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ORIGINAL ARTICLE

Alogliptin as an initial therapy in patients with newly diagnosed, drug naïve type 2 diabetes: a randomized, control trial

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Abstract The objectives of this study is to evaluate the efficacy and safety of alogliptin versus very low fat/calorie traditional Japanese diet (non-inferiority trial) as an initial therapy for newly diagnosed, drug naïve subjects with type 2 diabetes (T2DM). Study design was prospective, randomized, non-double-blind, controlled trial. The study was conducted at outpatient units of municipal hospital. Patients were newly diagnosed, drug naïve patients who visited the outpatient units. The patients randomly received 12.5–25 mg/day alogliptin ($n = 25$) or severe low calorie traditional Japanese diet ($n = 26$). The procedure of this trial was assessed by the consolidated standards of reporting trials statement. The primary end point was the change of HbA1c at 3 months. Secondary end points included the changes of fasting blood glucose, insulin, homeostasis model assessment-R (HOMA-R), HOMA-B, body mass index (BMI), and lipid parameters. Similar, significant reductions of HbA1c levels were observed in both groups (from 10.51 to 8.74% for alogliptin and from 10.01 to 8.39% for traditional Japanese diet) without any clinically significant adverse events. In the alogliptin group, some subjects (16%) had mild hypoglycemic evens which could be managed by taking glucose drinks by themselves. HOMA-B significantly increased in both groups with varying degrees, whereas HOMA-R significantly decreased only in the Japanese diet group. Atherogenic lipids, such as, total cholesterol, non-high density lipoprotein cholesterol, and low density lipoprotein cholesterol levels significantly decreased in both groups. BMI had no change in the alogliptin group, whereas it significantly decreased in the Japanese diet group. (1) Concerning its glycemic efficacy, alogliptin is effective and non-inferior to traditional Japanese diet as an initial therapeutic option for newly diagnosed T2DM. However, regarding the reductions of body weight and insulin resistance, traditional Japanese diet is superior. (2) Both alogliptin and traditional Japanese diet have favorable effects on atherogenic lipid profiles.

Keywords Incretin-based therapy · DPP-4 inhibitors · Alogliptin · Type 2 diabetes · Initial therapy · Insulin resistance · Beta-cell function

Introduction

Incretin-based drugs, glucagons like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors represent a new therapeutic approach for type 2 diabetes (T2DM) [1]. Active form of GLP-1 stimulates glucose-dependent insulin biosynthesis/secretion and suppresses glucagon release [2]. Since these actions are glucose concentration dependent, incretin-based drugs cause little hypoglycemic events. In comparison to GLP-1 analogs, DPP-4 inhibitors are weight neutral and have no effects on gastric emptying [2]. Incretin-based therapies are associated with enhanced beta-cell function, making them a good therapeutic option early in the disease (for example, newly diagnosed patients with T2DM) when the patients still maintain sufficient levels of beta-cell function [3].

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Alogliptin benzoate is a quinazolinone-based, non-covalent DPP-4 inhibitor currently available only in Japan and in advanced clinical phases in other countries including the USA and EU [4]. Alogliptin is a highly selective (>10,000-fold selectivity for DPP-4 compared with DPP-2, 8 or 9) inhibitor with sustained inhibition of DPP-4 activity resulting in increased circulating levels of intact GLP-1. DPP-4 activity is inhibited >80% at 24 h post-dosing [5, 6]. No drug–drug interactions are known to be associated with alogliptin till now [5, 6]. Favorable effects on beta-cell function were also observed, with an increase in HOMA-B ranging from 8 to 10% and a decrease in pro-insulin-to-insulin ratio of −0.04 [7]. One of the most remarkable differences from other DPP-4 is that alogliptin can be used with patients with renal or hepatic impairment without dose adjustment [8].

