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No Deterioration of Blood Glucose and Arterial Stiffness by Switching Metformin to 500 mg Once Daily

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Abstract

Purpose: Metformin is widely used not only for reducing blood glucose but also for preventing cardiovascular disease in patients with type 2 diabetes mellitus (T2DM). Metformin 500 mg/tablet and 250 mg/tablet have been available in Japan since 2013. Switching from 250 mg twice daily to 500 mg once daily is more convenient for patients. However, because of the short half-life, this switch may have a risk of deteriorating blood glucose control and macrovascular complications. We investigated the efficacy of metformin 500 mg once daily compared with metformin 250 mg twice daily.

Methods: In this prospective randomized study, 70 T2DM patients already treated with metformin 250 mg twice daily at Sakura Hospital were enrolled. Patients were divided into a group that switched from metformin 250 mg twice daily to metformin 500 mg once daily (once daily group, n=35) and a group that continued to take metformin 250 mg twice daily (twice daily group, n=35).We observed the changes in metabolic parameters and cardio-ankle vascular index (CAVI) that reflects arterial stiffness.

Results : After 6 months, fasting blood glucose (FBG) did not change significantly in both groups. Hemoglobin A1c (HbA1c) was almost unchanged in both groups. Changes in FBG and HbA1c were not significantly different between two groups. CAVI changed slightly in both groups, but the change in CAVI was not significantly different between two groups.

Conclusion: These results suggest that metformin 500 mg once daily did not deteriorate blood glucose control or arterial stiffness compared with metformin 250 mg twice daily.

Keywords: Metformin; 500 mg/day; Once daily; Twice daily; HbA1c

Introduction

Metformin is used to control blood glucose in patients with type 2 diabetes mellitus worldwide. A statement of the American Diabetes Association (ADA) and the Europe Association for the Study of Diabetes (EASD) recommends metformin as the first line of hypoglycemic agent [1]. Metformin improves insulin sensitivity and is thus important in the management of traditional cardiovascular risk factors such as a high hemoglobin (Hb) A1c level, dyslipidemia, hypertension and central obesity, all of which are associated with insulin resistance [2]. The United Kingdom Prospective Diabetes Study demonstrated that the risk of cardiovascular morbidity and mortality was reduced in patients with type 2 diabetes mellitus receiving intensive glucose control using metformin [3]. Thus, metformin improves not only blood glucose but also cardiovascular morbidity and mortality.

Prevention of macrovascular complications is very important for the treatment of diabetes. There are some surrogate markers of atherosclerosis in clinical situation. Arterial stiffness is a useful surrogate marker of atherosclerosis. Brachial-ankle PWV (baPWV) has been used to evaluate arterial stiffness or atherosclerosis in diabetic patients. An arterial stiffness parameter called cardio-ankle vascular index (CAVI) was developed as a marker of arteriosclerosis involving the aorta, femoral artery and tibial artery [4]. CAVI is measured from an electrocardiogram, phonocardiogram, brachial artery waveform and ankle artery waveform and is adjusted for blood pressure based on the stiffness parameter β [5]. CAVI is independent of blood pressure and has adequate reproducibility for clinical use, whereas baPWV is dependent on blood pressure [4]. Although arterial stiffness can be evaluated by measuring either baPWV or CAVI, CAVI is superior to baPWV as an index of arterial stiffness in patients who have undergone coronary angiography [5]. A report has shown that CAVI is useful for the detection of atherosclerotic diseases [4]. Some hypoglycemic agents improve CAVI within 6 months in several clinical studies [6-8]. Thus, CAVI is a very useful marker for evaluating atherosclerosis in diabetic patients.

