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Differential effects on metabolic parameters between sitagliptin and alogliptin in drug naïve subjects with type 2 diabetes

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Abstract

Background: Different dipeptidyl peptidase (DPP)-4 inhibitors show significant structural differences. The aim of this study was to find any differential effects on metabolic parameters between sitagliptin and alogliptin.

Methods: Drug naive subjects with type 2 diabetes (T2DM) were assigned to either 25-100mg/day sitagliptin (n=37) or 6.25-25mg/day alogliptin (n=35) monotherapy. At 3 months, the levels of glycemic and non-glycemic parameters were compared with those at baseline.

Results: At baseline, the levels of these parameters were similar between these two groups. At 3 months, similar glucose lowering efficacies were observed in both groups. However, distinct regulatory patters were observed with lipid profiles. In the sitagliptin group, high triglyceride (TG) and free fatty acid (FFA) levels significantly decreased. However, in the alogliptin group, significant reductions of total cholesterol (T-C), non-high density lipoprotein (non-HDL)-C and low density lipoprotein (LDL)-C levels were observed and changes of (Δ)HbA1c levels were weakly correlated with those of ΔT-C, Δnon-HDL-C or ΔLDL-C. Besides these lipid parameters, homeostasis model assessment (HOMA)-B increased in both groups (+52.3 % for sitagliptin and +91.2% for alogliptin) with significant inter-group differences (p<0.05). Both drugs are well tolerated and no clinically significant adverse events were observed. However, uric acid (UA) levels increased, although still within normal limit, in both groups.

Conclusions: This study suggests that: 1) both sitagliptin and alogliptin are effective and safe as an initial therapy for T2DM. 2) alogliptin can ameliorate atherogenic lipid profiles and these atherogenic lipids may be associated with the glycemic effect during alogliptin treatment. By contrast, sitagliptin can down-regulate high TG and FFA levels. 3) although similar glucose lowering efficacies were observed, sitagliptin had a higher degree of enhancing beta-cell function than alogliptin.

Keywords: Incretin based therapy, type 2 diabetes, DPP-4 inhibitor, sitagliptin, alogliptin

Introduction

Incretin-based drugs, glucagons like peptide-1 (GLP-1) receptor agonists and DPP-4 inhibitors represent a new therapeutic approach for T2DM [1,2,3]. Since incretin-based therapies enhance beta-cell function, they may be an appropriate therapeutic option early in the disease when the patients still maintain sufficient levels of beta-cell function [4]. However, to date, no evidence is available whether these drugs can be used as a first-line option for T2DM.

At the present time, at least six DPP-4 inhibitors are clinically available on the market (sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin and teneligliptin) and many others are coming soon. Although these drugs all inhibit the same enzyme (DPP-4) and display similar glucose lowering efficacies, they show clearly distinct chemical structures [5,6]. This fact implicates that these

drugs may have different pharmacological properties, such as half-life, systemic exposure, bioavailability, protein binding, metabolism, presence of active metabolites and excretion routes [6,7]. Data on non-glycemic parameters are scant at present and do not allow a comparison among DPP-4 inhibitors. Thus it is of therapeutic value to analyze the differences in glycemic and non-glycemic efficacies of the different DPP-4 inhibitors. To undertake such studies, it makes sense to perform with drug naïve subjects as monotherapy in order to eliminate the influences of other drugs as much as possible.

Sitagliptin is the first DPP-4 inhibitor on the market and is the most widely used drug of this class throughout the world. Its efficacy and safety are extensively studied and well acknowledged [8,9,10]. On the contrary, alogliptin 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 [11,12,13]. The reductions in HbA1c levels with alogliptin appear to be in the similar range as with the other DPP-4 inhibitors [4,14,15]. However, due to its limited availability (only in Japan) its effects are largely unknown in actual clinical settings. Overall, DPP-inhibitors are regarded as "lipid neutral" [16]. However, it was preliminarily shown that alogliptin has a favorable effect in down-regulating atherogenic lipid profiles and post-prandial lipid [4,17].

