Effect of Alogliptin, a DPP-4 Inhibitor, on Markers of Lipid Metabolism in Type 2 Diabetic Patients

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Abstract

Background: DPP-4 inhibitor has been shown to improve not only blood glucose levels but also dyslipidemia, but the effect remains controversial. Further, there are few reports regarding the influence on Apo B, Apo A-1 and Apo B/Apo A-1 in alogliptin.

Objective: Using the alogliptin, we focused on Apo B and Apo A-1, in addition to LDL-C, HDL-C and TG, and investigated the effect of alogliptin on markers predicting cardiovascular events, such as Apo B/Apo A-1 and LDL-C/Apo B.

Methods: This study was carried out with a single arm in an open label manner. 45 consecutive cases that could enroll between September 2011 and March 2012 were selected as the subjects for randomization. Alogliptin 25 mg/day was administered for eight weeks and non-fasting blood samples were collected 2-3 hours after breakfast, once at the beginning of the study and once eight weeks later, and changes in glucose and lipid metabolism markers were compared.

Results: Administration of alogliptin significantly reduced HbA1c levels and non-fasting blood glucose levels, and reduced LDL-C and non-fasting TG. Apo B was significantly reduced by alogliptin treatment but Apo A-1 was unchanged. The Apo B/Apo A-1 ratio was significantly decreased and the LDL-C/Apo B ratio significantly increased by alogliptin treatment. The change in the pre-administration Apo B/Apo A-1 ratio was positively correlated with body weight, TG, HbA1c, blood CPR and pooled urine CPR and negatively correlated with HDL-C.

Conclusion: Administration of alogliptin in type 2 diabetic patients significantly improved levels of blood glucose, in addition to those of lipid metabolism markers such as LDL-C and non-fasting TG, as well as sensitive predictive markers for the onset risk of cardiovascular events, such as the Apo B/Apo A-1 ratio and the LDL-C/Apo B ratio. These results suggest that alogliptin could potentially suppress atherosclerosis and prevent cardiovascular events (UMIN 000011470).

Keywords

Alogliptin, Type 2 diabetes, Lipid metabolism, Apo B/Apo A-1, LDL/Apo B

Introduction

It is widely known that patients with diabetes have a higher risk of onset and mortality from cardiovascular events [1,2]. Meta-analysis of UKPDS has shown that the primary risk factor for cardiovascular (CV) events in diabetic patients is neither blood glucose levels nor HbA1c, but rather LDL-C [3]. Accordingly, an improvement not only in blood glucose levels but also in dyslipidemia is considered important for the prevention and avoidance of CV events.

In type 2 diabetes, increased influx of FFA into the liver due to insufficient insulin activity increases VLDL production, while reduced LPL activity increases VLDL, LDL-C, IDL and accelerates atherosclerosis [4]. A number of large-scale clinical studies have proven that statins decrease LDL-C and prevent CV events [5,6]. However, even a reduction in LDL-C leaves a residual risk, and hypertriglyceridemia, in particular, as well as postprandial TG elevation [7] and hypohDLeemia are risk factors.

Given the above data, current guidelines on diabetes treatment recommend appropriate control of hypercholesterolemia, hypertriglyceridemia and hypohDLeemia to prevent CV events [8]. In diabetic patients, abnormalities in both the quantity, and quality of LDL-C, such as increased small dense LDL-C and production of glycosylated LDL-C, are thought to increase the onset risk of CV events [9]. Electrophoresis is the standard method for measuring small dense LDL-C, but a complicated procedure. The LDL-C/Apo B ratio is used as an alternative, and it has been reported that small dense LDL is increased in cases in which the LDL-C/Apo B ratio is 1.2 or lower [10].