In Japan, the maximum dose of metformin had been 750 mg/day for a long time. However, physicians have been able to prescribe metformin at a maximum dose of 2250 mg/day since 2010. Metformin 250 mg/tablet had been the only available formulation in Japan until metformin 500 mg/tablet was released at 2013. Many diabetic patients take metformin 250 mg twice daily, but now physicians can switch from metformin 250 mg twice daily to metformin 500 mg once daily by taking only one tablet. With the release of dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium

glucose cotransporter (SGLT)-2 inhibitors in recent years, many types of hypoglycemic agents are now available, and some patients are treated with multiple agents. If metformin 500 mg once daily has the same efficacy as metformin 250 mg twice daily, physicians can reduce the number of tablets which may increase compliance. However, because of the short half-life of metformin, metformin 500 mg once daily has a risk of deteriorating blood glucose control and macrovascular complications compared with metformin 250 mg twice daily [9].

In the present study, we investigated the effects of metformin 500 mg once daily on blood glucose control and atherosclerosis, and compared with metformin 250 mg twice daily.

Subjects and Methods

Subjects

The study was conducted in accordance with Helsinki Declaration and was approved by the institutional review board of Sakura Hospital Toho University Medical Center (No. 2013-039). Before participation, the purpose of the study was explained to each subject, and consent was obtained for both participation in the study and for release of the study data.

A randomized open-label study was performed. We enrolled 70 patients with type 2 diabetes mellitus, who had been treated with metformin 250 mg twice daily for at least 3 months Sakura Hospital and whose HbA1c had been steady for 3 months. The exclusion criterion was patients with renal dysfunction [estimated glomerular filtration (eGFR) <30 ml/min/1.73 m^2]. We divided the patients into 2 groups by simple randomization using a closed envelope. One group was switched from metformin 250 mg twice daily to metformin 500 mg once daily (once daily group, n=35), and the other group continued to take metformin 250 mg twice daily (twice daily group, n=35). Table 1 shows the clinical characteristics of the subjects at baseline. The subjects were observed for 6 months, and the following parameters were measured before and after 6 months: body weight (BW), body mass index (BMI), fasting blood glucose (FBG), glycosylated, hemoglobin (HbA1c), aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transpeptidase (γ-GTP), blood urea nitrogen (BUN), serum creatinine, eGFR, serum total cholesterol level (TC), serum triglycerides level (TG), serum high-density lipoprotein-cholesterol level (HDL-C) and serum low-density lipoprotein-cholesterol level (LDL-C). Systolic blood pressure (SBP), diastolic blood pressure (DBP) and CAVI were also measured before and after 6 months. During this study, all patients maintained the same diet and exercise therapies and did not change medications. All subjects received nutritional guidance from a dietitian every month. The dietitian analyzed the meals of the patients and suggested changes if necessary.

Body weight measurement and blood sampling

Body weight was measured and blood samples were collected in the morning after 12 hours of fasting. Serum was separated within 1 hour, and the sample was used for measurements of HbA1c, AST, ALT, γ-GTP, BUN, serum creatinine, eGFR and serum lipids.

Measurement of HbA1c and plasma lipid concentrations

For HbA1c measurement, blood was collected in tubes containing ethylene diamine tetra acetic acid (EDTA). The stable and unstable fractions of HbA1c were measured by a high-pressure liquid chromatography method using Hi-Auto A1c (Kyoto Daiichi Kagaku, Kyoto, Japan). Data of the stable form were used in the present analysis. The data of HbA1c was expressed as the value of the National Glycohemoglobin Standardization Program (NGSP).

Plasma TC and TG levels were measured enzymatically using kits from Nippon Shoji Co., Ltd. (Osaka, Japan) and a HITACHI 7150 analyzer (Hitachi, Ltd., Tokyo, Japan). HDL-C was measured by a selective inhibition assay (Daiichi Pure Chemicals Co., Ltd., Tokyo) [10]. Serum LDL-C levels were calculated using the Friedewald formula.

Measurement of CAVI, systolic and diastolic blood pressure

CAVI is obtained by measuring blood pressures and pulse wave velocity (PWV) according to the following formula: $CAVI = a\{(2\rho/\Delta P) \times \ln(Ps/Pd)PWV^2\}+b$, where Ps is systolic blood pressure; Pd is diastolic blood pressure; PWV is pulse wave velocity; ΔP is Ps - Pd; ρis blood density, and a and b are constants. The details of CAVI and the measurement of CAVI are described in our previous reports [4,7].

