Apart from the issues relating to the small number of patients as one of the reason for this result, it should also be considered that the 8-iso PGF2α levels at baseline were already lower (although not statistically significant) when the glimepiride was switched to repaglinide even if 8-iso PGF2α levels are influenced by the glucose level itself. We speculate that the possible planarization of glucose variation by mitiglinide compared with that by glimepiride might have resulted in the improvement of oxidative stress reflected by the low levels at baseline of 8-iso PGF2α. In this study, the 8-iso PGF2α levels at baseline in patients treated with mitiglinide were similar compared with that in healthy subjects. Importantly, although repaglinide therapy after the switch from glimepiride significantly reduced the 8-iso PGF2α levels, the levels were still

high compared with that in healthy subjects. Because mitiglinide was administrated for a long-term period over 3 months in most patients, this may explain its possible strong effect on oxidative stress. We previously reported that short-acting insulin therapy before each meal over about 10 days did not change the 8-iso PGF2α levels[20]. This may also suggest that long-term treatment is important for the improvement of the 8-iso PGF2α levels when the treatment for PPPG was targeted. Taken together, it may be possible that relatively low levels of 8-iso PGF2α at baseline weakened the potentially strong effect of repaglinide on oxidative stress.

In the current study, the significant correlation between the difference in the 8-iso PGF2α levels and that in FPG or in HbA1c levels 3 months after the switch to repaglinide was observed only in the mitiglinide-treated group. It is speculated that the switch from mitiglinide had less effect on the degree of glucose-variation compared with that from glimepiride. Therefore, since the 8-iso PGF2α levels are not only influenced by glucose-variation but also by the glucose level itself, it may be possible that the 8-iso PGF2α levels were more strongly influenced by the glucose level in the mitiglinide-treated group when compared with the glimepiride-treated group.

In the current study, HOMA-IR was basically unchanged by the switch from either glimepiride or mitiglinide to repaglinide, suggesting that these drugs are all active on insulin secretion. On the other hand, there was a tendency toward a decrease of HOMA-β in the group switching from glimepiride to repaglinide. This appears to be reasonable when it is considered that repaglinide is a short-acting drug, and the significant decrease of HbA1c after the switch to repaglinide may be explained by its possible stronger effect on postprandial glucose.

This study has several limitations. First, this study was a single arm study with a relatively small number of patients. Second, we could not evaluate PPPG in this study. Finally, the observation periods may have been relatively short. Further studies are warranted to investigate the possible beneficial effect on oxidative stress of repaglinide in patients with type 2 diabetes.

In conclusion, we investigated the effect of switching from either a low dose sulfonyl glimepiride treatment (1 mg once daily) or a glinide mitiglinide treatment (10 mg three times daily) to repaglinide 0.5 mg three times daily, on glycemic control and on oxidative stress as determined by urinary 8-iso-prostaglandin F2α levels. Despite the significant decrease of HbA1c in both groups, the 8-iso-prostaglandin F2α levels were decreased only in the group that switched from glimepiride to repaglinide. Possible improvement of glucose variability by repaglinide in addition to the potentially strong effect of this agent on glycemic control may partially explain these results.

Disclosure

The authors have nothing to disclose.

REFERENCES

1) The DECODE Study Group Glucose tolerance and cardiovascular mortality : comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med **161** : 397-405, 2001.
2) Balkau B, Shipley M, Jarrett RJ, et al : High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20 year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. Diabetes Care **21** : 360-367, 1998.
3) Tominaga M, Eguchi H, Manaka H, et al : The Funagata Diabetes Study. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. Diabetes Care **22** : 920-924, 1999.
4) Saydah SH, Miret M, Sung J, et al : Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. Diabetes Care **24** : 1397-1402, 2001.
5) Meigs JB, Nathan DM, D'Agostino RB Sr, et al : Fasting and postchallenge glycemia and cardiovascular disease risk : the Framingham Offspring Study. Diabetes Care **25** : 1845-1850, 2002.
6) Cavalot F, Petrelli A, Traversa M, et al : Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women : lessons from San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab **91** : 813-819, 2006.
7) Monnier L, Mas E, Ginet C, Michel F, et al : Activa-

tion of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA **295** : 1681-1687, 2006.

8) Brownlee M : The pathology of diabetic complications : a unifying mechanism. Diabetes **54** : 1615-1625, 2005.

9) Ceriello A : The possible role of postprandial hyperglycaemia in the pathogenesis of diabetic complications. Diabetologia **46** : M9-16, 2003.

10) Risso A, Mercuri F, Quagliaro L, et al : Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. Am J Physiol Endocrinol Metab **281** : E924-E930, 2001.

11) Gumieniczek A : Effect of repaglinide on oxidative stress in tissues of diabetic rabbits Diabetes Rec Clin Pract **68** : 89-95, 2005.

12) Yamazaki M, Hasegawa G, Majima S, et al : Effect of repaglinide versus glimepiride on daily blood glucose variability and changes in blood inflammatory and oxidative markers. Diabetology and Metabolic Syndrome **6** : 54, 2014.

13) Li Y, Xu L, Shen J, Ran J, et al : Effects of short-term therapy with different insulin secretagogues on glucose metabolism, lipid parameters and oxidative stress in newly diagnosed Type 2 Diabetes Mellitus. Diabetes Res Clin Pract **88** : 42-47, 2010.

14) Esposito K, Giugliano D, Nappo F, et al : Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation **110** : 214-219, 2004.

15) Kawamori R, Kaku K, Hanafusa T, et al : Efficacy and safety of repaglinide vs. nateglinide for treatment of Japanese patients with type 2 diabetes mellitus. J Diabetes Invest **3** : 302-308, 2012.

16) Patrono C, Fitzgerald GA : Isoprostanes : potential markers of oxidative stress in arterothrombotic disease. Arterioscler Thromb Vasc Biol **17** : 2309-2315, 1997.

17) Treatment guide for diabetes edited by Japan Diabetes Society 2007. Bunkodo, Tokyo, Japan

18) Helmersson J, Basu S : F_2-isoprostane excretion rate and diurnal variation in human urine. Prostaglandins Leukot Essent Fatty Acids. **61** : 203-205, 1999.

19) Ceriello A, Bonfigli AR, Esposito K, et al : The possible protective role of glucagon-like peptide 1 on endothelium during the meal and evidence for an "endothelial resistance" to glucagon-like peptide 1 in diabetes. Diabetes Care **34** : 697-702, 2011.

20) Naruse R, Takebayashi K, Morita M, Aso Y, Inukai T : Comparison of effects of insulin aspart three times a day versus insulin detemir once a day on oxidative stress in patients with type 2 diabetes. Endocr J **58** : 1055-63, 2011.