As an initial step towards investigating the differences between different DPP-4 inhibitors, comparison between sitagliptin and alogliptin on metabolic parameters was performed with drug naïve subjects of T2DM.

Subjects and methods
Subjects
Inclusion criteria were those who were newly diagnosed with type 2 diabetes (T2DM) or those who were previously diagnosed but were untreated. The diagnosis was made according to the criteria of the Japan Diabetes Society [18]. All the subjects had not received any regularly prescribed drugs in the 6 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 [brain natriuretic peptide (BNP)>70 pg/ml], hypertensive [blood pressure above 160/100 mmHg] disorders, type 1 diabetes (T1DM) and pregnancy. These subjects were recruited from the outpatient department of Diabetes and Endocrinology of Gyoda General Hospital (Saitama, Japan) and two other related hospitals. These patients received 25-100 mg/day sitagliptin (n=37) or 6.25-25 mg/day alogliptin monotherapy (n=35). The patients started with the lowest dose of these drugs (sitagliptin 25 mg/day and alogliptin 6.25 mg/day). The doses were increased according to the results of the glycemic control. At the end of the study, most subjects (approximately 90% in both groups) used the dose of sitagliptin 50 mg/day and alogliptin 12.5 mg/day. They were assigned without strict randomized procedure and the study design was not a blinded one. In both groups, the subjects were encouraged to follow the exercise and diet suggested by the American Diabetes Association [19]. Informed consents were obtained from the patients and the protocol of this study was approved by the Ethical Committee. This study was conducted in accordance with principles of Good Clinical Practice. In the case of unacceptable or undesirable therapeutic outcome, the patients were free to leave the therapy whenever they wished. The drop out subjects were excluded from data analysis.

Laboratory measurements
The primary end point was the changes in HbA1c levels from baseline to 3 months. The HbA1c values were assessed by the JDS standardization [20] throughout this manuscript. To convert these into the National Glycoprotein Standardization Program (NGSP), add approximately 0.4 % to the indicated values [20]. Patients with ≥1% reduction in HbA1c at 3 months were designated as responders and those with <1% reduction were designated as non-responders. This 1% cut off value has been traditionally used in other studies [21].

The secondary end point included fasting blood glucose (FBG), and other metabolic parameters including T-C, TG, HDL-C, LDL-C, UA, HOMA-R, HOMA-B and body mass index (BMI).

Blood was collected at the fasting state before breakfast and the standard technique was used to measure these parameters as described previously [21]. 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, nonHDL-C and LDL-C (measured by the kit from Nittobo, Tokyo, using Hitachi 7180 analyzer) was measured at the start (baseline) and at the end (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 [22]; HOMA-R=insulin (μU/mL) x FBG (mg/dL)/405, HOMA-B=insulin (μU/mL) x 360/FBG(mg/dL)−63. Liver (GOT, GPT, alkaline phosphatase: ALP, and gamma-glutamyl transpeptidase :γ-GTP) and renal (BUN and CRE) functions were also monitored monthly. In the case of any significant increases of these parameters, administration of sitagliptin or alogliptin was planned to discontinue. The drop-out subjects were excluded from data analysis.

Data analyses
Change was calculated as the values at 3 months (post-therapy) minus those at baseline (pre-therapy). Unpaired Student's t-test was employed to analyze the difference at baseline between these two groups (sitagliptin and alogliptin). When the data were normally distributed, paired Student's t-test was used to analyze the changes in each group (intra-group differences). When the data were not normally distributed, Wilcoxon signed-rank test was employed. An analysis of covariance (ANCOVA) was used to analyze the inter-group differences. To identify any factors that influence the efficacy of these drugs, multiple regression analyses between the changes of HbA1c levels and the baseline levels of other parameters were undertaken. 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 I**, the baseline characteristics were

