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Research Article
Effects of Long-term Treatment of Linagliptin on Glycemic Control in Japanese Patients with Type 2 Diabetes

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Abstract

Background and Objective: Dipeptidyl peptidase-4 (DPP-4) inhibitors contribute to glycemic control in diabetes patients. However, each DPP-4 inhibitor differs in effects on glycemic control when treated for longterm. In this study, the effects of a long-term treated with linagliptin on glycemic control and serum lipids were investigated. **Materials and Methods:** Linagliptin (5 mg day^{-1}) was administered to 25 type 2 diabetes patients for 18 months and assessed for its effects on hemoglobin A1c (HbA1c) and serum lipids. The two-side paired t-test and Dunett's *post hoc* test were used. **Results:** Three months after the start of linagliptin treatment, the HbA1c of the 13 patients was significantly lowered ($p<0.01$) and its effect continued for 18 months. In addition, serum total cholesterol and LDL cholesterol of the patients was also improved. On the other hand, HbA1c significantly increased in the12 patients from 6 months of linagliptin treatment ($p<0.05$) and linagliptin had no effect on the serum lipids. It was found that the HbA1c in patients whose HbA1c decreased with linagliptin was significantly high before treatment compared to the patients whose HbA1c increased after treatment($p<0.01$). Furthermore, the effects of linagliptin treatment on HbA1c was correlated with baseline HbA1c levels before treatment. **Conclusion:** About 18 month treatment with linagliptin significantly improved the glycemic control and serum lipids of diabetic patients with high HbA1c before treatment, whereas those parameters may not be improved in patients with low HbA1c.

Key words: Dipeptidyl peptidase-4 inhibitor, hemoglobin A1c, low density lipoprotein cholesterol, glycemic control, diabetes patients

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

According to National Diabetes Statistics Report from the Centers for Disease Control and Prevention in the United States (National Diabetes Statistics Report, April 2017), 9% (30.3 million) of the US population is diabetic and 34% (84.1 million) is pre-diabetic, as of 2015[1].

In Japan, it was estimated, in 2017, that diabetic patients and persons strongly suspected to have diabetes, i.e., about 10 million in number, account for 12% of the population (2017 National Health and Nutrition Survey, Ministry of Health, Labour and Welfare, Japan, September, 2017)[2]. These numbers appear to continue to increase, consistent with the trend worldwide. With the increase in the diabetic patient population, a wide variety of hypoglycemic agents with diverse mechanisms of action has been developed. Diabetes mellitus, especially a persistent hyperglycemic state, is associated with a high risk of development of atherosclerosis (myocardial infarction)[3]. Therefore, among the important attributes required of drugs used to treat diabetes is their ability to provide sustained and stable glycemic control and produce a sustained decrease of the HbA1c values, even during long-term treatment.

The objective of this study was to clarify the stability of blood glucose control in patients receiving long-term treatment with linagliptin, an inhibitor of DPP-4.

Favorable clinical results have been reported in regard to glycemic control by DPP-4 inhibitors for type 2 diabetes[4,5]. DPP-4 inhibitors have been expected to promote insulin secretion through increasing the amount of one of the incretins, active GLP-1 and on the other hand, the possibility has also been suggested that DPP-4 inhibition has effects other than on the blood glucose (BG) level, i.e., extra pancreatic effects. For example, it had been reported that long-term treatment of the DPP-4 inhibitor alogliptin to mice raised on a high-lipid diet improved atherosclerosis[6] and that the DPP-4 inhibitor teneligliptin improved blood lipids in a rat model of diabetes and improved both vascular endothelial function and insulin resistance in a rat model of metabolic syndrome[7,8]. The possibility that DPP-4 inhibitors have a beneficial effect on lipid metabolism and insulin resistance clinically as well had been suggested[9,10].

However, it had been reported in regard to long-term DPP-4 inhibitor treatment that alogliptin maintained a glycemic control ameliorating action for 2 years[11], whereas in patients given sitagliptin long-term its HbA1c-lowering action may have diminished within 6 months[12]. In other words, the possibility had been suggested that individual DPP-4 inhibitors have differing actions during long-term treatment.

In this study, DPP-4 inhibitor linagliptin was administered to Japanese type 2 diabetes patients for 18 months and investigated for its effects on glycemic control and serum lipids.

MATERIALS AND METHODS

Study design: This was a retrospective non-randomized study. The physician in charge explained the purpose of the trial to the patients who participated in the trial and confirmed their consent to participate. This clinical trial was officially registered as an open-label trial (ID: UMIN00018652). This study was conducted between January, 2016 and February, 2017.

Patient characteristics and medications are shown in Table 1.

