

Different daily glycemic profiles after switching from once-daily alogliptin plus twice-daily metformin to their once-daily fixed-dose combination in Japanese type 2 diabetic patients

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Abstract. The aim of this study was to investigate whether daily glycemic profiles and treatment satisfaction would be changed after switching from once-daily 25-mg alogliptin plus twice-daily 250-mg metformin to the fixed-dose combination of 25-mg alogliptin and 500-mg metformin once daily in type 2 diabetic patients. Twenty adult Japanese type 2 diabetic patients in whom once-daily 25-mg alogliptin plus twice-daily 250-mg metformin were switched to the fixed-dose combination of 25-mg alogliptin and 500-mg metformin once daily participated. Before and one month after the switch, participants were asked to perform one day of seven-point self-monitoring of blood glucose (SMBG), to wear a sensor of flash glucose monitoring for up to 14 days, and to respond to a questionnaire for treatment satisfaction. As a result, the SMBG profiles were significantly changed after the switch ($p = 0.021$); blood glucose levels 2 hours after breakfast were significantly elevated ($p = 0.022$), whereas those 2 hours after lunch were significantly reduced ($p = 0.036$). The flash glucose monitoring also demonstrated a significant change of daily glucose profiles ($p < 0.001$). The risk of glucose levels <80 mg/dL were decreased from evening to morning, while the risk of glucose levels ≥ 140 mg/dL were increased. Mean 24-hour glucose values were increased by 5 mg/dL on average ($p < 0.001$). Treatment satisfaction was significantly improved after the switch ($p < 0.001$). In conclusion, daily glycemic profiles were significantly changed after switching from once-daily 25-mg alogliptin plus twice-daily 250-mg metformin to the once-daily fixed-dose combination in Japanese type 2 diabetic patients. Treatment satisfaction was significantly improved after the switch.

Key words: Fixed-dose combination, Alogliptin, Once-daily metformin, Self-monitoring of blood glucose, Flash glucose monitoring

COMBINATION THERAPY of more than one oral antidiabetic agent is often required for type 2 diabetic patients to achieve optimal glycemic control [1]. On the other hand, prescribing multiple agents could lower patients' treatment satisfaction and medication adherence [2-4]. The introduction of fixed-dose combinations can reduce the number of tablets, which will improve treatment satisfaction and medication adherence [2-4].

Recently, the fixed-dose combination tablet of alogliptin 25 mg and metformin 500 mg has become clinically available in Japan. The tablet is developed to be taken

once daily, whereas metformin is long recommended in Japan to be administrated two or three times a day. In patients taking 25-mg/day alogliptin plus 500-mg/day metformin, the switch to the fixed-dose combination therefore means the decrease not only in tablet number but also in frequency, which is expected to further lessen the treatment burden [5].

The glucose-lowering effect of once-daily metformin plus alogliptin in Japanese type 2 diabetic patients was previously reported by a phase III clinical trial [5]. The study compared hemoglobin A1c levels between once-daily 500-mg and twice-daily 250-mg metformin as an add-on to once-daily 25-mg alogliptin, and demonstrated the non-inferiority of the former to the latter in hemoglobin A1c levels. The difference of hemoglobin A1c levels (the former minus the latter) was reported to be +0.11% [95% confidence interval: -0.026 to 0.247%], being

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lower than the prespecified non-inferiority margin of +0.3% [5].

However, the difference of daily glycemic profiles between the two treatments was not assessed in the trial, and remained so far unrevealed. The aim of the current study was to investigate whether daily glycemic profiles would be changed after switching from once-daily 25-mg alogliptin and twice-daily 250-mg metformin to the fixed-dose combination of 25-mg alogliptin and 500-mg metformin once daily, with the use of self-monitoring of blood glucose (SMBG) and the flash glucose monitoring system. The current study also examined the change of the treatment satisfaction after the switch.