Table I. Baseline characteristics of the subjects in the sitagliptin and alogliptin groups

	sitagliptin	alogliptin	p-values
age (years old)	53.5±11.5	50.0±12.9	n.s.
sex (F/M)	7/30	4/31	n.s.
FBS (mg/dl)	226.1±64.6	221.4±53.7	n.s.
HbA1c (%)	10.43±2.21	10.40±2.08	n.s.
T-C (mg/dl)	227.1±42.2	240.8±40.8	n.s.
TG (mg/dl)	231.6±222.0	209.0±220.0	n.s.
HDL-C (mg/dl)	52.4±12.5	52.4±17.9	n.s.
nonHDL-C (mg/dl)	174.6±41.3	188.4±41.0	n.s.
LDL-C (mg/dl)	147.7±32.2	155.9±52.4	n.s.
FFA (eEq/l)	0.957±0.333	0.808±0.300	n.s.
UA (mg/dl)	5.11±1.42	4.81±1.47	n.s.
insulin (μU/ml)	6.86±4.52	8.03±6.02	n.s.
HOMA-R	3.79±2.91	4.48±3.51	n.s.
HOMA-B	18.33±15.59	20.26±20.00	n.s.
BMI	25.22±4.63	26.51±5.84	n.s.

similar and no differences of these parameters (age, gender, FBG, HbA1c, T-C, TG, HDL-C, non-HDL-C, LDL-C, FFA, UA, insulin, HOMA-R, HOMA-B and BMI) were observed between these two groups.

At 3 months, similar, significant reductions of HbA1c and FBG levels were observed in these two groups (compare **Table IIA1** and **IIB**). 13 out of 37 subjects (35.1 % in the sitagliptin group) and 13 out of 35 subjects (37.1 % in the alogliptin group) were non-responders whose HbA1 had less than (<) a 1% reduction from the baseline.

In an effort to find any predictive parameters for the efficacy of sitagliptin or alogliptin, multiple regression analysis was performed between the changes of (Δ)HbA1c levels and the baseline levels of the metabolic parameters including FBG, HbA1c, T-C, TG, HDL-C, non-HDL-C, LDL-C, FFA, UA, insulin, HOMA-R, HOMA-B or BMI. Among these factors, baseline HbA1c levels were chosen as the significant contributing factor for the glycemic efficacy (ΔHbA1c) both in the sitagliptin and alogliptin groups. To further consolidate this finding, simple regression analysis was performed between ΔHbA1c and baseline HbA1c levels. As shown in **figure 1**, significant correlations were observed in both groups (R=-0.536 for sitagliptin, R=-0.345 for alogliptin).

Differential effects between sitagliptin and alogliptin on beta beta-cell function

DPP-4 inhibitors are known to augment beta-cell function, however, their effects on insulin resistance (sensitivity) or body weight 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 II A1** and **II B**, no changes, if any, were observed

### Table II Changes of glycemic and other parameters. A1) sitagliptin

	baseline	3 month	p-values
FBS (mg/dl)	226.1±64.6	190.4±78.7	<0.002
HbA1c (%)	10.43±2.21	8.24±2.18	<0.00001
T-C (mg/dl)	227.1±42.2	221.2±42.3	n.s.
TG (mg/dl)	231.6±222.0	195.6±167.7	0.0651
HDL-C (mg/dl)	52.4±12.5	53.5±11.5	n.s.
nonHDL-C (mg/dl)	174.6±41.3	167.6±41.6	n.s.
LDL-C (mg/dl)	147.7±32.2	145.9±35.9	n.s.
FFA (eEq/l)	0.957±0.333	0.810±0.334	<0.05
UA (mg/dl)	5.11±1.42	5.67±1.35	<0.0005
insulin (μU/ml)	6.82±4.52	8.34±6.83	<0.005
HOMA-R	3.79±2.91	4.09±4.54	n.s.
HOMA-B	18.33±15.59	35.05±42.71	<0.005
BMI	25.22±4.63	25.41±4.56	n.s.