In Japan, DPP-4 inhibitors have been used as oral antidiabetic agents since 2011, and have also been shown to improve dyslipidemia. It has been reported that sitagliptin decreased TG and RLP-C without affecting levels of LDL-C and HDL-C [11]. Different from this result, another group showed it could decrease T-C and TG [12]. Thus, effects of sitagliptin toward dyslipidemia are still controversial. A meta-analysis of the effect on TC and TG has demonstrated differences in improvements in lipid metabolism markers and efficacy [13]. The non-fasting Apo B/Apo A-1 ratio has been proven...
as a useful marker for predicting CV events [14]. According to the INTERHEART study, the non-fasting Apo B/Apo A-1 ratio may be a more sensitive predictive marker for acute myocardial infarction than either non-HDL-C or the T-C/HDL-C ratio. Additionally, the non-fasting Apo B/Apo A-1 ratio was not significantly influenced by age, gender or races. With regard to the influence of DPP-4 inhibitors on apoprotein, previous studies have examined decrease of postprandial chyloplomicron and Apo B48 levels with a focus on postprandial TG in sitagliptin [15] and in vildagliptin [16]. However, the measurement of both of Apo B, Apo A-1 is reported only in sitagliptin [15], and no report has studied the Apo B/Apo A-1 ratio with any DPP-4 inhibitors.

Thus, in this study, we highlighted Apo B and Apo A-1 and studied the effect of the DPP-4 inhibitors alogliptin [17,18] on Apo B and Apo A-1, in addition to lipid metabolism markers, and investigated the effect of alogliptin on markers predicting CV events, such as Apo B/Apo A-1 and LDL-C/Apo B.

Patients and Methods

Patients

Subjects were type 2 diabetic patients aged 20 years or older at our hospital that were taking oral antidiabetic agents and had HbA1c levels of 6.9% or higher for three months or longer. Exclusion criteria were: patients receiving insulin therapy; severe liver or renal dysfunction; patients with hypersensitivity to alogliptin; patients that had their hypoglycemic agents changed within three months; pregnant women or breast-feeding mothers; and excessive alcohol drinkers.

This study was carried out with a single arm in an open label manner. After informed consent was obtained from patients, 45 consecutive cases that could enroll between September 2011 and March 2012 were selected as the subjects for randomization. In the 45 cases, alogliptin 25 mg/day was administered for eight weeks and non-fasting blood samples were collected 2-3 hours after breakfast, once at the beginning of the study and once eight weeks later, and changes in height, body weight, blood pressure, glucose metabolism markers and lipid metabolism markers were compared. Dietitians analyzed the ingredient of the breakfast by inquiring from 15 patients selected at random. The energy of their breakfast was 450Kcal, of which 32% was from fat. All the subjects take the same menu of the breakfast at random. The energy of their breakfast was 450Kcal, of which 32% was from fat. All the subjects take the same menu of the breakfast at random.

Background information in the 45 cases that received alogliptin is shown in Table 1. Antidiabetic agents were administered as follows: sulfonylurea (SU), 27 cases; α-glucosidase inhibitors (α-GIs), 21; glinides, 14; biguanides (BGs), 18; and TZD, 11. Of these, all α-GIs and glinides were changed to alogliptin. Doses of BGs and TZD were unchanged and co-administered with alogliptin co-administered. With regard to SU, the dose was unchanged in 15 cases, reduced in 10, and increased, or another drug was necessary, in two. During administration, no adverse events occurred and administration was not discontinued in any case.

Biochemical analyses

Non-fasting blood samples were collected 2–3 hours after breakfast, once at the beginning of the study and once eight weeks later. Apo A-1 and Apo B were measured by immune nephelometry with BMI8060. HbA1c levels were measured by HPLC with HLC-72300G. Measurements were converted to NGSP values with a conversion table recommended by the Japan Diabetes Society [19]. LDL-C and HDL-C were measured by the direct method, while TG was measured by the enzymatic colorimetric method with BM 2250.

Table 1: Patient backgrounds and status of concomitant drug administration

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male 35</th>
<th>Status of complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Sex

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>61.1 ± 12.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>68.5 ± 12.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 ± 4.0</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4 ± 1.0</td>
</tr>
<tr>
<td>Non-fasting Glu (mg/dL)</td>
<td>164.6 ± 39.2</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>102.9 ± 19.7</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>60.7 ± 19.3</td>
</tr>
</tbody>
</table>

Status of antihypertensive drug administration

| Non-fasting TG (mg/dL) | 137.4 ± 93.9 |
| SBP (mmHg) | 125.2 ± 12.8 |
| DBP (mmHg) | 67.6 ± 9.0 |