Materials and Methods

The current prospective observational study was conducted between January and July 2018, and a total of 20 adult Japanese type 2 diabetic patients in whom alogliptin 25 mg once daily plus metformin 250 mg twice daily were switched to the fixed-dose combination of alogliptin 25 mg and metformin 500 mg once daily participated. All participants were treated in Shiraiwa Medical Clinic, Kashiwara City, Osaka, Japan. The current study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committees of Osaka University Hospital. Informed consent was obtained from every participant. The inclusion criteria were as follows: 1) glycemic control was stable under the treatment with once-daily 25-mg alogliptin plus twice-daily 250-mg metformin, and 2) once-daily 25-mg alogliptin plus twice-daily 250-mg metformin was planned in clinical practice to be switched to the fixed-dose combination of 25-mg alogliptin and 500-mg metformin once daily. The exclusion criteria were as follows: 1) other medications were planned to be changed during the study period, 2) the fixed-dose combination was planned to be stopped due to surgery or contrast agent use during the study period, 3) patients were not expected to live a regular life with good adherence to diet or exercise therapy, and 4) poor medication adherence was evident.

Before switching to the fixed-dose combination of 25-mg alogliptin and 500-mg metformin once daily (*i.e.*, while taking alogliptin 25 mg once daily plus metformin 250 mg twice daily), participants were asked to perform one day of seven-point SMBG (before and 2 hours after meals and before sleep) using NIPROCAREFAST Link® (Nipro Corporation, Osaka, Japan), and to wear a sensor of FreeStyle Libre Pro™ Flash Glucose Monitoring System (Abbott Japan Co., Ltd., Tokyo, Japan) on the back of an upper arm for up to 14 days. To minimize the invasiveness of the study, we asked the study participants to perform seven-point SMBG for just one day. The day

when SMBG was performed was at the patients' discretion. We just encouraged the patients to perform SMBG on the day when they did not have any special events and when they were expected to live a regular life and to complete perform SMBG without difficulty. The pre-switch SMBG data collected in the current study were therefore for only one day.

The study participants also responded to a questionnaire for oral medication satisfaction [6]. The details of the questionnaire and its validation were reported previously [6]. Briefly, the questionnaire contains a total of 10 statements related to treatment satisfaction and asks to what extent a respondent agrees with each statement, based on a 7-point Likert scale, ranging from 0, which corresponds to "strongly disagree," to 6, which corresponds to "strongly agree." The 10 statements consist of 6 positively and 4 negatively worded ones. The questionnaire was originally developed under the concept that all items would, either positively or negatively, reflect a single underlying factor, namely satisfaction with oral treatment, and the calculation of a total score was expected. Validity was confirmed using a factor analysis with a varimax rotation in 1,071 patients with lifestyle-related chronic diseases [6]. Consequently, the one-factor structure explained 42% of variance, and all 10 items had >0.40 of the absolute loading values. Their communalities were ranged from 0.223 to 0.598. The item-total correlations were ranged from 0.490 to 0.665, and Cronbach's α was as high as 0.862, which was never exceeded if any item was deleted. These findings indicated a high internal consistency, suggesting that all 6 positive and 4 negative items related to one underlying factor, and a total satisfaction score was developed by summing the scores from all 10 items, with the rating of the 4 negatively worded items reversed. The possible range in total score was between 0 (no satisfaction) and 60 (full satisfaction) [6]. Note that the score was highly correlated with the factor score ($r = 0.975$). The construct validity was confirmed by the fact that the frequency of dosing were negatively associated with the total satisfaction score [6], and was also suggested by our longitudinal study showing that the total satisfaction score was increased after readjusting oral medication regimens with the dosing frequency decreased and the number of pills reduced, based on the patients' wishes [7].

One month after switching to the fixed-dose combination, the participants were again asked to perform one day of seven-point SMBG, to wear a sensor of the flash glucose monitoring for up to 14 days, and to respond to the questionnaire for treatment satisfaction. Note that the post-switch SMBG was also performed for just one day. These data were statistically compared with those obtained before the switch.

Before the switch, once-daily alogliptin was taken after breakfast, and twice-daily metformin was taken after breakfast and dinner. After the switch, the fixed-dose combination tablet of 25-mg alogliptin and 500-mg metformin was taken after breakfast.