Linagliptin (5 mg day^{-1} q.d.) was administered orally once in the morning for 18 months. A casual blood specimen was collected in the morning before treatment and at 1, 3, 6, 9, 12 and 18 months after the start of treatment and the serum obtained was used as the specimen to measure blood biochemistry parameters.

Blood analyses: The BG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) were measured. The measurements were outsourced to the Handa Medical Association Health Center (Aichi, Japan), which used an auto analyzer (JCA-BM8000 series, JAOL, Tokyo, Japan) to make them. An automated high-performance liquid chromatograph (HLC-723GX, Tosoh Corporation, Tokyo, Japan) was used to measure HbA1c.

Table 1: Characteristics of patients enrolled in the study

Number of patients	25
Male/female	13/12
Age (years)	66.0±12
Duration of diabetes (years)	6.2±5.1
Concomitant medication	
Therapy for diabetes (n)	
None	4
Biguanide	7
Sulfonylurea	3
Alpha-glucosidase inhibitor	11
Thiazolidinedione	8
Lipid-modifying agents	17

Data are expressed as Mean±SD

Statistical analysis: The data were expressed as Mean±SD. Logarithmic values were used to statistically analyze the TG data. The two-sided paired t-test was used to detect the effect of the drug on HbA1c. Changes in BG and serum lipids after administration were analyzed by one-way analysis of variance followed by Dunnett's *post hoc* test. p-value<0.05 was used as the criterion of statistical significance. Correlation analysis was done with Pearson (two-tailed).

RESULTS

The patients were divided to two groups according to whether linagliptin treatment had resulted in a decrease in their HbA1c level and then analyzed the results of the trial.

In the group of patients whose HbA1c level had decreased in response to linagliptin treatment the HbA1c level before treatment was 7.8±1.8%. The HbA1c level of this group had decreased significantly from 3 months onward after the start of linagliptin treatment and this effect continued until 18 months (Fig. 1a). In the group whose HbA1c level had not decreased in response to linagliptin treatment the HbA1c level before treatment was 5.9±0.6%. The HbA1c level of this group did not decrease in response to linagliptin and after treatment for 6 months ($p<0.05$), 12 months ($p<0.01$) and 18 months ($p<0.01$), it had significant increased instead (Fig. 1b).

The results for the effect of linagliptin treatment on BG levels showed that the BG level of the patients whose HbA1c level had decreased in response to linagliptin treatment had begun to decrease at one month after the start of treatment and this action continued until 18 months after the start of treatment (Fig. 1c). By contrast, a decrease in BG was not seen in the patients whose HbA1c level did not decrease in response to linagliptin treatment (Fig. 1d).

The results for blood lipids showed that in the group whose HbA1c level had decreased the TC level began to decrease at 6 months and this effect continued until 18 months (Fig. 2a). By contrast, no decrease in TC was seen in the group of patients whose HbA1c level had not decreased (Fig. 2b). In the group whose HbA1c level had decreased, the same as seen in the changes in TC, a decrease in LDL-C level was seen at 6 months after the start of linagliptin administration and this effect continued until after 18 months