With an increasing number of newly diagnosed patients with T2DM worldwide, it is important to establish therapeutic strategies for those patients. Treatment often begins with life-style modifications (diet/exercise), which is regarded as the initial therapeutic option in the ADA/EASD consensus statement [9, 10]. However, many patients require or desire pharmacotherapy from the beginning. Currently, metformin is regarded as the first drug to choice in the treatment of T2DM [9, 10], although other drugs could be a potential candidate as well. Recent algorithms developed by the ADA/EASD have recommended the use of GLP-1 receptor agonists (monotherapy or combination therapy) on the basis of their effective glycemic efficacy, low frequency of hypoglycemic events, body weight loss, and overall safety profiles [9, 10]. On the contrary, due to their limited glucose-lowering efficacy and lack of long-term safety profile, DPP-4 inhibitors are not actively considered for a well-validated therapeutic option by these algorithms [9, 10]. At the present time, use of DPP-4 inhibitors as add on to other drugs in more advanced diabetic subjects who require insulin is more common in actual clinical practice. However, it is no doubt that they have gained an important position in the actual clinical practice in the past several years.

Since alogliptin is currently available only in Japan, little data and information of this drug are available in the actual clinical settings. Thus, it is of therapeutic value to analyze the glycemic and non-glycemic efficacies of alogliptin under such circumstances. To undertake such studies, it makes sense to perform with drug naïve subjects as monotherapy in order to eliminate the influences of other factors as much as possible. As an initial step toward investigating these issues, alogliptin monotherapy was performed with newly diagnosed drug naïve subjects, and a number of glycemic and other parameters were studied. Since life-style changes are essential and regarded as the first-line and well-validated therapy for T2DM [9, 10], very low fat/calorie traditional Japanese diet was used as a comparator.

Materials and methods

Subjects and protocol

The subjects in this study were recruited from the outpatient department of Diabetes and Endocrinology of Gyoda General Hospital (Saitama, Japan) and other associated hospitals. Most of these patients were identified by the health check screening system usually performed twice a year in Japan or were referred from non-specialist physicians in the nearby regions. Inclusion criteria were those who had been recently diagnosed with T2DM according to the criteria of the Japan Diabetes Society [11] and had not received any regularly prescribed drugs in the 3 months prior to the study. Exclusion criteria were those with clinically significant renal [creatinine (CRE) > 1.5 mg/dl], liver [glutamic oxalacetic transaminases/glutamic pyruvic transaminases (GOT/GPT) > 70/70 IU/l], heart [enlarged heart by chest X-ray or brain natriuretic peptide (BNP) > 70 pg/ml], hypertensive (blood pressure above 160/100 mmHg) disorders, type 1 diabetes (T1DM) and pregnancy. The patients had not taken any regularly prescribed drugs including anti-hypertensive and anti-hyperlipidemic agents within the last 3 months prior to the study.

One of the authors of this article, EK, was the responsible physician who recruited the subjects and delivered the care to these patients. Thus, this is not a blinded study. The details of the protocol and the number of participants are shown as a consolidated standards of reporting trials (CONSORT) diagram [12] (Fig. 1). These patients were randomly assigned to a 12.5–25 mg/day alogliptin group or a traditional Japanese diet group when they visited the outpatient clinic for the first time. The randomization was carried out by throwing away a coin which is marked "diet" on one side and "alogliptin" on the other side. Details of the "traditional Japanese diet" have been previously described and this diet has been shown to be effective and appropriate for patients with T2DM or hyperlipidemia [13, 14]. It was strongly instructed that the subjects in this group only adhere to traditional Japanese diet. The precise dietary instruction was given by one of the authors (EK) and his associated dieticians. Briefly, this diet has very low fat contents as well as low calories (see references [13, 14]). It mainly consists of vegetables, fishes (no meats) and rice, which are cooked without any additive omega 6 fatty acids containing oils. In the alogliptin group, no special effort to change the diet style has been suggested. In both groups, the subjects were encouraged to follow the exercise suggested by the American Diabetes Association [15]. The subjects visited the outpatient unit once a month and the assessment of whether they were following the therapeutic procedures was made.