Statistical analysis

Data are given as means and standard deviation for continuous variables and as percentages for discrete variables, if not otherwise mentioned. A $p < 0.05$ was considered statistically significant. The change of seven-point daily blood glucose profiles after the switch were tested by the analysis of variance for the linear mixed model. The change of blood glucose levels at each time point was examined by the paired t test. Note that the Kolmogorov-Smirnov normality test showed that the distribution of the blood glucose levels were not significantly different from the normal distribution (all $p > 0.05$). On the other hand, some of the treatment satisfaction scores had a distribution significantly different from the normal one, and the Wilcoxon signed-rank test, instead of the paired t test, was performed to assess the change of the treatment satisfaction after the switch. The impact of sulfonylurea use on the change of blood glucose levels was evaluated by the interaction term in the linear mixed model, based on the following hypothesis. In contrast to alogliptin and metformin, sulfonylureas have an evident risk of hypoglycemia. If the current switch (*i.e.*, changing the pattern of metformin administration) strengthened the glucose-lowering effect at some specific time points, blood glucose levels might be lowered to the level of hypoglycemia at the time points in sulfonylurea users, whereas blood glucose levels would never be lowered to such extent in patients not receiving sulfonylureas. On the other hand, the current switch might weaken the glucose-lowering effect at other specific time points, which might relieve sulfonylurea users from the risk of hypoglycemia at the time points, whereas in patients not receiving sulfonylureas, the risk of hypoglycemia would remain as low as before the switch. We therefore hypothesized that blood glucose levels might be changed differently between patients with and without sulfonylureas, and that was why we performed this supplementary analysis. The change of mean 24-hour glucose levels measured by the flash glucose monitoring were assessed by the analysis of variance for the linear mixed model. The change of the hourly proportion of glucose levels <80 mg/dL and ≥ 140 mg/dL was investigated using the generalized linear mixed model with a logit-link function. The hourly proportion was investigated using a simple moving average with a 3-hour tolerance. All statistical analyses were performed with R version 3.1.0 (R Development Core Team, Vienna, Austria).

Table 1 Clinical characteristics of study population

<i>n</i>	20
Male sex	9 (45%)
Age (years)	64 \pm 7
Duration of diabetes (years)	9 \pm 6
Body mass index (kg/m ²)	24.5 \pm 3.1
Hemoglobin A1c (%)	6.8 \pm 0.3
Sulfonylurea use	8 (40%)
Use of other hypoglycemic agents	0 (0%)
Hypertension	11 (55%)
Dyslipidemia	18 (90%)

Results

Table 1 summarizes baseline clinical characteristics of the study population. Mean duration of diabetes was 9 \pm 6 years, and mean hemoglobin A1c levels were 6.8 \pm 0.3%. Forty percent of the patients took sulfonylureas. None used other hypoglycemic agents than alogliptin, metformin, and sulfonylureas.

The SMBG findings are shown in Fig. 1. SMBG was not performed as instructed in one patient and therefore the SMBG data were analyzed in the remaining 19 of the 20 study patients. The analysis of variance demonstrated that the daily blood glucose levels were significantly changed after the switch ($p = 0.021$); blood glucose levels 2 hours after breakfast were significantly elevated ($p = 0.022$), whereas those 2 hours after lunch were significantly reduced ($p = 0.036$) (Fig. 1a). There was no significant difference between patients with sulfonylurea use and those without it (Fig. 1b). Fig. 2a demonstrates 24-hour glucose levels measured by the flash glucose monitoring, indicating that after the switch, glucose levels from evening to morning tended to be elevated whereas those early in the afternoon were on a downward trend. The analysis of variance showed that glucose levels were significantly changed after the switch ($p < 0.001$). The risk of glucose levels <80 mg/dL was decreased from evening to morning (Fig. 2b), when the risk of glucose levels ≥ 140 mg/dL was increased (Fig. 2c). On the whole, mean 24-hour glucose values were increased from 137 [95% confidence interval: 131 to 145] mg/dL to 143 [136 to 150] mg/dL on average after the switch (difference: +5 [3 to 7] mg/dL, $p < 0.001$), and the 24-h area under the glucose curve (≥ 0 mg/dL) was significantly increased from 3,306 [3,141 to 3,470] mg·h/dL to 3,434 [3,269 to 3,599] mg·h/dL (difference: +128 [82 to 174] mg·h/dL, $p < 0.001$). The standard deviation of the values was 34 [95% confidence interval: 30 to 38] mg/dL before the switch and 33 [29 to 37]