In the present study, CAVI was measured using a VaSera CAVI instrument (Fukuda Denshi Co., Ltd., Tokyo, Japan) as described previously [4]. Systolic and diastolic blood pressures were measured at the time of CAVI measurement.

Statistical analysis

Data were expressed as mean ± SD. Normal distribution was tested by the Shapiro-Wilk test. Some data were not normally distributed, and normality was obtained by logarithmic transformation. Statistical analysis was performed using the Student's t-test and ANOVA. All analyses were performed using the JMP version 9.0 (SAS, Cary, NC, USA). P values <0.05 were considered significant.

Results

Baseline characteristics in once daily group and twice daily group

There were no significant differences in baseline parameters between once daily group and twice daily group (Table 1). Use of other hypoglycemic agent was also almost the same in the two groups (Table 1), except that use of thiazolidinediones was four times higher in twice daily group than in once daily group. Only one patient took glinide in this study (Table 1). No patients used glucagon-like peptide-1 (GLP-1) agonists. No patients took SGLT-2 inhibitors, because all subjects in this study were registered before SGLT-2 inhibitors were available in Japan.

Comparisons of changes of clinical parameters after 6 months in two groups

Comparison between the two groups revealed that the change in FBG was -1.51 ± 62.55 mg/dl in once daily group and +14.91 ± 57.64 mg/dl in twice daily group, but the difference was not significant (P=0.2572) (Table 2). Serum creatinine and eGFR apparently deteriorated slightly in once daily group and improved slightly in twice daily group. However, changes of these two parameters were not significantly different between two groups (Table 2). Changes in other clinical parameters also were not significantly different between two groups (Table 2).

Metformin-related adverse effects such as lactic acidosis, anxiety and confusion signs were not observed in any of the patients.

Change in HbA1c in once daily group and twice daily group

In the once daily group, HbA1c was 7.58 ± 0.93 at baseline and 7.83 ± 1.13 at 6 months (Figure 1A). HbA1c in twice daily group was 7.68 ± 1.00 at baseline and 7.81 ± 1.02 at 6 months (Figure 1B). The changes in both groups were not significant (P=0.0849 in once daily group, P=0.2523 in twice daily group). The changes in HbA1c during this study are shown in Figure 1C. The change in HbA1c was not significantly different between once daily and twice daily groups (+0.25 ± 0.66 vs. +0.13 ± 0.68, P=0.5247).

Change in CAVI in once daily group and twice daily group

In once daily group, CAVI was unchanged after 6 months (from 9.50 ±

	Once daily group	Twice daily group	P-value
No. of subjects (male/female)	35 (22/13)	35 (22/13)	
Age (years)	62.66 ± 9.88	65.51 ± 6.24	0.1527
BW (kg)	66.11 ± 15.96	65.99 ± 10.60	0.8175
BMI (kg/m^2)	24.89 ± 4.93	24.60 ± 2.75	0.9660
SBP (mmHg)	149.09 ± 20.57	141.77 ± 14.38	0.1128
DBP(mmHg)	87.94 ± 13.06	83.80 ± 10.25	0.1696
FBG (mg/dl)	166.83 ± 56.59	160.69 ± 45.80	0.6193
HbA1c (%)	7.58 ± 0.93	7.68 ± 1.00	0.6849
AST (IU/L)	26.20 ± 13.98	23.49 ± 11.66	0.3555
ALT (IU/L)	24.71 ± 14.72	22.31 ± 13.80	0.3667
gamma-GTP (IU/L)	38.49 ± 32.72	45.06 ± 43.51	0.7372
BUN (mg/dl)	15.40 ± 4.96	16.71 ± 4.42	0.1570
serum creatinine (mg/dl)	0.77 ± 0.20	0.81 ± 0.24	0.5148
eGFR (ml/min/1.73 m^2)	75.11 ± 19.15	72.29 ± 22.15	0.4484
TC (mg/dl)	190.74 ± 35.34	200.14 ± 32.92	0.2535
TG (mg/dl)	154.63 ± 84.86	167.26 ± 80.46	0.3103
HDL-C (mg/dl)	49.23 ± 12.04	49.40 ± 11.37	0.9513
LDL-C (mg/dl)	115.40 ± 28.72	124.54 ± 27.42	0.1776
CAVI	9.50 ± 1.00	9.36 ± 0.86	0.5524
Use of other hypoglycemic agents			
none	7 (20%)	7 (20%)	
sulfonylurea	19 (54.3%)	20 (57.1%)	
DPP-4 inhibitors	16 (45.7%)	14 (40%)	
alpha-glucosidase inhibitors	2 (5.7%)	3 (8.6%)	
thiazolidinediones	2 (5.7%)	7 (20%)	
insulin	2 (5.7)	4 (11.4%)	
glinide	1 (2.9%)	0 (0%)	

