

Effect of Switching From an Anti-Diabetic Loose Dose Combination to a Fixed Dose Combination Regimen at Equivalent Dosage for 6 Months on Glycemic Control in Japanese Patients With Type 2 Diabetes: A Pilot Study

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Abstract

Background: Patients with type 2 diabetes mellitus often take multiple anti-diabetic drugs for a long period. Fixed dose combination (FDC) therapy is expected to improve drug adherence for patients with diabetes. The effect of switching from a loose dose combination (LDC) regimen to an FDC regimen at equivalent dosage on glycemic control has not been evaluated fully. Therefore, we investigated the effect of switching from LDC to FDC at equivalent dosage for 6 months on glycemic control in Japanese patients with type 2 diabetes.

Methods: Thirty-eight Japanese patients with type 2 diabetes who were taking anti-diabetic drugs including pioglitazone + metformin, pioglitazone + alogliptin, or pioglitazone + glimepiride were enrolled. These drugs were switched to an FDC of Metact[®], Liobel[®] or Sonias[®], respectively, at equivalent dosage. Other anti-diabetic drugs and units of insulin were not changed during the study if possible. HbA1c and body weight were measured 0, 2, 4 and 6 months after switching from an LDC to FDC. We also conducted a questionnaire survey 2 months after the start of the FDC regimen.

Results: HbA1c levels at 2, 4, and 6 months were not significantly changed compared with prior to switching from an LDC to FDC regimen. Moreover, 74.2% of patients considered decreasing the number of drugs to be “very good” or “good”.

Conclusion: HbA1c levels did not differ between patients receiving LDC and FDC therapy at equivalent dosage in this study.

Keywords: Fixed dose combination; Loose dose combination; Type 2 diabetes

Introduction

Patients with type 2 diabetes often take multiple anti-diabetic drugs for a long period. As they often have comorbidities such as hypertension and hyperlipidemia, they may take other drugs daily as well. Medication non-adherence is prevalent among patients with diabetes mellitus and is associated with adverse clinical outcomes such as increased risks for all-cause hospitalization and all-cause mortality [1]. Therefore, the maintenance of good long-term adherence is important for the treatment of diabetes. Good adherence may be difficult to obtain, particularly among patients with busy social lives.

Recently, we investigated how to improve the drug adherence of patients with type 2 diabetes who are taking alpha glucosidase inhibitors, glinides, and dipeptidyl peptidase-4 (DPP-4) inhibitors [2-4]. Fixed dose combination (FDC) therapy or a weekly DPP-4 inhibitor is expected to improve drug adherence for patients with diabetes [5, 6]. Many FDC regimens for hypertension are available in Japan, but only five for diabetes. In retrospective studies, switching from loose dose combination (LDC) therapy to FDC therapy improved adherence [7, 8]. In another retrospective study, the most recent HbA1c level of patients who took an FDC of DPP-4 inhibitor and metformin was lower than that of patients who took an LDC of DPP-4 inhibitor and metformin free form [9]. Glycemic control may be improved by increased drug adherence due to the administration of FDC therapy. However, the effect of switching from an LDC to an FDC at equivalent dosage on glycemic control has

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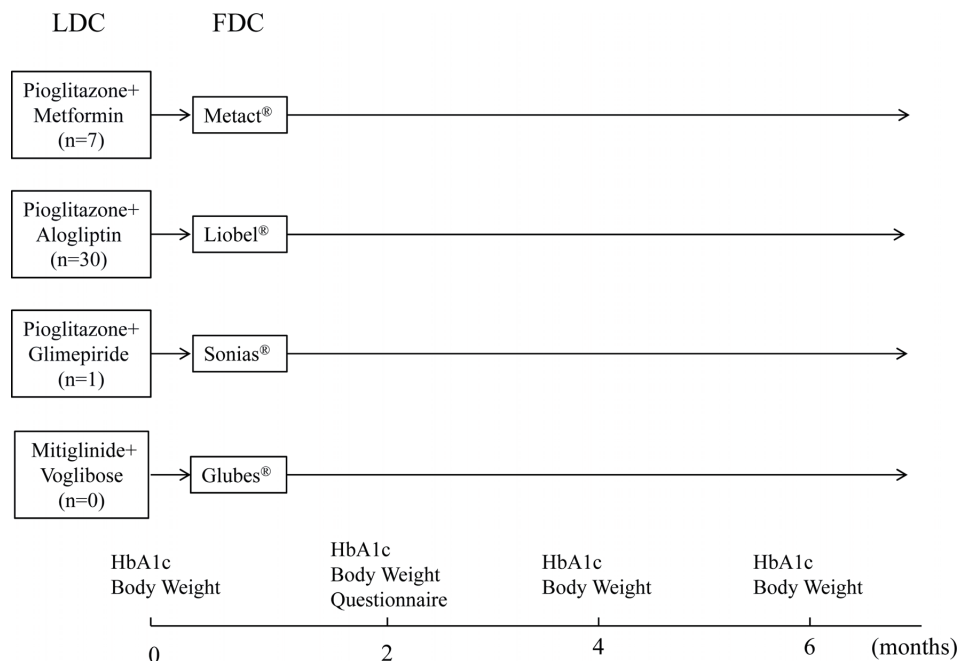