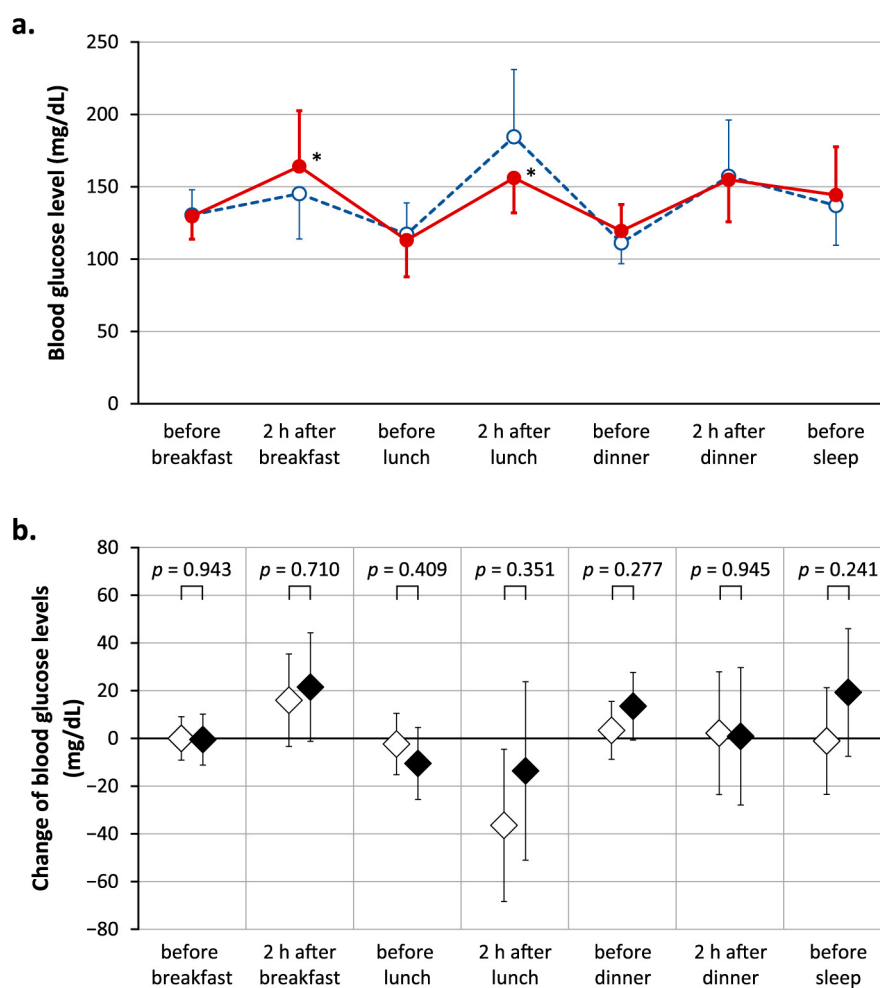


Fig. 1 Self-monitoring of blood glucose

a: Seven-point blood glucose levels before and after the switch to the fixed-dose combination. Data are means and standard deviation. Blank circles with dotted lines (blue) represent blood glucose levels before the switch, whereas filled circles with solid lines (red) represent those after the switch. * $p < 0.05$. b: The change of blood glucose levels after the switch in patients without sulfonylurea use (blank diamonds) and those with sulfonylurea use (filled diamonds). Error bars represent 95% confidence intervals. P values demonstrated are for interaction (*i.e.*, difference between patients with and without sulfonylurea use).