Table 1: Comparison of baseline characteristics in the two groups

Data are presented as mean ± SD or number (%). BW: Body Weight; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBG: Fasting Bood Glucose; HbA1c: Glycosylated hemoglobin; AST: Aspartate Transaminase; ALT: Alanine Transaminase; GTP: Glutamyl Transpeptidase; BUN: Blood Urea Nitrogen; eGFR: estimated Glomerular Filtration Rate; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High Density Lipoprotein-Cholesterol; LDL-C: Low Density Lipoprotein-Cholesterol; CAVI: Cardio-Ankle Vascular Index; DPP-4: Dipeptidyl Peptidase-4.

	Change from baseline		P-value
	Once daily group	Twice daily group	
ΔBW (kg)	-0.18 ± 2.75	+0.04 ± 1.90	0.8793
ΔBMI (kg/m^2)	-0.04 ± 1.00	+0.04 ± 0.64	0.8793
ΔSBP (mmHg)	-1.89 ± 13.73	+0.17 ± 16.77	0.6820
ΔDBP (mmHg)	-1.69 ± 8.08	-0.54 ± 7.52	0.7451
ΔFBG (mg/dl)	-1.51 ± 62.55	+14.91 ± 57.64	0.2572
ΔAST (IU/L)	-2.49 ± 10.14	+1.57 ± 12.86	0.1042
ΔALT (IU/L)	-2.20 ± 12.17	+2.43 ± 11.18	0.0519
Δgamma-GTP (IU/L)	-2.74 ± 22.30	-0.37 ± 20.87	0.4703
ΔBUN (mg/dl)	+0.62 ± 3.23	+0.54 ± 5.12	0.4313
Δserum creatinine (mg/dl)	+0.046 ± 0.1366	-0.007 ± 0.112	0.0808
ΔeGFR (ml/min/1.73 m^2)	-3.14 ± 12.04	+0.23 ± 9.70	0.1037
ΔTC (mg/dl)	-0.54 ± 25.07	+2.77 ± 28.00	0.6036
ΔTG (mg/dl)	+7.26 ± 89.67	+9.83 ± 102.24	0.9472
ΔHDL-C (mg/dl)	-0.46 ± 6.30	+1.60 ± 5.98	0.1656
ΔLDL-C (mg/dl)	+0.26 ± 19.35	-1.29 ± 23.13	0.7631

Table 2: Comparison of the changes in clinical parameters after 6 months in the two groups
Data are presented as mean ± SD. Δ denotes the difference between the value at baseline and that after 6 months. Abbreviations are as in Table 1.

1.00 to 9.54 ± 1.11, P=0.8504) (Figure 2A). CAVI in twice daily group also did not change significantly (P=0.2964) (Figure 2B). The changes in CAVI were not significantly different between once daily and twice daily groups (+0.04 ± 0.73 vs. +0.11 ± 0.62, P=0.5815) (Figure 2C).