Table II A2) TG changes in sitagliptin group

	baseline	3 months	p-values
normal TG (≤199 mg/dl)	117.6±45.1	138.0±70.4	n.s.
high TG (≥200mg/dl)	469.9±256.7	315.5±241.0	<0.001

Table II B) Alogliptin

	baseline	3 month	p-values
FBS (mg/dl)	221.4±53.7	192.3±60.5	<0.02
HbA1c (%)	10.40±2.08	8.80±2.32	<0.00001
T-C (mg/dl)	240.8±40.8	225.7±38.5	<0.02
TG (mg/dl)	209.0±220.0	171.9±131.0	n.s.
HDL-C (mg/dl)	52.4±17.9	53.2±13.2	n.s.
nonHDL-C (mg/dl)	188.4±41.0	172.5±39.0	<0.005
LDL-C (mg/dl)	155.9±52.4	145.1±45.5	<0.05
FFA (eEq/l)	0.808±0.300	0.722±0.277	n.s.
UA (mg/dl)	4.81±1.47	5.45±1.65	<0.00001
insulin (μU/ml)	8.03±6.02	9.52±7.27	0.0052
HOMA-R	4.48±3.51	4.67±3.92	n.s.
HOMA-B	20.26±20.00	30.87±25.35	<0.001
BMI	26.51±5.84	26.52±5.66	n.s.
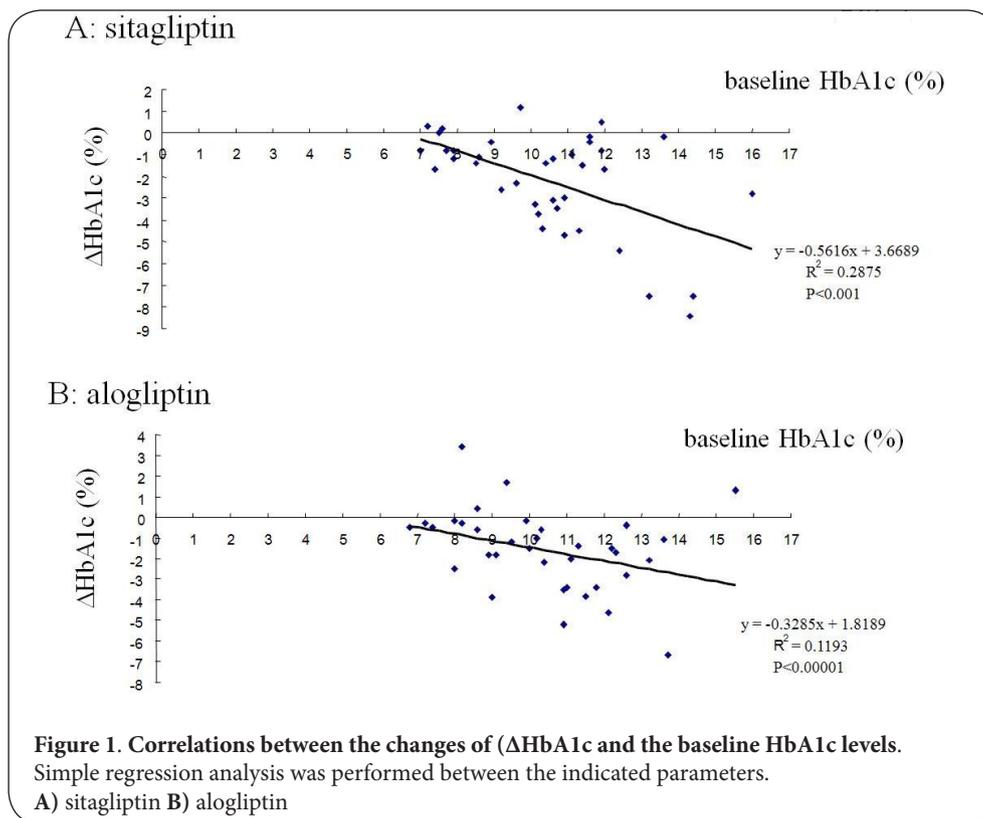
Figure 1. **Correlations between the changes of (ΔHbA1c and the baseline HbA1c levels.**
Simple regression analysis was performed between the indicated parameters.
A) sitagliptin **B)** alogliptin