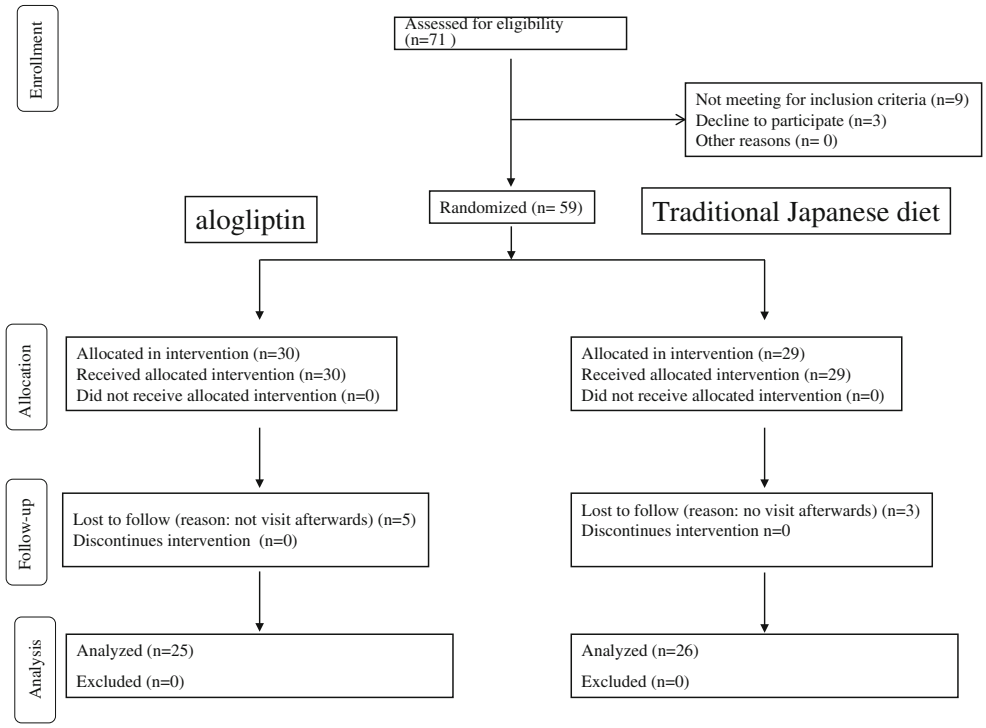

Fig. 1 CONSORT diagram

Informed consents were obtained from the patients, and the protocol for this study was approved by the Ethical Committee. In the case of unacceptable or undesirable therapeutic outcome, the patients were free to leave therapy whenever they wished. This is a clinical study of general standard which was funded by Japanese national health insurance system. Other general costs were also covered by Biomedical Center.

Laboratory measurements

The primary efficacy end point was the change of HbA1c from baseline to 3 months. Secondary endpoint was other parameters including fasting blood glucose (FBG), insulin, HOMA-B, homeostasis model assessment-R (HOMA-R), body mass index (BMI), total cholesterol (T-C), TG, HDL-C, non-high density lipoprotein cholesterol (non-HDL-C), and low density lipoprotein cholesterol (LDL-C). Blood was collected in the fasting state before breakfast. Measurements of HbA1c and FBG (measured by the system form Arkray, Shiga, Japan) were performed once a month. Insulin (measured by the kit from Abbott Japan, Tokyo), T-C, TG, HDL-C, and LDL-C (measured by the kit from Nittobo, Tokyo, using Hitachi 7180 analyzer) was measured at the start (baseline) and at 3 months of the study. Anti-glutamic acid decarboxylase (GAD) antibody was measured in some suspected patients in order to exclude those with T1DM (Mitsubishi BML, Tokyo, Japan). HOMA-R and HOMA-B were calculated as described [16] HOMA-R = IRI (μU/ml) × FBG (mg/dl)/405, HOMA-B = IRI (μU/ml) × 360/FBG (mg/dl) − 63. Liver [GOT, GPT, alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GTP)] and renal (CRE) functions were also monitored monthly. In the case of any significant increase in these parameters, administration of alogliptin was planned to discontinue. However, none of them had discontinued the therapy because of these reasons.