Comparison between male and female in each group

We investigated the sexuality effect or relationship between male and female in this study. We compared the differences between male and female in each group. At baseline, BW and HbA1c were significantly different between male and female in once daily group (Table 3). However, the change in BW, BMI, FBG, HbA1c and CAVI were not significantly different between male and female in once daily group (Table 3). In twice daily group, BW and CAVI were significantly different between male and female at baseline. BW and BMI were significantly decreased in male subjects after 6 months, but the change in FBG, HbA1c and CAVI were not significantly different between male and female in twice daily group (Table 3).

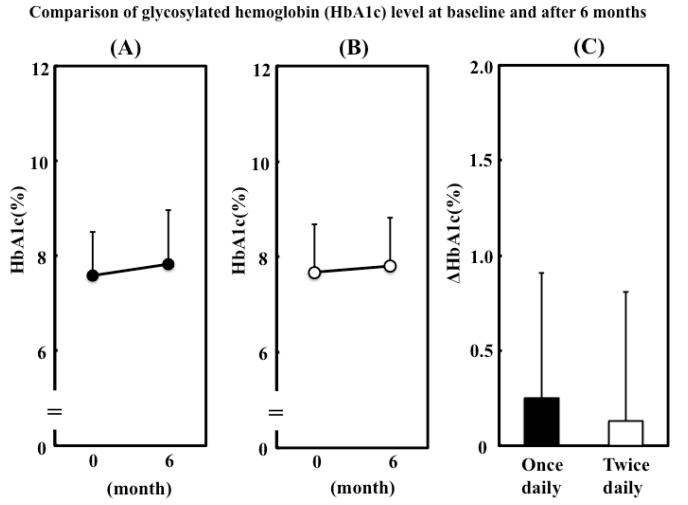

Figure 1: Comparison of glycosylated hemoglobin (HbA1c) level at baseline and after 6months.
(A) Change in HbA1c in patients who switched to metformin 500 mg once daily. (B) Change in HbA1c in patients who continued to take metformin 250 mg twice daily. (C) Changes in HbA1c after 6 months in two groups. Data are presented as mean ± S.D. Δ denotes the difference between the value at baseline and that after 6 months.

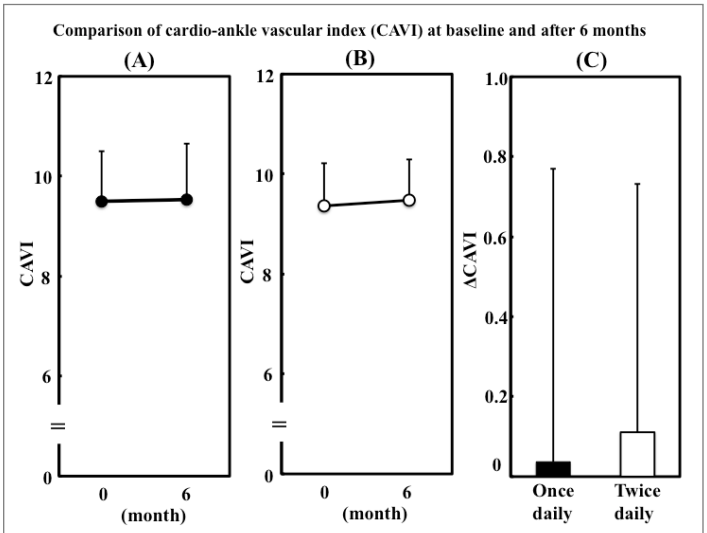

Figure 2: Comparison of cardio-ankle vascular index (CAVI) at baseline and after 6 months.
(A) Change in CAVI in patients who switched to metformin 500 mg once daily. (B) Change in CAVI in patients who continued to take metformin 250 mg twice daily. (C) Changes in CAVI after 6 months in two groups. Data are presented as mean ± S.D. Δ denotes the difference between the value at baseline and that after 6 months.