with HOMA-R and BMI levels in both groups. By contrast, HOMA-B levels significantly increased in both groups (see **Figure 2**, +91.2% increase for sitagliptin and +52.3% increase for alogliptin) with significant inter-group differences (p<0.05).

Next, one interesting question is whether the reductions (Δ) in glucose levels have any correlations with the changes (Δ) of beta-cell function (assessed by HOMA-B). For this purpose, simple regression analysis was performed using these parameters. Both in the sitagliptin and alogliptin groups, strong negative correlations were observed between ΔHbA1c and ΔHOMA-B (R=-0.638 for sitagliptin and R=-0.565 for alogliptin, **figure 3A** and **B**).

Differential effects on lipid profiles between sitagliptin and alogliptin

Effects on DPP-4 inhibitors on other metabolic parameters, for example, lipid profiles, remain largely uncharacterized. As an initial step towards investigating this question, a number of lipid parameters including T-C, TG, HDL, non-HDL-C, LDL-C and FFA were monitored.

In the sitagliptin group (**Table IIA1**), TG levels had a tendency to decrease (-15.4%, p=0.0651) and FFA levels significantly decreased (-15.3%, p<0.05). Then, baseline TG levels were divided into two groups; those with above

(≥)200mg/dl (high TG group) and others with below (≤) 199 mg/dl (normal TG group). While no changes were observed in the normal TG group, significant reductions of TG levels were observed in the high TG group (-32.7%, **Table IIA2**). No correlations were observed between the changes of HbA1c levels and those of TG or FFA (results not shown). In contrast to this, no changes of T-C, non-HDL, or LDL-C levels were observed (**Table IIA1**). In the alogliptin group (**Table IIB**), T-C, non-HDL and LDL-C levels significantly decreased while TG or FFA levels had no change. Interestingly, weak-moderate correlations were observed between the changes of (Δ)HbA1c and ΔT-C (R=0.265), Δnon-HDL-C (R=0.301) or ΔLDL-C (R=0.339) in the alogliptin group as shown in **Table III**. No changes in HDL-C levels were observed in either sitagliptin or alogliptin group (**Table IIA1** and **IIB**). Blood pressure was also monitored. However, the variations were so large and no conclusions have been made regarding the effect of sitagliptin or alogliptin on blood pressure (results not shown).