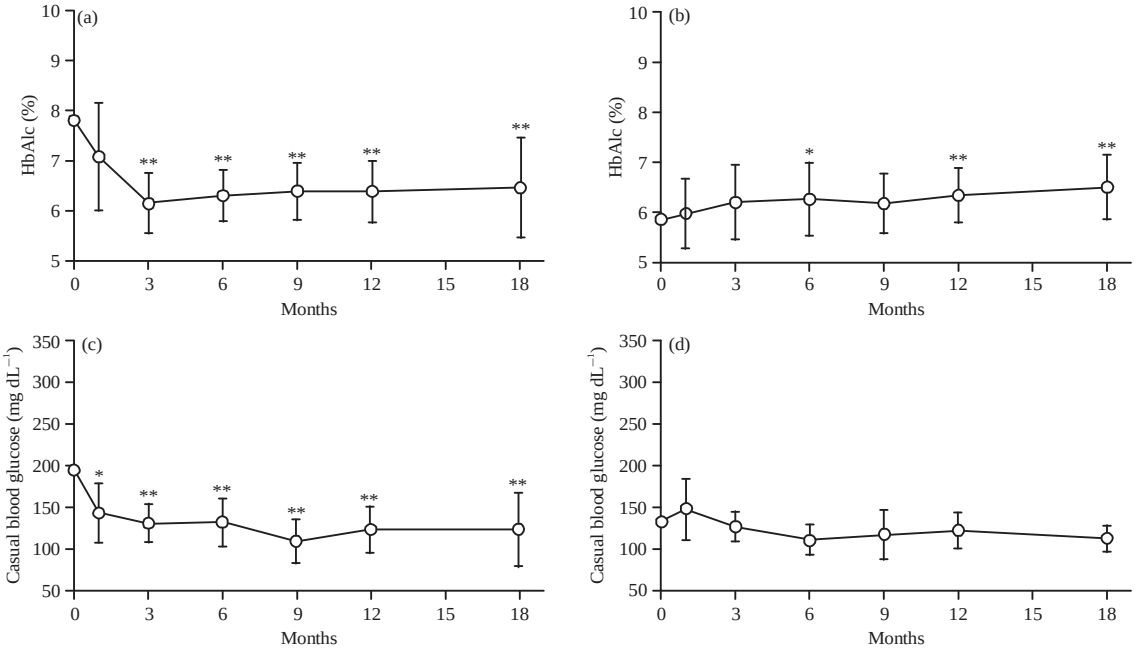

Fig. 1(a-d): Changes in HbA1c and blood glucose levels after linagliptin treatment

About 25 patients who were given linagliptin into a group of patients whose hemoglobin A1c (HbA1c) level had decreased 18 months after the start of linagliptin treatment (n = 13) and a group of patients whose HbA1c level had not (n = 12) and analyzed their data. (a) Changes in the HbA1c level of the patients whose HbA1c level had decreased in response to linagliptin treatment, (b) Changes in the HbA1c level of the patients whose HbA1c level had not decreased in response to linagliptin treatment, (c) Changes in the blood glucose (BG) level of the patients whose HbA1c level had decreased in response to linagliptin treatment (c, d) Changes in the BG level of the patients whose HbA1c level had not decreased in response to linagliptin treatment. Data are expressed as Mean±SD. **p<0.01, *p<0.05 vs. value before treatment

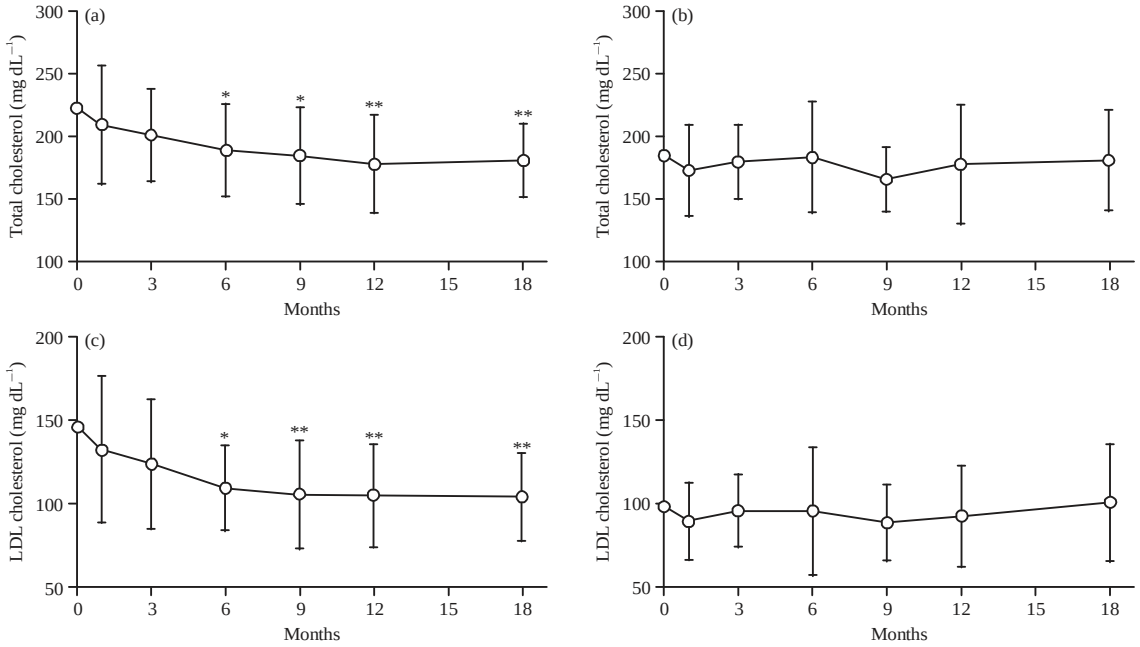

Fig. 2(a-d): Changes in blood lipid levels after linagliptin treatment

We divided the 25 patients who were given linagliptin into a group of patients whose hemoglobin A1c (HbA1c) level had decreased 18 months after the start of linagliptin treatment (n = 13) and a group of patients whose HbA1c level had not (n = 12) and analyzed their data (a) Changes in the serum total cholesterol (TC) level of the patients whose HbA1c level had decreased in response to linagliptin treatment, (b) Changes in the serum TC level of patients whose HbA1c level had not decreased in response to linagliptin treatment, (c) Changes in the serum low-density lipoprotein cholesterol (LDL-C) level of the patients whose HbA1c level had decreased in response to linagliptin treatment and (d) Changes in the serum LDL-C level of the patients whose HbA1c level had not decreased in response to linagliptin treatment (D). Data are expressed as Mean±SD. **p<0.01, *p<0.05 vs. value before treatment