Data analyses

Change was calculated as the values at 3 months (post-therapy) minus those at baseline (pre-therapy). Since there were no drop-out subjects because of adverse events or intolerability, all the available data were used. Only the data from those who lost contact were excluded from data analysis. A sample size estimation indicated that more than nine patients were required to compare two groups to have sufficient statistical power (99.5%). Unpaired Student's *t* test was employed to analyze the difference at baseline between these two groups (alogliptin or traditional Japanese diet). Paired Student's *t* test was used to analyze the changes in each group (intra-group differences). 95% confidence interval (95% CI) was also calculated for the change of the parameters. Significant inter-group differences were assessed whether the 95% CI values overlap or not. Analysis of covariance (ANCOVA) was also used to observe if any inter-group differences of the changes of these parameters exist. Simple regression analysis was

performed to analyze the changes between measured parameters. The results were expressed as the mean ± SD. Throughout the statistical analysis, values of $P < 0.05$ were considered significant.

Results

Baseline characteristics and changes of the parameters at 3 months

As shown in Table 1, the baseline characteristics were similar and no differences of these parameters (FBG, HbA1c, T-C, TG, HDL-C, non-HDL-C, LDL-C, insulin, HOMA-R, HOMA-B, and BMI) were observed between these two groups.

At 3 months, the changes of these parameters were calculated with 95% CI (Table 2). While the changes of BMI levels between these two groups (inter-group differences) were significantly different, those of other parameters were not significantly different. However, the changes of insulin, HOMA-R, HOMA-B, or HDL-C levels had a tendency to be different between these two groups. However, using another method of analysis (ANCOVA), significant inter-group differences were observed in the changed of BMI ($P < 0.005$), insulin ($P < 0.01$), or HOMA-R ($P < 0.005$) and a tendency to have inter-group differences were observed with HOMA-B and HDL-C (both $P < 0.1$).

Effect on glycemic control

At 3 months, similar, significant reductions of HbA1c and FBG levels were observed in these two groups (Tables 3, 4).

Table 1 Baseline characteristics of the subjects

	Alogliptin	Japanese diet
Age	47.9 ± 13.4	50.5 ± 11.4
F/M	5/20	8/18
HbAlc (%)	10.51 ± 1.78	10.01 ± 1.12
FBG (mg/dl)	227.5 ± 51.7	220.6 ± 42.9
Insulin (μU/ml)	8.10 ± 5.77	7.34 ± 4.59
BW (kg)	74.65 ± 17.72	71.24 ± 15.2
BMI	26.35 ± 5.18	26.31 ± 4.87
HOMA-R	4.79 ± 3.82	3.92 ± 2.50
HOMA-B	18.11 ± 11.64	19.20 ± 17.22
T-C (mg/dl)	241.7 ± 43.0	221.2 ± 30.4
TG (mg/dl)	228.4 ± 245.1	155.3 ± 97.6
HDL-C (mg/dl)	50.2 ± 12.0	55.8 ± 12.1
Non-HDL-C (mg/dl)	191.56 ± 43.22	165.3 ± 28.8
LDL-C (mg/dl)	158.4 ± 58.8	142.8 ± 33.5

Table 2 95% CI of the changes of the glycemic and extra-glycemic parameters between alogliptin and Japanese diet