Safety and tolerability

4 out of 37 subjects in the sitagliptin group and 3 out of 35 subjects in the alogliptin group reported mid hypoglycemic events, which could be easily managed by taking glucose drinks or sweet candies by themselves. In most cases, this
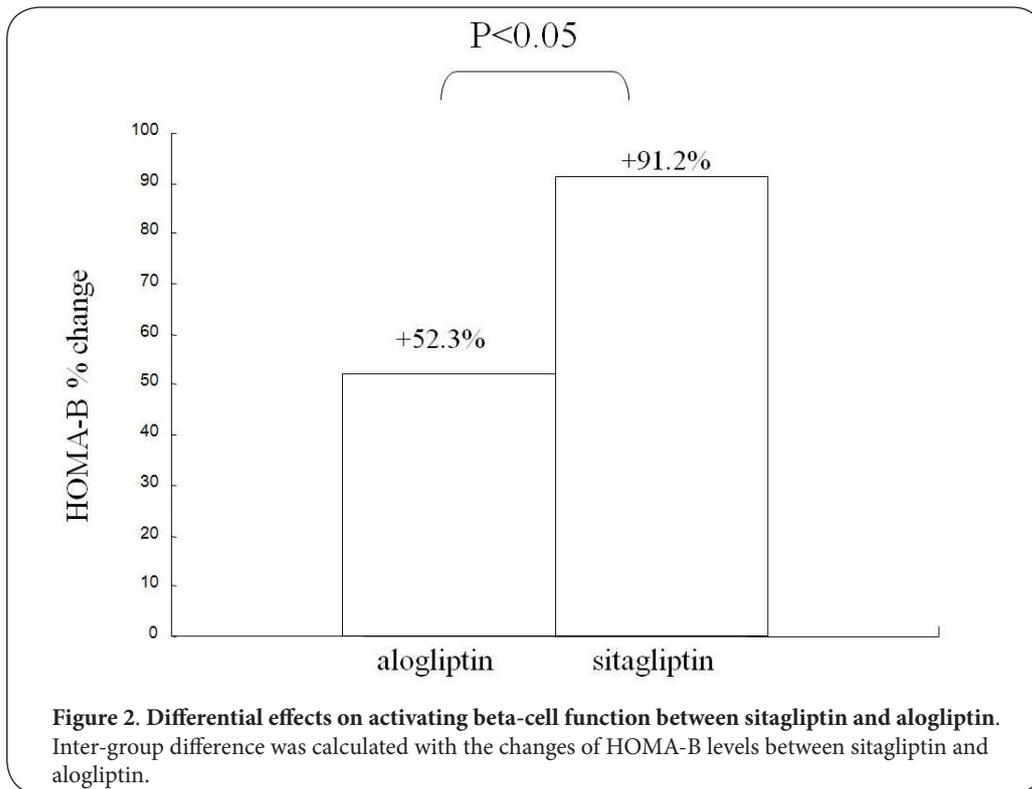
Figure 2. **Differential effects on activating beta-cell function between sitagliptin and alogliptin**. Inter-group difference was calculated with the changes of HOMA-B levels between sitagliptin and alogliptin.
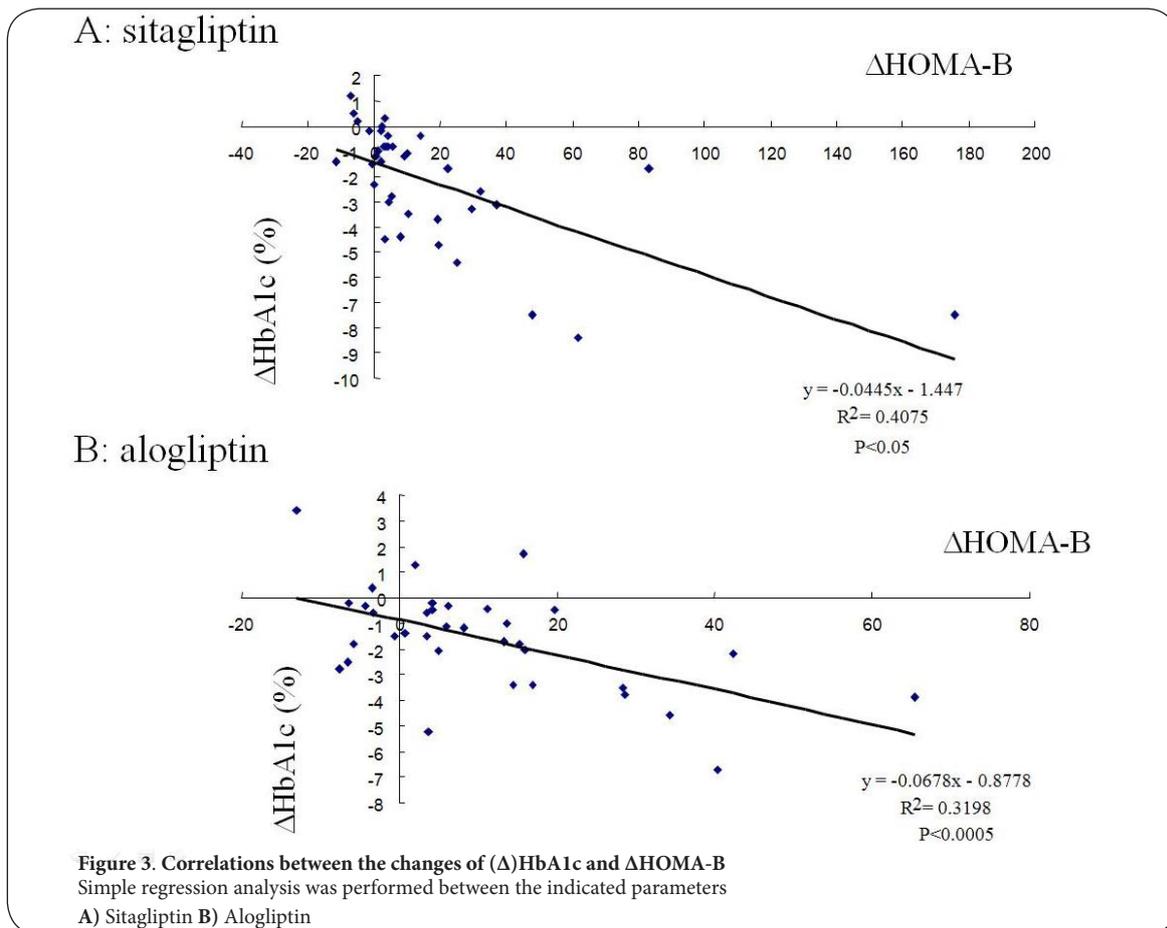
Figure 3. **Correlations between the changes of (Δ)HbA1c and ΔHOMA-B**
Simple regression analysis was performed between the indicated parameters
A) Sitagliptin **B)** Alogliptin