Discussion

In the present study, switching from metformin 250 mg twice daily to metformin 500 mg once daily did not affect blood glucose control, and also did not change CAVI that reflects arterial stiffness and is a surrogate marker of atherosclerosis. Furthermore, there were no metformin-related adverse effects, and lipid metabolism and parameters of liver and kidney function were also unchanged. There was no sexuality effect or relationship between male and female in this study.

Metformin, an insulin sensitizer, has been shown to reduce the incidence of myocardial infarction compared with sulfonylurea agents in a large-scale study [3]. This result may be one of the reasons why metformin is recommended as the first-line hypoglycemic agent. Patients usually take metformin two or three times daily because of its short half-life. In the present study, we compared the efficacy of metformin 500 mg once daily with metformin 250 mg twice daily. Fasting blood glucose was unchanged and HbA1c did not change significantly in once daily group. The change in HbA1c was not significantly different between once daily and twice daily groups. Hwang et al. [11] reported that glimepiride 2 mg and metformin 500 mg once daily was as effective as glimepiride 1 mg and metformin 250 mg twice daily. Although the half-life of glimepiride is also relatively short, glimepiride and metformin once daily showed high efficacy [11,12]. Our study using only metformin showed the same result as Hwang et al. [11] who used glimepiride and metformin. In the Japanese package insert for metformin, the T_{max}, C_{max}, AUC_{0-48} and $T_{1/2}$ for 250 mg are 1.9 h, 898 ng/ml, 4861 ng•hr/ml and 2.9 h; while the corresponding data for 500 mg are 2.3 h, 1341 ng/ml, 8019 ng•hr/ml and 4.0 h. Other reports on metformin 500 mg show T_{max} of 2.4 h, C_{max} of 1420 ng/ml, and $T_{1/2}$ of 3.16 h [13,14], and these figures are similar to those shown in the Japanese package insert. Although the half-life is not remarkably different between metformin 250 mg and 500 mg, C_{max} and AUC_{0-48} of metformin 500 mg are clearly larger than those of metformin 250 mg. The large C_{max} and AUC_{0-48} may be a reason why metformin 500 mg once daily has the same effectiveness in controlling blood glucose as metformin 250 mg twice daily.

Cardiovascular disease is the leading cause of death among type 2 diabetic patients [15]. Preventing macrovascular complications is a very important goal for the treatment of diabetes. There are some surrogate markers for atherosclerosis. Arterial stiffness is closely related to atherosclerosis, and several reports show that CAVI is a useful surrogate marker for atherosclerosis in patients with or without diabetes [16-18]. CAVI decreases through improvement of postprandial hyperglycemia or insulin resistance in type 2 diabetes patients [6-8]. In the present study, metformin 500 mg once daily did not change CAVI, and the changes in CAVI in once daily and twice daily groups were not significantly different. These results indicate that switching from metformin 250 mg twice daily to metformin 500 mg once daily does not deteriorate atherosclerosis in type 2 diabetes patients.

Some clinical studies have shown that metformin improves the lipoprotein profile in patients with diabetes [19-21]. Metformin also improves the qualities of LDL-cholesterol. Metformin enlarges LDL particle size and reduces circulating malondialdehyde-modified LDL, which is one of the oxidized LDLs [22,23]. Thus, metformin also affects lipid metabolism. In the present study, metformin 500 mg once daily had no negative effect on lipid metabolism compared with 250 mg twice daily. The half-life of metformin is short, and metformin 500 mg once daily does not deteriorate blood glucose concentration, arterial stiffness, or lipid metabolism compared with metformin 250 mg twice daily.

Lactic acidosis is the most well known and serious adverse effect of metformin. Lactic acidosis usually occurs due to drug overdose or in some contraindicated conditions such as liver or kidney dysfunction [24]. For this reason, we excluded patients with kidney dysfunction (eGFR<30 ml/min/1.73 m^2). Metformin at 500 mg/day is not an overdose, but administration of 500 mg per dose may be high for some patients. In the present study, none of the patients had lactic acidosis. Therefore, metformin 500 mg once daily is safe in patients without kidney dysfunction.