Figure 1. Study design. Thirty-eight Japanese patients with type 2 diabetes who were taking anti-diabetic drugs including LDC such as pioglitazone + metformin, pioglitazone + alogliptin, or pioglitazone + glimepiride were enrolled. These drugs were switched to an FDC of Metact®, Liobel® or Sonias®, respectively, at equivalent dosage. No patients in the study took mitiglinide + voglibose, which can be switched to Glubes®. HbA1c and body weight were measured 0, 2, 4 and 6 months after switching from an LDC to FDC. We also conducted a questionnaire survey 2 months after the start of the FDC regimen.

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Materials and Methods

This study was a prospective observational study to investigate the clinical effects of FDC therapy in patients with type 2 diabetes. After obtaining approval from the Institutional Ethics Review Committee of Yokohama City University, the objective of the study was explained to all subjects, and written informed consent was obtained prior to the start of the study. A total of 38 patients were recruited during the study registration period (from February 2013 to March 2016) and their data were analyzed in a pilot study (Figure 1).

Japanese patients with type 2 diabetes who were taking anti-diabetic drugs including pioglitazone + metformin, pioglitazone + alogliptin, pioglitazone + glimepiride, or mitiglinide + voglibose were enrolled between February 2013 and March 2016. The hospital or clinics that participated this study were Yokohama City University Hospital, Nagakura Clinic, Nakajima Naika Clinic, Oka Naika Clinic, Furuie Naika Clinic, IHI Yokohama Clinic, and Masumura Naika Clinic. Herein, a regimen comprising 15 mg of pioglitazone and 500 mg of metformin was switched to Metact® LD (FDC at equivalent doses of pioglitazone and metformin). Similarly, 30 mg of pioglitazone and 500 mg of metformin were switched with Metact® HD (FDC at equivalent doses of pioglitazone and metformin),

15 mg of pioglitazone and 25 mg of alogliptin were switched with Liobel® LD (FDC at equivalent doses of pioglitazone and alogliptin), 30 mg of pioglitazone and 25 mg of alogliptin were switched with Liobel® HD (FDC at equivalent doses of pioglitazone and alogliptin), 15 mg of pioglitazone and 1 mg of glimepiride were switched with Sonias® LD (FDC at equivalent doses of pioglitazone and glimepiride), 30 mg of pioglitazone and 1 mg of glimepiride were switched with Sonias® HD (FDC at equivalent doses of pioglitazone and glimepiride) and 10 mg of mitiglinide and 0.2 mg of voglibose were switched with Glubes® (FDC at equivalent doses of mitiglinide and voglibose). Other anti-diabetic drugs and units of insulin were not changed through the study if possible.

The HbA1c level and body weight were measured 0, 2, 4 and 6 months after switching from an LDC to FDC. We also conducted a questionnaire survey 2 months after the start of FDC. Question 1: How do you feel about the decrease in the number of drugs? Question 2: Has the number of medicine doses you have forgotten decreased? Question 3: How much of a benefit have you experienced in decreasing drug costs? Question 4: Do you feel there has been a change in your glycemic control? Question 5: Which do you prefer to take: FDC or LDC?

Data are expressed as the mean \pm standard error. SAS software (SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis. The HbA1c levels and body mass index (BMI) of patients were analyzed using a mixed model; we compared each value at 2, 4, and 6 months with that at 0 months and differences with P values less than 0.05 were considered significant.