mg/dL after the switch (difference: -1 [-2 to 0] mg/dL, $p = 0.217$). The proportion of glucose < 80 mg/dL was decreased from 0.9% [0.4 to 1.7%] to 0.4% [0.2 to 0.8%] (odds ratio: 0.45 [0.38 to 0.52], $p < 0.001$), whereas that of glucose ≥ 140 mg/dL was increased from 39% [31 to 47%] to 44% [36 to 52%] (odds ratio: 1.23 [1.18 to 1.28], $p < 0.001$). The 24-h area under the glucose curve (≥ 140 mg/dL) was calculated to be significantly increased from 346 [248 to 443] mg·h/dL to 406 [308 to 503] mg·h/dL (difference: $+60$ [30 to 90] mg/dL, $p < 0.001$), whereas the 24-h area over the glucose curve (< 80 mg/dL) was significantly decreased from 4 [2 to 7] mg·h/dL to 2 [0 to 4] mg·h/dL (difference: -3 [-5 to -1] mg/dL, $p = 0.008$).

Treatment satisfaction was significantly improved after the switch, especially in regard to convenience and adherence (Table 2). The total satisfaction score was ele-

vated from 39 ± 11 to 50 ± 7 ($p < 0.001$). Body weight was 65.5 ± 11.1 kg before the switch and 65.5 ± 11.1 kg one month after the switch ($p = 0.946$), whereas hemoglobin A1c levels were $6.8 \pm 0.3\%$ before the switch and $6.8 \pm 0.4\%$ one month after the switch ($p = 0.359$). No remarkable adverse events were observed during the study.

Discussion

The current study demonstrated that daily glycemic profiles were significantly changed after switching to the fixed-dose combination of 25-mg alogliptin and 500-mg metformin once daily in Japanese type 2 diabetic patients who took alogliptin 25 mg once daily and metformin 250 mg twice daily. The SMBG findings indicated that blood glucose levels 2 hours after breakfast were elevated