AST and ALT showed apparent decreases in once daily group and increases in twice daily group, although all the levels were within normal ranges. The changes in AST and ALT tended to be different between once daily and twice daily groups (p=0.1042 and 0.0519, respectively), and the difference was almost significant for AST. Metformin reduces hepatic steatosis via activating AMP-activated protein kinase (AMPK) and

	Once daily group			Twice daily group		
	Male (n=22)	Female (n=13)	P-value	Male (n=22)	Female (n=13)	P-value
Baseline						
Age (years)	61.32 ± 11.18	64.92 ± 7.00	0.3040	65.50 ± 7.49	65.54 ± 3.48	0.986
BW (kg)	71.04 ± 17.49	57.77 ± 8.16	0.0113	71.03 ± 9.24	57.48 ± 6.61	<0.0001
BMI (kg/m^2)	25.34 ± 5.64	24.12 ± 3.53	0.5415	25.23 ± 2.75	23.53 ± 2.51	0.078
FBG (mg/dl)	166.23 ± 57.16	167.85 ± 57.91	0.9363	171.77 ± 51.16	141.92 ± 27.52	0.061
HbA1c (%)	7.30 ± 0.72	8.05 ± 1.08	0.0266	7.81 ± 0.83	7.45 ± 1.23	0.227
CAVI	9.46 ± 1.12	9.57 ± 0.80	0.6892	9.58 ± 0.82	8.98 ± 0.82	0.044
after 6 months						
ΔBW	-0.67 ± 3.08	+0.66 ± 1.90	0.1687	-0.56 ± 1.49	+1.05 ± 1.59	0.002
ΔBMI	-0.22 ± 1.11	+0.27 ± 0.73	0.1687	-0.20 ± 0.51	+0.43 ± 0.64	0.002
ΔFBG	-6.95 ± 58.22	+7.69 ± 70.76	0.5114	+27.14 ± 65.34	-5.77 ± 34.68	0.103
ΔHbA1c	+0.22 ± 0.67	+0.28 ± 0.66	0.8058	+0.20 ± 0.54	+0.00 ± 0.88	0.558
ΔCAVI	+0.11 ± 0.77	-0.08 ± 0.67	0.5542	+0.03 ± 0.65	+0.25 ± 0.56	0.314

Table 3: Comparison between male and female in each group

Data are presented as mean ± SD. Δ denotes the difference between the value at baseline and that after 6 months. Abbreviations are as in Table 1.

inactivating acetyl-CoA carboxylase (ACC) [25], which may improve liver function. Since C_{max} and AUC_{0-48} of metformin 500 mg are much higher than those of metformin 250 mg, metformin 500 mg once daily may have more potent effect on liver function compared with metformin 250 mg twice daily.

There are two limitations to the present study. The study duration was only 6 months. Thus, the long-term efficacy and safety of metformin 500 mg once daily is still unclear. Further investigation with longer evaluations may be necessary. However, we were able to show that metformin 500 mg once daily does not deteriorate blood glucose control, lipid metabolism, or arterial stiffness for at least 6 months. Another limitation is that we did not evaluate microvascular complications. Microvascular complications are as important as macrovascular complications in diabetic patients. Therefore, investigation of the progression of microvascular complications may be necessary. However, HbA1c was almost unchanged in this study. Since diabetic microvascular complications are strongly associated with HbA1c [26], we speculate that microvascular complications might not be different between two groups.

In summary, switching from metformin 250 mg twice daily to metformin 500 mg once daily did not deteriorate blood glucose control or arterial stiffness. Furthermore, no adverse effects including lactic acidosis were observed associated with this switch. These results suggest that metformin 500 mg once daily is safe and has the same efficacy compared with metformin 250mg twice daily.

Disclosure

Potential conflicts of interest with any of the authors: None

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