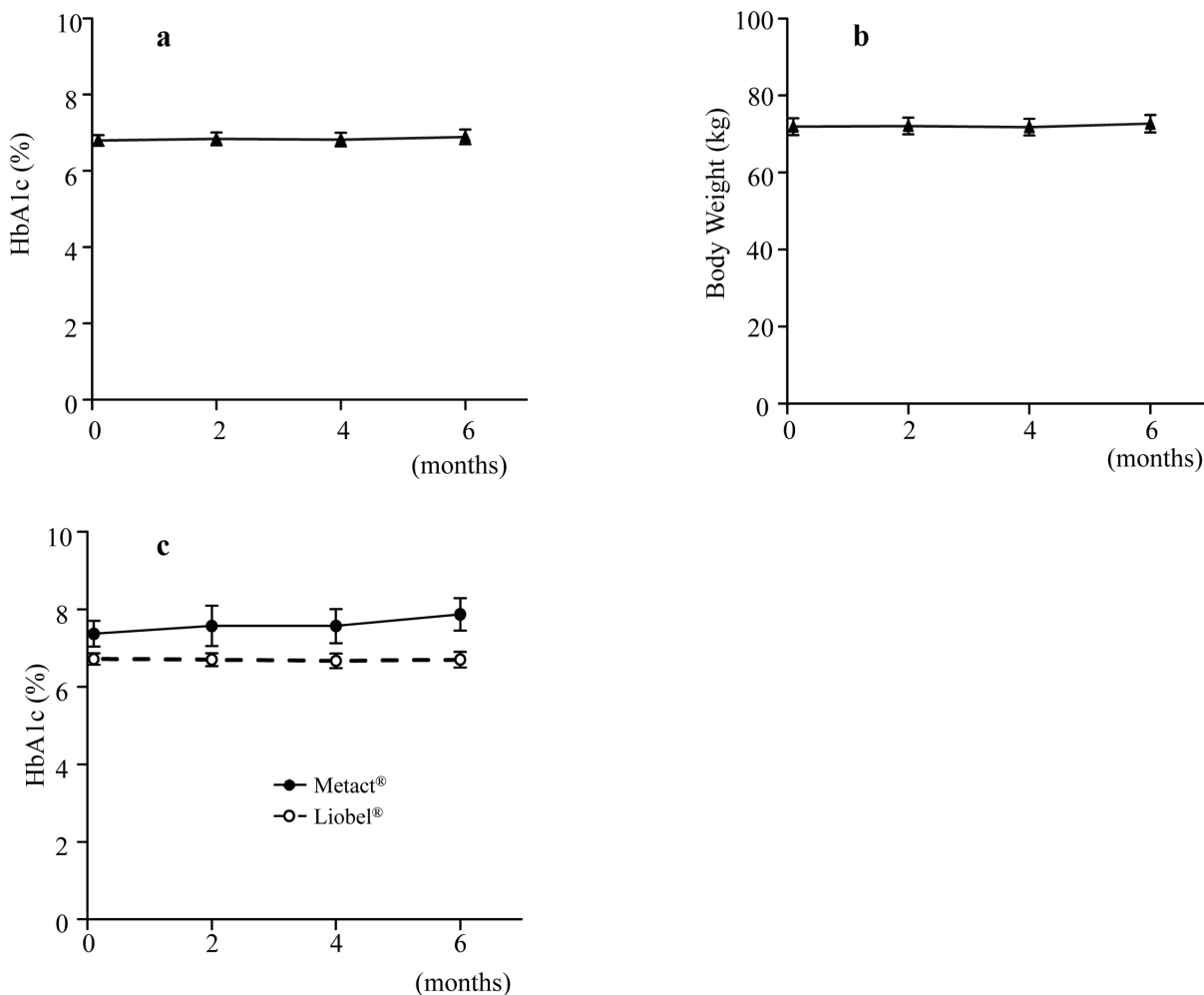


Figure 2. Changes in HbA1c and body weight after switching from an LDC to FDC. (a) HbA1c levels of all patients. (b) Body weight of all patients. (c) HbA1c levels of patients taking Metact® (FDC of pioglitazone and metformin, n = 7) or Liobel® (FDC of pioglitazone and alogliptin, n = 30).

Results

Baseline characteristics

A total of 38 patients (29 male and nine female) with a mean age of 63.0 ± 1.5 years and a mean body mass index (BMI) of 26.7 ± 2.7 kg/m² were enrolled. The mean HbA1c level was $6.8 \pm 0.1\%$, and the average duration of diabetes was 8.3 ± 0.8 years.

The number of types of all drugs taken was 5.3 ± 0.3 , and the number of all drugs taken was 8.1 ± 0.8 . The number of types of anti-diabetic drugs taken was 2.9 ± 0.1 , and the number of anti-diabetic drugs taken was 4.6 ± 0.8 .