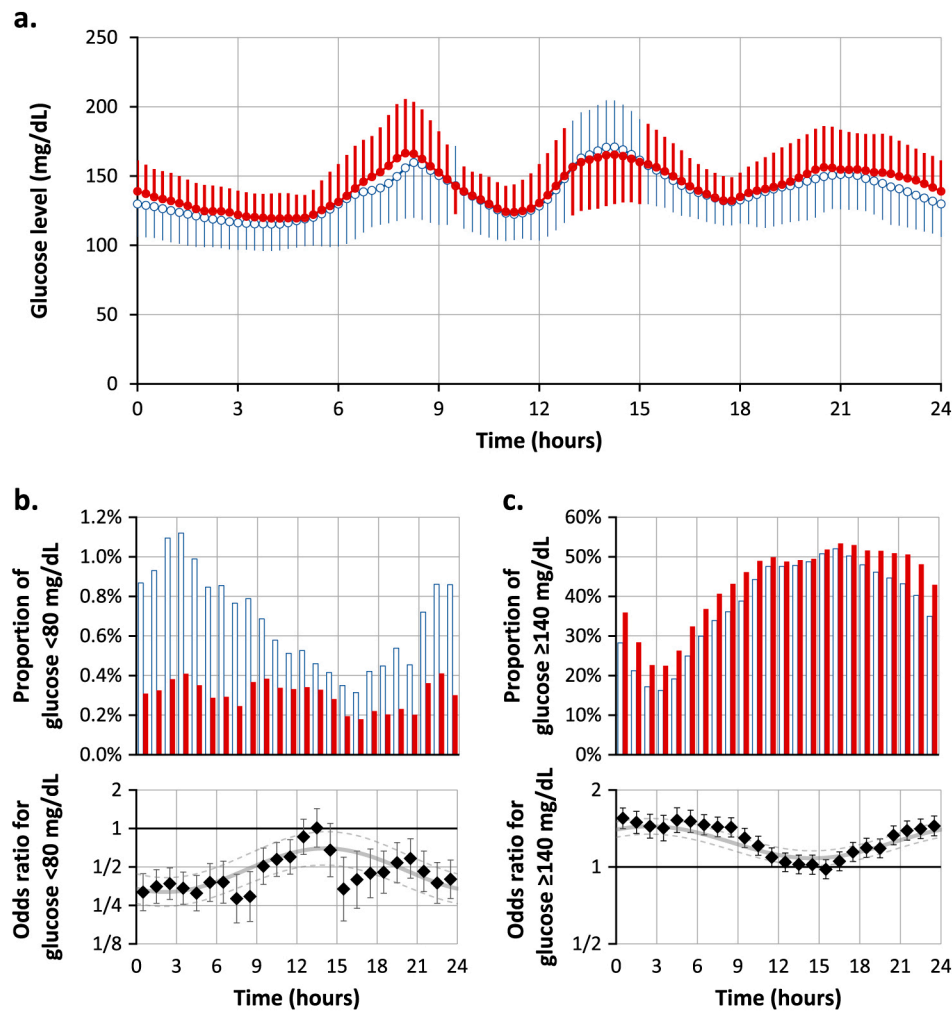


Fig. 2 Flash glucose monitoring

a: Data are the mean and standard deviation of glucose levels measured by the flash glucose monitoring before and after the switch to the fixed-dose combination. Blank circles with thin lines (blue) represent glucose levels before the switch, whereas filled circles with bold lines (red) represent those after the switch. b: The hourly proportions of glucose levels <80 mg/dL in the flash glucose monitoring measurements (upper panel) and the odds ratios after *versus* before the switch (lower panel). Blank bars (blue) represent the proportions before the switch, whereas filled bars (red) represent those after the switch. Odds ratios are presented with 95% confidence intervals. c: The hourly proportions of glucose levels ≥140 mg/dL in the flash glucose monitoring measurements (upper panel) and the odds ratio after *versus* before the switch (lower panel). Blank bars (blue) represent the proportions before the switch, whereas filled bars (red) represent those after the switch. Odds ratios are presented with 95% confidence intervals.

whereas those 2 hours after lunch were reduced. The flash glucose monitoring demonstrated that the risk of glucose levels <80 mg/dL were decreased from evening to morning, when the risk of glucose levels ≥140 mg/dL were increased. On the whole, mean 24-hour glucose values were slightly but significantly increased. Treatment satisfaction was significantly improved after the switch.

Since metformin 500 mg is recommended to be administrated twice daily in Japan, the switch to the fixed-dose combination in patients treated with 25-mg alogliptin plus 500-mg metformin means that the administration of metformin is changed from twice to once

daily. The decrease of dose frequency is expected to promote treatment satisfaction and medication adherence. On the other hand, it might produce a different effect on controlling daily glycemic profiles.

The current study demonstrated that daily glycemic profiles were significantly changed after the switch. The change would be explained by a pharmacokinetic difference between once-daily and twice-daily administration of metformin. The plasma concentration of metformin reaches a maximum about 3 hours after the oral administration, and is thereafter lowered with 4 to 5 hours of the biological half-life [8]. Compared to the twice-daily administration of 250-mg metformin (after breakfast and

Table 2 Treatment satisfaction

	Before switch	After switch	<i>p</i> value
1. Convenience	4 (3–5)	6 (5–6)	0.001
2. Encouragement of adherence	4 (3–6)	6 (5–6)	0.001
3. Control over diseases	4 (3–5)	4 (3–5)	0.506
4. Feeling of healthiness	4 (2–5)	5 (4–6)	0.053
5. Troublesomeness	2 (1–3)	1 (0–1)	0.004
6. Fear of forgetting to take medicines	2 (1–5)	1 (0–1)	0.004
7. Suspicion about efficacy	2 (0–3)	2 (1–3)	0.799
8. Undesirably weakened disease awareness	1 (0–3)	1 (0–2)	0.012
9. Satisfaction	4 (3–5)	5 (5–6)	0.037
10. Hope for receiving the treatment	4 (3–5)	5 (4–6)	0.017
Total satisfaction score	38 (32–47)	52 (44–55)	0.001

Data are medians (interquartile range). Individual item scores of agreement were ranged from 0 (“strongly disagree”) to 6 (“strongly agree”). The total satisfaction score, with possible range between 0 and 60, was calculated by summing the scores of all 10 items, after the rating of the 4 negatively worded items (no. 5, 6, 7, and 8) reversed.