Table 2: Changes in glucose level and lipid metabolism markers by alogliptin

<table>
<thead>
<tr>
<th>Before administration</th>
<th>After administration</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>7.4 ± 1.0 %</td>
<td>7.0 ± 0.7 %</td>
</tr>
<tr>
<td>Non-fasting Glu</td>
<td>164.6 ± 39.2 mg/dL (9.14 ± 2.18 mmol/L)</td>
<td>141.2 ± 35.6 mg/dL (7.84 ± 1.98 mmol/L)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>102.9 ± 19.7 mg/dL (2.66 ± 0.51 mmol/L)</td>
<td>97.9 ± 22.5 mg/dL (2.53 ± 0.58 mmol/L)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>60.7 ± 19.3 mg/dL (1.57 ± 0.50 mmol/L)</td>
<td>81.8 ± 18.3 mg/dL (1.60 ± 0.47 mmol/L)</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>1.83 ± 0.60</td>
<td>1.68 ± 0.53</td>
</tr>
<tr>
<td>Non-fasting TG</td>
<td>137.4 ± 93.9 mg/dL (1.55 ± 1.06 mmol/L)</td>
<td>116.0 ± 71.1 mg/dL (1.31 ± 0.80 mmol/L)</td>
</tr>
</tbody>
</table>

Figure 1a: HbA1c changes and combination drugs with alogliptin

Statistical analysis

In this study, all clinical data are expressed as means ± standard deviation. The influence of alogliptin on HbA1c, non-fasting blood glucose, LDL-C, HDL-C, non-fasting TG, body weight, BMI, and blood pressure were statistically analyzed by the paired t-test. The effect of alogliptin on Apo B, Apo A-1, Apo B/Apo A-1 and LDL-C/Apo B was statistically analyzed by the non-parametric Wilcoxon matched pair test. SPSS (Version 11) was used for analysis.

Results

Effect of alogliptin on glycemic control

Alogliptin administration significantly reduced HbA1c levels from 7.4 ± 1.0% to 7.0 ± 0.7 % (p<0.0001) (Table 2). HbA1c levels were reduced from 20.0% before treatment to lower than 6.9% after administration in 50.6% of cases (p<0.001). HbA1c levels were improved significantly irrespective of the concomitant drugs, with the exception of the group that switched from glinides (Figure 1a). HbA1c levels were

![Figure 1a: HbA1c changes and combination drugs with alogliptin](image-url)
also significantly reduced at -0.5% even in the reduced dose SU group (Figure 1b). There was no significant difference in the degree of reduction by alogliptin between obese patients with BMI ≥ 25 kg/m² and non-obese patients with BMI < 25 kg/m² (Figure 1c). Non-fasting blood glucose levels were significantly reduced by alogliptin from 164.6 ± 39.2 mg/dL (9.14 ± 2.18 mmol/L) to 141.2 ± 35.6 mg/dL (7.84 ± 1.98 mmol/L) (p < 0.001) (Table 2).

Effect of alogliptin on lipid metabolism

Alogliptin administration reduced LDL-C from 102.9 ± 19.7 mg/dL (2.66 ± 0.51 mmol/L) to 97.9 ± 22.5 mg/dL (2.53 ± 0.58 mmol/L) (p < 0.01). Alogliptin elevated HDL-C from 60.7 ± 19.3 mg/dL (1.57 ± 0.50 mmol/L) to 61.8 ± 18.3 mg/dL (1.60 ± 0.47 mmol/L), but the change was not significant. In contrast, the LDL-C/HDL-C ratio significantly decreased from 1.83 ± 0.60 to 1.68 ± 0.53 (p < 0.01). Moreover, non-fasting TG significantly decreased from 137.4 ± 93.9 mg/dL (1.55 ± 1.06 mmol/L) to 116.0 ± 71.1 mg/dL (1.31 ± 0.80 mmol/L) (p < 0.05) (Table 2).

The changes (amount and rate) of LDL-C, HDL-C, non-fasting TG were compared between obese (BMI ≥ 25 kg/m²) and non-obese patients (BMI < 25 kg/m²). The changes HDL-C in the obese patients were significantly more than the non-obese patients. There were no significant differences in the changes of LDL-C, HDL-C, and non-fasting TG between anti-diabetic agents (metformin, α-GIs, glinide, pioglitazone and sulfonylureas) combined with alogliptin.