	Alogliptin 95% CI	Japanese diet 95% CI	*P* values
HbAlc (%)	−2.44 to −1.08	−2.14 to −1.08	n.s.
FBS (mg/dl)	−62.02 to −17.41	−57.20 to −25.63	n.s.
Insulin (μU/ml)	−0.44 to 2.90	−2.05 to −0.03	n.s.
BMI	−0.51 to 0.30	−1.26 to −0.54	<0.05
HOMA-R	−1.38 to 1.04	−1.78 to −0.60	n.s.
HOMA-B	5.46 to 16.70	3.02 to 9.97	n.s.
T-C (mg/dl)	−27.0 1 to −3.54	−22.70 to −5.60	n.s.
TG (mg/dl)	−104.93 to 13.49	−39.71 to 16.63	n.s.
HDL-C (mg/dl)	−0.28 to 4.76	−3.47 to 0.70	n.s.
Non-HDL-C (mg/dl)	−28.36 to −6.67	−20.39 to −5.14	n.s.
LDL-C (mg/dl)	−25.41 to −1.46	−18.81 to −1.64	n.s.

Table 3 Changes of glycemic and other parameters in alogliptin group

	Baseline	3 Months	% Change	*P* values
Age	47.9 ± 13.4			
F/M	5/20			
HbA1c (%)	10.51 ± 1.78	8.74 ± 1.73	−16.8	<0.00001
FBG (mg/dl)	227.5 ± 51.7	187.8 ± 57.5	−17.4	<0.002
Insulin (μU/ml)	8.10 ± 5.77	9.33 ± 5.56	15.1	n.s.
HOMA-R	4.79 ± 3.82	4.62 ± 3.86	−3.5	n.s.
HOMA-B	18.11 ± 11.64	29.20 ± 15.72	61.2	<0.001
BMI	26.35 ± 5.18	26.25 ± 4.77	−0.37	n.s.
T-C (mg/dl)	241.7 ± 43.0	226.4 ± 40.8	−6.3	<0.02
TG (mg/dl)	228.4 ± 245.1	182.7 ± 145.1	−20	n.s.
HDL-C (mg/dl)	50.2 ± 12.0	52.4 ± 13.2	4.3	n.s. (<0.1)
Non-HDL-C (mg/dl)	191.56 ± 43.22	174.04 ± 40.50	−9.1	<0.005
LDL-C (mg/dl)	158.4 ± 58.8	145.0 ± 50.12	−8.4	<0.05

In the alogliptin group, 6 out of 25 subjects were non-responders whose HbA1 had less than a 0.5% reduction from the baseline. In the Japanese diet group, 8 out of 26 subjects were non-responders (<0.5% reduction of HbA1c).

In an effort to find any predictive parameters for the efficacy of these therapies (alogliptin and Japanese diet), simple regression analysis were performed between the changes of (Δ)HbA1c levels and the baseline levels of the

Table 4 Changes of glycemic and other parameters in Japanese diet group

	Baseline	3 Months	% Change	*P* values
Age	50.5 ± 11.4			
F/M	6/20			
HbA1c (%)	10.01 ± 1.12	8.39 ± 1.57	−16.1	<0.00001
FBG (mg/ml)	220.6 ± 42.9	179.2 ± 55.8	−18.7	<0.00001
Insulin (μU/ml)	7.34 ± 4.59	6.29 ± 3.81	−14.3	0.0532
HOMA-R	3.92 ± 2.50	2.72 ± 1.86	−30.6	<0.001
HOMA-B	19.20 ± 17.22	25.70 ± 21.95	33.8	<0.02
BMI	26.31 ± 4.87	25.40 ± 4.80	−3.3	<0.00001
T-C (mg/dl)	221.2 ± 30.4	207.1 ± 33.4	−6.3	<0.005
TG (mg/dl)	155.3 ± 97.6	143.7 ± 91.5	−7.4	n.s.
HDL-C (mg/dl)	55.8 ± 12.1	54.5 ± 12.6	−2.3	n.s.
Non-HDL-C (mg/dl)	165.3 ± 28.8	152.6 ± 31.3	−7.6	<0.005
LDL-C (mg/dl)	142.8 ± 33.5	132.5 ± 29.4	−7.2	<0.05

parameters including HbA1c, insulin, HOMA-R, HOMA-B, or BMI. Among these factors, the baseline HbA1c levels had good negative correlations with ΔHbA1c in the alogliptin group ($R = -0.517$). By contrast, in the Japanese diet group, the baseline HbA1c levels had only weak negative correlations with ΔHb1c ($R = -0.219$).