adverse event occurred within the first 2 weeks of the initiation of these drugs. Otherwise in both groups, 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. However, UA levels significantly increased in both groups (**Table IIA1** and **IIB**).

Discussion
Glycemic effects and safety
In this present work, both sitagliptin 25-100 mg/day and alogliptin 6.25-25mg/day monotherapy in newly diagnosed, drug naïve Japanese subjects with T2DM were shown to be rather effective and safe. However, around 10% subjects in both groups reported mild (not serious) hypoglycemic events. In addition, significant increases of UA levels were observed in both groups, though still within normal range (**Table IIA1** and **IIB**). The clinical significance of the increased UA levels remains to be investigated.

In both groups, approximately 35% subjects were non-responders whose HbA1c levels had less than 1% decrease in 3 months period. Currently we are investigating the clinical characterizations between responders and non-responders with these drugs. In analogy to other oral hypoglycemic agents (OHAs), the response to sitagliptin or alogliptin is proportional to the baseline HbA1c levels (**Figure 1**). In this connection, both sitagliptin and alogliptin are rather effective with poorly controlled drug naïve subjects (HbA1c above 10%). Although the numbers of the subjects in this study are small and the study duration is short, these results may implicate that both sitagliptin and alogliptin may be used as one of the first-line drugs for T2DM.