Effect of alogliptin on apoprotein

Apo B was significantly reduced by alogliptin treatment from 91.0 ± 16.4 mg/dL (0.91 ± 0.16 g/L) to 85.0 ± 14.0 mg/dL (0.85 ± 0.14 g/L) (p < 0.01). Apo A-1 was unchanged in response to alogliptin. In contrast, the Apo B/Apo A-1 ratio was significantly decreased by alogliptin from 0.61 ± 0.15 to 0.57 ± 0.12 (p < 0.05), and the LDL-C/Apo B ratio significantly increased from 1.16 ± 0.11 to 1.20 ± 0.13 (p < 0.01) (Table 3).

The changes (amount and rate) of Apo B, Apo A-1, Apo B/Apo A-1, LDL/Apo B were compared between obese (BMI ≥ 25 kg/m²) and non-obese patients (BMI < 25 kg/m²). The changes Apo A-1 in the obese patients were significantly more than the non-obese patients (Table 4). There were no significant differences in the changes of Apo B, Apo A-1, Apo B/Apo A-1, LDL/Apo B between anti-diabetic agents (metformin, α-GIs, glinide, pioglitazone and sulfonylureas) combined with alogliptin.

The change in the pre-administration Apo B/Apo A-1 ratio was positively correlated with body weight, TG, HbA1c, blood CPR and pooled urine CPR and negatively correlated with HDL-C (Table 5). Changes in LDL and HbA1c before and after administration were positively correlated (Table 6).
Table 6: Correlations between change in Apo B/Apo A-1 and parameters (changes)

<table>
<thead>
<tr>
<th>Correlation coefficient (R)</th>
<th>Contribution rate (R^2)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>-0.081</td>
<td>0.007</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.687</td>
<td>0.472</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-0.166</td>
<td>0.028</td>
</tr>
<tr>
<td>TG</td>
<td>0.336</td>
<td>0.113</td>
</tr>
<tr>
<td>Hba1c</td>
<td>0.463</td>
<td>0.215</td>
</tr>
<tr>
<td>Glu</td>
<td>-0.104</td>
<td>-0.011</td>
</tr>
<tr>
<td>Pooled urine CPR</td>
<td>0.532</td>
<td>0.283</td>
</tr>
</tbody>
</table>

Effect of alogliptin on blood pressure

Alogliptin effect was seen in patients with SBP 130mmHg or higher prior to administration. Ogawa et al. [29] have reported that administration of sitagliptin [29] and GLP-1 analog administration is known to upregulate LDL receptor expression in the liver [21], while several reports have shown that alogliptin increases LDL-C particle diameter [26-28], this effect was also observed in surrogate markers.

In this study, alogliptin administration increased the LDL-C/Apo A-1 ratio. The LDL/Apo A-1 ratio was considered a marker for risk of acute myocardial infarction [14]. In particular, the Apo B/Apo A-1 ratio represented the highest odds ratio among predictive markers and it has been considered a marker that would negatively predict acute myocardial infarction independent of race, gender, age or diet. In this study eight weeks of alogliptin administration significantly reduced Apo B and the Apo B/Apo A-1 ratio. Since the possibility that DPP4 inhibitors may prevent CV events has attracted attention, the results of this study suggest the potential of this drug for suppressing CV events. When we examined factors that influenced the improvement in the Apo B/Apo A-1 ratio by alogliptin, we found significant positive correlations with body weight, TG, Hba1c, and blood and pooled urine CPR prior to administration, and a significant negative correlation with HDL-C.

In metabolic syndrome cases where body weight and TG are increased and intrinsic insulin secretion is maintained or is slightly increased due to insulin resistance, an improvement in Apo B/Apo A-1 is unusual. CETP activity is increased under insulin resistance, and excessive TG levels increase cholesterol transfer from HDL-C to VLDL, and reduce HDL-C. Therefore, alogliptin was more effective in cases where HDL-C levels were reduced. In this study, by comparison of all cases, Apo A-1 and HDL-C did not have the significant difference with about administration of alogliptin. However, when they divided it into the obesity patient and the non-obesity patient, HDL-C and Apo A-1 were significantly more in the obesity patients compared with the non-obesity patient. Administration of alogliptin to the obesity patient may contribute to anti-atherosclerosis by increase LDL-C and Apo A-1.