Effect on beta-cell function and insulin resistance

DPP-4 inhibitors are known to augment beta-cell function; however, their effects on insulin resistance (sensitivity) remain somewhat elusive. This question has been investigated using HOMA-B (for beta-cell function) and HOMA-R (for insulin resistance) indexes. As shown in Table 3, HOMA-B levels significantly increased while HOMA-R and BMI levels had no change in the alogliptin group. On the other hand, HOMA-B levels significantly increased, while HOMA-R and BMI (or BW) levels significantly decreased in the Japanese diet group (Table 4).

Next, one interesting question is whether the reductions in glucose levels have any correlations with the changes (Δ) of the above mentioned parameters. For this purpose, simple regression analysis was performed using these parameters. (1) In the alogliptin group, strong negative correlations were observed between the changes of (Δ) HbA1c and ΔHOMA-B ($R = -0.570$), but not between ΔHbA1c and ΔHOMA-R. (2) In the Japanese diet group, moderate correlations were observed between ΔHbA1 and ΔHOMA-R ($R = 0.333$), and strong correlations between ΔHbA1c and ΔHOMA-B ($R = -0.610$)/ΔBMI ($R = 0.566$).

Effect of alogliptin on lipid profiles

Effects on DPP-4 inhibitors on other metabolic parameters, for example, lipid profiles, remain largely uncharacterized. Overall, it is regarded as "lipid neutral." As an initial step toward investigating this question, a number of lipid parameters including T-C, TG, HDL, non-HDL-C, and LDL-C were monitored. In the alogliptin group, T-C, non-HDL, and LDL-C levels significantly decreased while TG levels had no change. HDL-C had a tendency to increase (Table 3).

Interestingly, weak correlations were observed between the changes of (Δ)HbA1c and ΔT-C ($R = 0.251$), Δnon-HDL-C ($R = 0.279$) or ΔLDL-C ($R = 0.319$). In the Japanese diet group, significant reductions of T-C, non-HDL-C, and LDL-C levels were also observed as expected (Table 4). Good correlations were observed between ΔHbA1c and ΔT-C ($R = 0.434$), Δnon-HDL-C ($R = 0.4859$), or ΔLDL-C ($R = 0.620$).

Blood pressure was also monitored. The variations were so large and no conclusions have been made regarding the effect of alogliptin on blood pressure (results not shown).

Safety and tolerability

Four out of 25 subjects (16%) in the alogliptin group reported mild hypoglycemic events, which could be easily managed by taking glucose drinks by themselves. In most cases, this adverse event occurred in the first 4 weeks of the initiation of the drug. Otherwise no subjects had any clinically significant elevations of renal or hepatic enzymes and no gastrointestinal complains were observed. No subject had dropped out because of intolerance or adverse events.

Discussion

Glycemic efficacy and safety of alogliptin

In this study, alogliptin 12.5–25 mg/day monotherapy on newly diagnosed, drug naïve Japanese subjects with T2DM was shown to be rather effective and safe in reducing blood glucose levels (HbA1c from 10.51 to 8.74% in 3 months, Table 3), suggesting that it can be used an initial therapy for the treatment of T2DM. Surprisingly, alogliptin was not better than traditional Japanese diet in terms of reductions in HbA1c and is worse in

terms of reductions in body weight or insulin resistance (compare Tables 3, 4).

These backgrounds may suggest that, for newly diagnosed patients with T2DM, very low fat/calorie diets such as traditional Japanese foods, should be tried as a initial therapy. However, it appears that the glucose control in the Japanese diet group was not sustainable after 3 months, while that of alogliptin was durable after this period (E. Kutoh, personal observation). Since it is empirically known that the patients can make dietary efforts for a short period but it is hard for them to continue for a long time. In other words, "rebound" often happens with severe low calorie diet. The long-term effect is now been followed up. In analogy to other oral hypoglycemic agents (OHAs), the response to alogliptin is proportional to the baseline HbA1c levels ($R = -0.517$), suggesting that it can be effectively used for subjects with advanced T2DM.