Changes in HbA1c level and body weight

In this study, five patients took 15 mg of pioglitazone and 500 mg of metformin, which were switched to Metact® LD,

and two patients took 30 mg of pioglitazone and 500 mg of metformin, which were switched to Metact® HD. Nineteen patients took 15 mg of pioglitazone and 25 mg of alogliptin, which were switched to Liobel® LD, and 11 patients took 30 mg of pioglitazone and 25 mg of alogliptin, which were switched to Liobel® HD. One patient took 15 mg of pioglitazone and 1 mg of glimepiride, which were switched to Sonias® LD. No patients in the study took mitiglinide and voglibose, which can be switched to Glubes®. Five patients dropped out of the study. Two patients did not visit the hospital or clinic at 2 or 6 months, respectively. One patient had another anti-diabetic drug added to the regimen. One patient stopped taking Sonias® LD due to edema. One patient stopped taking Metact® HD because of the increasing drug cost (generics for pioglitazone and metformin are available in Japan).

As shown in Figure 2a and b, HbA1c levels and body weight were not significantly different at 2, 4, and 6 months compared to that at 0 months. As shown Figure 2c, HbA1c levels did not differ at 2, 4, and 6 months compared to that at 0 months in the Metact® (n = 7) group or Liobel® group (n

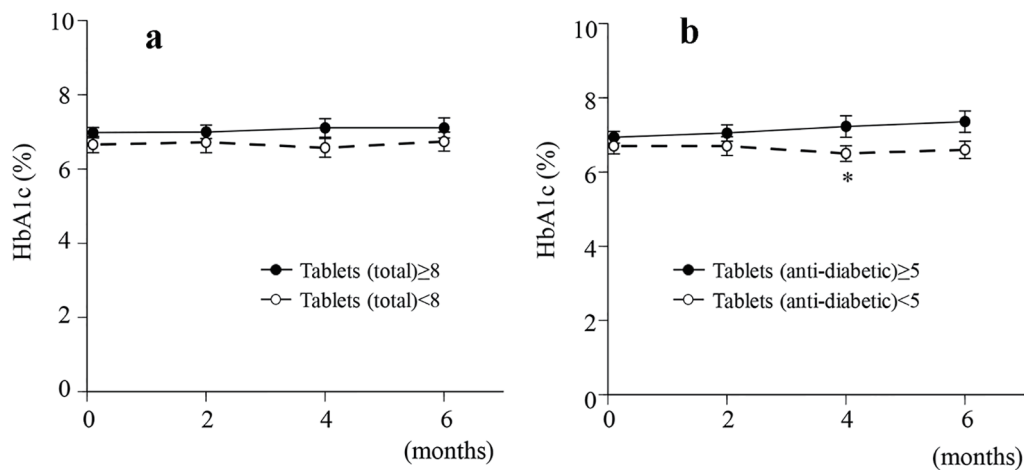


Figure 3. Changes in HbA1c after switching from an LDC to FDC. (a) HbA1c levels of patients taking more than eight tablets (n = 17) or less than eight tablets (n = 21) in total. (b) HbA1c levels of patients taking more than five anti-diabetic tablets (n = 16) or less than five anti-diabetic tablets (n = 22). *P < 0.05 vs. 0 months in each group.

= 30). As shown in Figure 3a, HbA1c levels were not different at 2, 4, and 6 months compared to that at 0 months in the group taking more than eight tablets in total (n = 17) and the group taking less than eight tablets in total (n = 21). As shown in Figure 3b, HbA1c levels were not different at 2, 4, and 6 months compared to that at 0 months in the group taking more than five anti-diabetic tablets (n = 16). In the group taking less than five anti-diabetic tablets (n = 22), the HbA1c levels were significantly decreased at 4 months compared to that at 0 months; however, the HbA1c levels were not different at 2 and 6 months compared to that at 0 months (Fig. 3b).

Questionnaire

With respect to question 1, 74.2% of subjects responded “very good” or “good” (Table 1). With respect to question 2, 54.8% selected “decreased” or “decreased a little”, but 45.2% of patients selected “not changed”. With respect to question 3, 38.7% of patients saw significant or modest benefits; however, 61.3% of patients saw “almost no benefit” or “no benefit or unchanged”. With respect to question 4, 42% of patients answered “improved” or “improved slightly”, but 54.8% of patients answered “not changed”. With respect to question 5, 54.8% of patients preferred to receive an FDC, and 41.9% of patients answered “either”.

Discussion

The most important finding in our study was the fact that the HbA1c level did not significantly differ after switching from an LDC to FDC at equivalent dosage.