of administration (Fig. 2c). By contrast, the LDL-C level did not decrease in the group whose HbA1c level had not decreased (Fig. 2d).

Correlations of the baseline blood HbA1c level with the post-treatment rates of change of the HbA1c, blood glucose, serum total cholesterol and serum LDL-cholesterol levels were determined. There was a strong correlation between the baseline blood HbA1c level and the post-treatment rate of change of the HbA1c value, with a correlation coefficient (R) of 0.84 ($p<0.01$) (Fig. 3a). A significant correlation was also noted between the baseline HbA1c level and the post-treatment rate of change of the blood glucose level (Fig. 3b), as well as between the baseline HbA1c level and the post-treatment rate of change of the total cholesterol level (Fig. 3c). On the other hand, there was no correlation between the baseline HbA1c level and the post-treatment rate of change of the serum LDL-cholesterol level (Fig. 3d).

DISCUSSION

The DPP-4 inhibitor linagliptin has been reported to reduce the BG level of type 2 diabetes patients and improve their HbA1c level. However, an ideal antidiabetic drug should provide long-sustained effective blood glucose control. Araki *et al.*[13], reported finding that decreases in the HbA1c and BG levels of Japanese type 2 diabetes patients in response to linagliptin were maintained for 52 weeks. On the other hand, it has been pointed out that while the DPP-4 inhibitor sitagliptin decreases the HbA1c level of type 2 diabetes patients, its effect may be diminished by long-termtreatment[11].

Since there are no reports in regard to linagliptin treatment periods that exceeded 52 weeks, this study was conducted by a long-term treatment with linagliptin for 18 months (72 weeks), assess its impact on HbA1c and BG and clarify the relation between the duration of the period of treatment and its effects.

Next, the data of individual patients were reviewed on the effect of 18-month treatment. It was found that some of the 25 patients showed the effects of linagliptin and others did not show the effects. In view of this, this study carried out statistical analysis of the data of these 25 patients (divided to two groups, i.e., patients who showed a decrease of the HbA1c in response to linagliptin treatment and those who did not