Effect of alogliptin on beta-cell function and insulin sensitivity

Alogliptin and traditional Japanese diet were similarly effective in reducing HbA1c or FBG levels (Tables 2, 3, 4), however, these two therapeutic regimens may have distinct glucose-lowering mechanisms, since (1) differential effects on HOMA-B and HOMA-R levels were observed (both alogliptin and traditional Japanese diet up-regulated HOMA-B while only Japanese diet down-regulated HOMA-R, Tables 3, 4) and (2) the reductions of HbA1c levels were strongly correlated with those of HOMA-B ($R = -0.570$) in the alogliptin group while the reductions of HbA1c levels were moderately strongly correlated with those of HOMA-R ($R = 0.333$) and HOMA-B ($R = -0.620$) in the Japanese diet group. These backgrounds may indicate that glycemic efficacy of alogliptin is obtained through activating beta-cell function, while that of traditional Japanese diet is obtained through both reliving insulin resistance and activating beta-cell function. These observations may indicate that traditional Japanese diet may be superior in controlling beta-cell function and insulin resistance. Furthermore, significant body weight reductions were observed with traditional Japanese diet. Nevertheless, alogliptin was not inferior to traditional Japanese diet in its efficacy in reducing HbA1c and FBG levels (Tables 2, 3, 4). There are several explanations. For example, (1) although no statistically significant inter-group differences were observed in HOMA-B levels (Table 2), the degree of activating beta-cell function with alogliptin may be stronger than that with traditional Japanese diet. Indeed 61.2% (with alogliptin) versus 33.8% (with traditional Japanese diet) increases in HOMA-B were observed (Tables 3, 4). (2) Recently, it was reported that the glycemic efficacy of sitagliptin is not mediated by enhancing beta-cell function in patients lacking residual beta-cell function, but possibly through other mechanisms independent from insulin [3]. Alogliptin may also have such pharmacological effects which traditional Japanese diet does not possess.

Effect of alogliptin on lipid profiles

Effects on lipid parameters with DPP-4 inhibitors are inconsistent [17–19]. In this study, it was shown that alogliptin significantly reduced T-C, non-HDL-C, or LDL-C levels and had a tendency to increase HDL-C levels. However, it had no effect on TG levels (Table 3). However, alogliptin was not better than traditional Japanese diet in terms of reducing these atherogenic lipids (Tables 2, 3, 4). Anyway, the pharmacological efficacy of alogliptin to ameliorate these atherogenic cholesterols is an advantage and this drug may reduce the risks of cardiovascular disorders. Indeed it was very recently shown that long-term treatment of alogliptin could reduce atherosclerosis and inflammation via the effects on monocyte recruitment and chemotaxis in animal models [20]. Molecular mechanisms of alogliptin in ameliorating these atherogenic lipids remain to be investigated.

One interesting observation in this study is that in the alogliptin group, the changes of HbA1c levels were weakly correlated with those of T-C ($R = 0.251$), non-HDL-C ($R = 0.279$), or LDL-C ($R = 0.319$). At the present time, whether the changes of these atherogenic lipids are the cause or the consequence of the reduced glucose levels remains to be investigated. Anyhow, these atherogenic lipids may be an independent marker for assessing the glycemic efficacy of alogliptin.

Limitations and strengths of the study

The limitations of this study are that the number of the subjects was small and the study duration was short. However, one can assume that the observed changes were caused exclusively by alogliptin based on the design of the study (monotherapy with drug naïve patients). Further randomized, double-blind, placebo-controlled longer period study with increased number of subjects will be necessary to strengthen the finding in this study.

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Conflict of interest The authors have nothing to disclose.

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