In Japan, FDC for anti-diabetic drugs comprise combinations of pioglitazone + metformin, pioglitazone + glimepiride, pioglitazone + alogliptin, and voglibose + mitiglinide; recently, metformin + vildagliptin has become available as well. The

benefits of an FDC are 1) a decrease in the number of drugs, 2) decreased drug costs in most cases, and 3) an improvement in drug adherence due to 1) and 2). In fact, an FDC regimen was shown to improve medication adherence in a meta-analysis [10]. A 10% increase in adherence to anti-diabetic drugs is associated with a 0.1% decrease in HbA1c level [11]. In a retrospective study, patients with type 2 diabetes treated with FDC had a low rate of non-persistence [7]. Drug adherence was reported to increase when patients were switched from LDC therapy with pioglitazone and metformin to analogous FDC therapy [8]. It was reported that treatment with FDC was associated with lower costs and increased possibility of achieving the target HbA1c in a retrospective study [12]. Indeed, the HbA1c level of patients who took an FDC of DPP-4 inhibitor and metformin was lower than that of patients who took an LDC of DPP-4 inhibitor and metformin free form in the retrospective study [9]. However, whether switching from an anti-diabetic LDC to FDC regimen at equivalent dosages in patients with type 2 diabetes improves glycemic control remains poorly understood. We evaluated this prospective observational pilot study and HbA1c levels did not significantly differ after switching from an LDC to FDC at equivalent dosage. HbA1c levels were not different at 2, 4, and 6 months compared to that at 0 months in both the group taking more than eight tablets and the group taking less than eight tablets in total. HbA1c levels were not different at 2, 4, 6 months compared to that at 0 months in the group taking more than five anti-diabetic tablets. In the group taking less than five anti-diabetic tablets, HbA1c levels were significantly decreased at 4 months compared to that at 0 months; however, HbA1c levels were not different at 2 and 6 months compared to that at 0 months. When the number of anti-diabetic drugs taken is low, switching from an LDC to FDC regimen may be effective; however, this effect is limited.

As the mean number of all drugs taken was 8.1 ± 0.8 , the effect of switching from an LDC to FDC regimen on drug adherence and glycemic control by decreasing the number of

Table 1. Questionnaire Survey

Q1: How do you feel about the decrease in the number of drugs?					
Answer	Very good	Good	Not changed	Not good	Bad
n (%)	7 (22.6)	16 (51.6)	8 (25.8)	0 (0.0)	0 (0.0)
Q2: Has the number of medicine doses you have forgotten decreased?					
Answer	Decreased	Decreased a little	Not changed	Increased a little	Increased
n (%)	13 (41.9)	4 (12.9)	14 (45.2)	0 (0.0)	0 (0.0)
Q3: How much of a benefit have you experienced in decreasing drug costs?					
Answer	Significant benefit	Modest benefit	Almost no benefit	No benefit or unchanged	
n (%)	1 (3.2)	11 (35.5)	7 (22.6)	12(38.7)	
Q4: Do you feel there has been a change in your glycemetic control?					
Answer	Improved	Improved slightly	Not changed	Worsen slightly	Worsen
n (%)	6 (19.4)	7 (22.6)	17 (54.8)	1 (3.2)	0 (0.0)
Q5: Which do you prefer to take: FDC or LDC?					
Answer	LDC	FDC	Either		
n (%)	1 (3.2)	17 (54.8)	13 (41.9)		

drugs might be small. On the questionnaire, many patients indicated that decreasing the number of drugs is preferable; however, the effects of switching from an LDC to FDC regimen on the number of forgotten doses of medicine and on costs are limited. Therefore, 41.9% of patients said either FDC or LDC would be best. We would like to evaluate this switching effect in patients who are taking two or three anti-diabetic drugs.

The present study had several limitations. As the number of subjects in this study was small and the term of the study was short, larger-scale and longer-term studies are needed in the future. We also would like to evaluate adherence after switching from an LDC to FDC in a further study.

In conclusion, many patients felt positively about decreasing the number of drugs they took, and HbA1c levels did not differ after switching from an LDC to FDC at an equivalent dosage in this study.

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Conflicts of Interest

Yasuo Terauchi received honoraria for lectures from MSD; Ono Pharmaceutical Co. Ltd; Boehringer Ingelheim GmbH; Takeda Pharmaceutical Company Ltd; Tanabe-Mitsubishi Pharma; Daiichi-Sankyo Company Ltd; Sanwa Kagaku Kenkyusho Co., Ltd; Novo Nordisk Pharma Ltd; Eli Lilly and Company; Sanofi; DaiNippon-Sumitomo; Shionogi & Co., Ltd; Bayer Yakuhin Ltd; Astellas Pharma Inc.; and Astra Zeneca and ob-

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