dinner), the once-daily administration of 500-mg metformin (after breakfast) would therefore bring a higher plasma concentration of metformin during daytime, but a lower concentration from evening to morning. The glycemic trend indicated by the flash glucose monitoring would reflect these pharmacokinetic characteristics. SMBG found that post-lunch blood glucose levels was lower after the switch, whereas post-breakfast blood glucose levels got higher. The trend was not significantly different between patients with and without sulfonylureas. One possible speculation would be that lower post-lunch blood glucose levels might reflect a greater glucose-lowering effect during daytime, whereas higher post-breakfast blood glucose levels suggest that metformin administrated after breakfast might be insufficient to manifest the post-breakfast glucose-lowering effect [9]; the effect might be inferior to that of half-dose metformin administrated last evening. However, these speculations did not answer why significant differences were observed only during postprandial periods and not during preprandial periods. Future well-designed larger studies comparing glucose-lowering effect between once-daily and twice-daily administration of metformin, especially using continuous glucose monitoring system, will be needed.

In clinical settings, daily glycemic profiles would vary from patient to patient. Switching to the fixed-dose combination (*i.e.*, administrating metformin once daily) would decrease the risk of nocturnal low glucose levels, and therefore would be beneficial for patients at risk of nocturnal hypoglycemia under the administration of twice-daily 250-mg metformin plus once-daily 25-mg

alogliptin. On the other hand, in patients demonstrating high nocturnal glucose levels, the switch might further deteriorate their nocturnal glycemic control. It would be better to note the possible pharmacokinetic difference between the fixed-dose combination and the original regimen, when the switch is planned.

The flash glucose monitoring showed that 24-h mean glucose values were increased with statistical significance. The increase might be again explained by the pharmacokinetic profiles of once-daily metformin. Once-daily administration of metformin would not keep a sufficiently high circulating concentration of metformin throughout 24 hours; the sufficient glucose-lowering effect might be achieved for a shorter time compared to its twice-daily administration. It is well known that hemoglobin A1c levels have a tight linear relationship with average blood glucose levels, and the linear regression equation is now available [10]. Based on the equation, the difference of hemoglobin A1c levels demonstrated in the previous phase III trial [5] corresponded to +3.2 [0.7 to 7.1] mg/dL of average glucose values, whereas the non-inferiority margin was equivalent to 8.6 mg/dL of average glucose values. The increase of mean glucose levels observed in the current study therefore seemed compatible to the previous finding, and might be within a clinically tolerable range, although the values were measured by the flash glucose monitoring, and not by continuous glucose monitoring or self-monitoring of capillary glucose.

The questionnaire survey in the current study demonstrated that treatment satisfaction was significantly improved after the switch, especially in regard to con-

venience and adherence. Adherence to medications is a key factor in the management of type 2 diabetes [11], and it is well known that treatment satisfaction is a major determinant of adherence [12]. The switch to the fixed-dose combination decreases not only the number of tablets but also the dose frequency, and both aspects would improve treatment satisfaction [2].

The current study had some limitations. First, the study was performed in a single-arm, observational fashion. In addition, the sample size was limited. Future randomized-controlled trials with larger sample size will be needed to validate the current findings. Second, pharmacokinetic profiles of the medications were not assessed, and therefore it remained unknown whether the current findings regarding daily glycemic profiles really came from the pharmacokinetic change. Third, the data on medication adherence were not collected in the current study. In addition, patients with evidently poor medication adherence were excluded in the current study, and therefore it remained unrevealed whether the switch to the fixed-dose combination would increase medication adherence, especially in patients with poor medication adherence. Fourth, other questionnaires of treatment satisfaction were not used. Fifth, the daily glycemic profiles were assessed by the flash glucose monitoring and not by

the continuous glucose monitoring. Furthermore, the meal time as well as daily activity during the flash glucose monitoring was not recorded, and therefore the analysis of glucose profiles with meal time synthesized was unable to be performed. Future studies collecting these data will be needed.

In conclusion, daily glycemic profiles were significantly changed after switching to the fixed-dose combination of 25-mg alogliptin and 500-mg metformin once daily in Japanese type 2 diabetic patients who took alogliptin 25 mg once daily and metformin 250 mg twice daily. Treatment satisfaction was significantly improved after the switch.

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