Differential effects on beta-cell function
Both sitagliptin and alogliptin were able to enhance beta-cell function as measured by the increase of HOMA-B levels, however, sitagliptin had a higher degree of up-regulating this parameter (**Figure 2**). The reductions of (Δ) HbA1c levels had strong, negative correlations with the increases of (Δ)HOMA-B levels in both groups, however, the degrees of correlations might be somewhat different between sitagliptin (R= -0.638) and alogliptin (R= -0.565). These results indicate that glycemic efficacy of sitagliptin or alogliptin is obtained through activating beta-cell function, although with distinct degrees. So why do these two drugs have similar glucose lowering effects in spite of the fact that sitagliptin has a higher degree of enhancing beta-cell activity? One potential explanation for this question is the existence of GLP-1 independent pathway of DPP-4 inhibitors as has been hypothesized [**23**]. In that paper, it was proposed that the glycemic efficacy of DPP-4 inhibitors were medicated by not only through GLP-1 dependent pathway but also by other GLP-1 independent pathways (beyond inhibition of

DPP-4). Accordingly, the balance of dependency of DPP-4 inhibitors between these pathways (GLP-1 dependent and independent) may differ among different DPP-4 inhibitors; *e.g.* alogliptin has a higher degree of enhancing this GLP-1 independent pathway than sitagliptin. Further studies using molecular and cellular approaches will be necessary to investigate the mechanisms as questioned above.

Differential effects on lipid profiles
Effects on non-glycemic parameters, for example, lipid profiles, with DPP-4 inhibitors are inconsistent [**16**]. One of the novel findings in this work is that aloglitin could significantly reduce T-C, non-HDL-C or LDL-C levels, while sitagliptin could reduce high TG and FFA levels. Neither drug had effects on HDL-C levels (**Table IIA1** and **IIB**). These effects differ from those of pioglitazone, a TZD class of insulin sensitizer which significantly reduced TG and increased HDL-C levels while it had inconsistent effects on T-C or LDL-C levels [**21**]. In this respect, combination of alogliptin and pioglitazone may be beneficial in controlling the overall lipid profiles in patients with T2DM. 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, potent antiatherosclerotic effects of alogliptin in addition to its potent antidiabetic effects are recently speculated [**4,17,24**]. One interesting observation in this study is that the changes of HbA1c levels were weakly correlated with those of T-C, non-HDL-C or LDL-C in the alogliptin group (**Table III**). At the present time, it remains to be investigated whether the changes of these atherogenic lipids are the cause or the consequence of the reduced glucose levels by alogliptin. Anyhow, these atherogenic lipids may be an independent marker for assessing the glycemic efficacy of alogliptin. At the same time, the molecular and cellular mechanisms of how these drugs lower lipid levels (*e.g.* effects on synthesis, secretion, absorption or clearance) will be an interesting research topic.

To this end, it is of interest to monitor the effect of other DPP-4 inhibitors (*e.g.* vildagliptin, saxagliptin) on lipid profiles. Although the mechanism of the action and the glycemic efficacy are comparable, these DPP-4 inhibitors show significant structural differences [**5,6**]. Several clinical trials of newer generations of DPP-4 inhibitors are currently ongoing. These results will help identify differences among these compounds.

Table III. Correlations between the changes of (ΔHbA1c and those of lipid parameters in the alogliptin group.
Simple regression analysis was performed between the indicated lipid parameters.

ΔHbA1 vs. ΔT-C	R=0.265
ΔHbA1c vs. ΔnonHDL-C	R=0.301
ΔHbA1c vs. ΔLDL-C	R=0.339

The limitations and strengthens of the study

The limitations of this study are that the number of the subjects is small and the study duration is short. Furthermore, it is not strictly randomized. However one can assume that the observed changes were caused exclusively by these drugs (sitagliptin or 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.

Conclusions

This study suggests that both sitagliptin and alogliptin are effective and safe as an initial therapy for T2DM. However differential effects are observed on non-glycemic parameters including lipid and beta-cell function. Accordingly, the choice of sitagliptin or alogliptin (or other OHAs) is dependent on the characteristics of the patients. For example, sitagliptin is suitable for those with high TG and/or FFA levels while alogliptin is useful for those with high atherogenic cholesterols (*e.g.* LDL-C and non-HDL-C). Further sitagliptin can be preferentially used in those with low beta-cell function (low insulin secretory capacity).

Competing interests

The authors declare that they have no competing interests.

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Publication history

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