In the context of DPP-4 inhibitors, the degree of Hba1c reduction has been seen to be larger in cases with higher Hba1c levels before administration [24] and, similarly, we observed an improvement in the Apo B/Apo A-1 ratio. In response to postprandial hyperglycemia, DPP-4 inhibitors increase GLP-1 and insulin secretion and suppress glucagon secretion. In cases with higher remaining capability of insulin secretion, reactive insulin secretion and suppression of glucagon secretion were more pronounced and both blood glucose levels and lipid metabolism were improved.

We have shown that improvement in Apo B/Apo A-1 has a significant positive correlation with change in LDL-C and Hba1c before and after the administration of alogliptin. A positive correlation with Hba1c suggests that the improvement in glycemic control by alogliptin contributed to an improvement in the Apo B/A-1 ratio. In this study, postprandial blood CPR was not significantly different before and after the administration, which we speculate is related to reduced insulin resistance by suppression of glucagon secretion.

In animal experiments, GLP-1 signal activation has been shown to suppress cholesterol absorption from the intestine [21] and GLP-1 analog administration is known to upregulate LDL receptor expression in the liver [25], suggesting a possible mechanism of not only LDL-C reduction via insulin but also direct reduction of GLP-1.

In many clinical studies, it has been reported that DPP-4 inhibitors could decrease fasting serum TG. Furthermore, in this study, we have shown here for the first time that administration of alogliptin over an eight week period at 25 mg/day improved not only blood glucose levels, but also blood levels of LDL-C and non-fasting TG. Glucose lowering by improving Apo B levels, alogliptin significantly reduced the Apo B/Apo A-1 ratio, a reliable predictive marker for the onset risk of acute myocardial infarction. It also significantly increased the LDL-C/Apo B ratio, which correlated with small dense LDL, which would be expected to reduce the proportion of small dense LDL.

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In this context, it can be speculated that continuous suppression by alogliptin of the enzymatic activity of DPP-4 results in chronically elevated GLP-1 levels, and suppression of postprandial TG elevation.

In many clinical studies, it has been reported that administration of LDL-C could prevent CV events. The effect of DPP-4 inhibitors on LDL-C is still controversial. Sitagliptin [12,15] and vildagliptin [23] have been shown to reduce TG, but not LDL-C. In addition, a meta-analysis of the effect of DPP-4 inhibitors on T-C showed that vildagliptin and alogliptin decreased T-C in contrast to sitagliptin [13], suggesting the possibility that distinct DPP-4 inhibitors have different effects on cholesterol metabolism. In this study, alogliptin administration reduced postprandial LDL-C.

According to the INTERHEART study, non-fasting Apo B and Apo B/Apo A-1 are important predictive markers for the onset risk of acute myocardial infarction [14]. In particular, the Apo B/Apo A-1 ratio corresponded to the highest odds ratio among predictive markers and it has been considered a marker that would negatively predict acute myocardial infarction independent of race, gender, age or diet. In this study eight weeks of alogliptin administration significantly reduced Apo B and the Apo B/Apo A-1 ratio. Since the possibility that DPP4 inhibitors may prevent CV events has attracted attention, the results of this study suggest the potential of this drug for suppressing CV events. When we examined factors that influenced the improvement in the Apo B/Apo A-1 ratio by alogliptin, we found significant positive correlations with body weight, TG, Hba1c, and blood and pooled urine CPR prior to administration, and a significant negative correlation with HDL-C.

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analysis of phase II and phase III clinical trials in the U.S. which has shown that alogliptin reduced the major adverse CV events [31]. In EXAMINE trial, patients with CVD were subjected. In the view of alogliptin effect, improved glucose and lipid metabolism and direct action of GLP-1 for cardiac function may be beneficial for CVD. However the risk reduction in the diabetic patients with CVD is difficult and earlier intervention should be needed.

Conclusions
Alogliptin administration in type 2 diabetic patients significantly improved levels of blood glucose, in addition to those of lipid metabolism markers such as LDL-C and non-fasting TG, as well as sensitive predictive markers for the onset risk of CV events, such as the Apo B/Apo A-1 ratio and the LDL-C/Apo B ratio. These results suggested the possibility that alogliptin could potentially suppress atherosclerosis and prevent CV events.

References