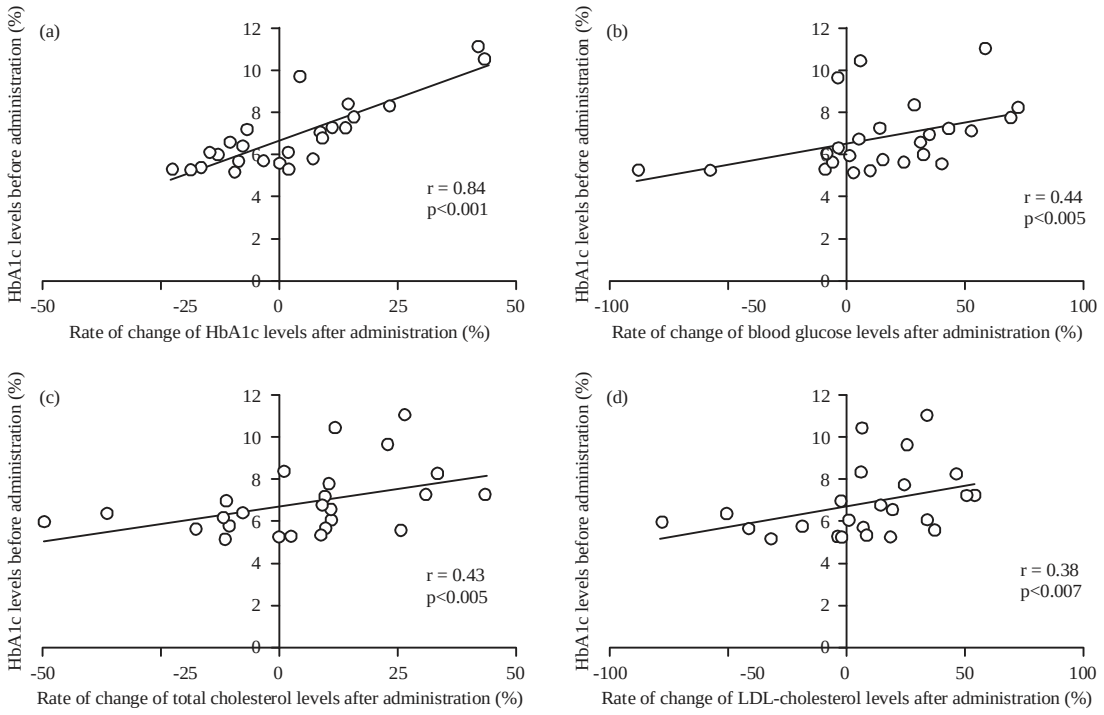

Fig. 3(a-d): Correlations between HbA1c levels before linagliptin treatment and the rate of change four variable, (a) HbA1c, (b) Blood glucose, (c) Total cholesterol and (d) LDL-cholesterol, after linagliptin treatment

Change (%) = [(Value before treatment-Value after treatment) /value before treatment]×100

show any decrease of the HbA1c) in response to linagliptin treatment. The results revealed that the patients whose HbA1c level decreased in response to linagliptin treatment were patients who had a high HbA1c level before treatment (7.8±1.8%) and its lowering action continued until 18 months after the start of treatment. By contrast, the HbA1c level in response to treatment of linagliptin in the patients with a low HbA1c level before treatment (5.9±0.6%) was found to increase. The HbA1c increase was not accompanied by an increase in BG.

The BG, TC and LDL-C levels of the patients whose HbA1c level decreased in response to linagliptin also decreased and the lowering effects continued until 18 months. None of these parameters decreased in the group whose HbA1c level had not decreased in response to linagliptin treatment. This showed that the decrease in HbA1c level and changes in blood lipids in response to linagliptin are coupled.

It has been reported that the HbA1c-ameliorating action of the DPP-4 inhibitor alogliptin was positively correlated with HbA1c levels before treatment[14]. In this study, the correlation of HbA1c levels before treatment and the rates of changes of HbA1c, blood glucose, total cholesterol and LDL-cholesterol levels after linagliptin administration were examined before and after treatment. It was found that the rates of changes (HbA1c, BG and TC after linagliptin treatment) were correlated with HbA1c levels before administration (Fig. 3). These results indicated that linagliptin improves the HbA1c level of the patients who had a relatively high HbA1c level, whereas the HbA1c level of the patients who had a relatively low HbA1c level does not improve. These results indicated that while considering linagliptin therapy in a diabetic patient, the patient's pre-treatment HbA1c should be measured to determine the suitability of the drug for the patient.

Many type 2 diabetes patients have hyperlipidemia as well as hyperglycemia[15] and the persistence of a hyperglycemic state and hyperlipidemic state in patients leads to atherosclerosis[16,17]. Moreover, postprandial hyperglycemia is said to be a strong risk factor for myocardial infarction[18,19]. Consequently, compounds that possess a combination of an antihyperlipidemic therapeutic effect as well as a blood-glucose-lowering action are desirable as drugs for the treatment of diabetes. DPP-4 inhibitors have been

suggested to contribute to improving blood lipids as well as to the glycemic control of type 2 diabetes patients[9]. In the present study the TC and LDL-C levels decreased in the patients whose HbA1c level had decreased in response to linagliptin treatment and an anti-atherosclerotic action is also expected. Among the important limitations of this study were its retrospective design and small sample size. Further investigation in a larger number of cases is warranted.

CONCLUSION

It was concluded that when type 2 diabetes patients with a relatively high HbA1c level (7.8±1.8%) were treated with DPP-4 inhibitor linagliptin, their HbA1c, BG, TC and LDL-C levels decreased and its lowering actions continued until 18 months after the start of treatment. By contrast, linagliptin did not lower any of those parameters in type 2 diabetes patients who had a relatively low HbA1c level (5.9±0.6%). In the linagliptin treatment of type 2 diabetes patients, it would be very important to measure the baseline (pre-treatment) HbA1c level and select suitable candidates for linagliptin treatment.

SIGNIFICANCE STATEMENT

The present study evaluated the efficacy of long-term treatment of DPP-4 inhibitor linagliptin in patients with type 2 diabetes. This study demonstrated that linagliptin improved the glycemic control and serum lipids of the patients with a high hemoglobin A1c (HbA1c) level before administration and continued to exert those effects for 18 months, whereas those parameters were not ameliorated in patients with a low HbA1c level. Thus, a new theory on the usefulness of long-term treatment of DPP-4 inhibitor linagliptin in type 2 diabetic patients with and possibly other combinations, may be arrived at.

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