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# Comparison of Glycemic Control Indicators and Safety Evaluation during Linagliptin Treatment over 6 Months in Japanese Type 2 Diabetic Patients with and without Nephropathy

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## Abstract

**Objective:** This retrospective study was undertaken to compare hemoglobin A1c and glycoalbumin levels as glycemic control indicators during linagliptin treatment in diabetic patients with or without nephropathy. The efficacy and safety of linagliptin were also examined.

**Methods:** The subjects were 127 outpatients with type 2 diabetes, including 69 patients with nephropathy. The hypoglycemic effect of linagliptin and the factors contributing to its hypoglycemic effect were examined. Several clinical parameters were compared before and after the initiation of linagliptin to evaluate the drug's safety.

**Results:** Linagliptin significantly decreased hemoglobin A1c and glycoalbumin levels at 3 and 6 months after treatment initiation. At 6 months, changes in hemoglobin A1c levels from baseline were strongly correlated with changes in glycoalbumin levels in diabetic patients with and without nephropathy. Changes in hemoglobin A1c and glycoalbumin at 6 months were significantly greater in patients with higher baseline values and shorter diabetes duration. Linagliptin decreased both hemoglobin A1c and glycoalbumin levels, irrespective of the baseline estimated glomerular filtration rate. No changes in clinical parameters thought to indicate adverse events were noted.

**Conclusions:** Glycoalbumin is an equivalent glycemic control indicator and predictor to hemoglobin A1c during linagliptin treatment. Linagliptin is safe and effective in diabetic patients with or without nephropathy.

**Keywords:** Linagliptin; Hemoglobin A1c; Glycoalbumin; Type 2 diabetes mellitus; Diabetic nephropathy

## Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used to treat diabetes because of their robust hypoglycemic effect and the minimal risks of hypoglycemia and weight gain [1]. As such, they occupy an important position in any diabetes treatment strategy.

Hemoglobin A1c (HbA1c) has been the gold standard for evaluating glycemic control in patients with diabetes mellitus since the Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study established its importance as an outcome predictor. However, some diabetes patients develop vascular complications despite relatively low HbA1c levels. Recent studies have suggested that vascular complications are caused by increased glycemic variability [2]. Although postprandial hyperglycemia, which is the cause of glycemic variability, is frequently observed in patients with uncontrolled diabetes, it has also been reported in diabetes patients with intermediate HbA1c levels [3,4].

As glycoalbumin (GA) is generated 4–6 times faster than HbA1c, it responds to changes in blood glucose levels faster than HbA1c. It is suggested that GA could be a better marker for glycemic excursion, which is considered to be a major cause of atherosclerosis, than HbA1c [5]. A study using continuous glucose monitoring revealed that GA but not HbA1c is associated with blood glucose variability [6]. In addition, HbA1c appears to be less precise in patients with advanced stages of chronic kidney disease, particularly in patients with anemia treated with erythropoietin [7]. This phenomenon might reflect shortened red blood cell survival in patients with advanced kidney disease. In these patients, the time for glucose and hemoglobin to chemically interact is shortened [8].

In contrast to other DPP-4 inhibitors, linagliptin is excreted unchanged in bile and stool, which makes dose adjustment unnecessary in patients with renal dysfunction [9,10]. As conventional oral hypoglycemic agents have limitations regarding their administration to patients with advanced kidney disease, the prescription of linagliptin is expected to increase in these patients. Moreover, as GA is more precise than HbA1c in patients with severe renal impairment, GA will likely be measured more frequently than HbA1c in diabetes patients receiving linagliptin. Consequently, comparing the usefulness of GA with that of HbA1c as indicators of glycemic control in diabetes patients with renal dysfunction is clinically relevant.

Therefore, we retrospectively evaluated the usefulness of HbA1c and GA as glycemic control indicators and predictors during linagliptin treatment in diabetes patients with and without diabetic nephropathy. In addition, we investigated the efficacy and safety of linagliptin, in particular in patients with a low estimated glomerular filtration rate (eGFR).

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## Materials and Methods

### Patients

The subjects were 127 outpatients with type 2 diabetes who started linagliptin treatment from March 1, 2012 to March 31, 2014 at our hospital and continued the treatment for more than 6 months.

### Compliance with ethical standards

This study was approved by the Ethics Committee of the Keio University School of Medicine and was performed in accordance with the Declaration of Helsinki.

### Data collection

In this retrospective study, basic demographic data were collected from medical records, including sex, age, height, weight, diabetes duration, HbA1c, GA, blood glucose, C-peptide immunoreactivity (CPR), and hemoglobin levels, eGFR, lipid profile (total cholesterol [TC], high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides levels), and liver function enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and γ-glutamyl transpeptidase [γ-GTP] levels). Number of sampling for GA is as same as that for HbA1c. Furthermore, the CPR index, which is thought to reflect β-cell function, was calculated as follows: plasma CPR [ng/mL] / glucose [mg/dL] × 100. All measurements were performed by the Department of Laboratory Medicine of the Keio University School of Medicine using routine automated laboratory methods [11]. Data on complications such as hypertension (blood pressure ≥ 140/90 mmHg and/or the use of antihypertensive drugs) and dyslipidemia (TC ≥ 220 mg/dL and/or HDL cholesterol < 40 mg/dL and/or triglycerides ≥ 150 mg/dL and/or taking a hypolipidemic agent) were also collected. Fasting was not required at blood sample collection. Body mass index (BMI) was calculated as weight divided by height squared (kg/m$^2$).

Diabetic retinopathy was assessed through dilated pupils by an ophthalmologist using an ophthalmoscope. It was classified according to the modified Davis classification as no diabetic retinopathy, simple diabetic retinopathy, preproliferative diabetic retinopathy, or proliferative diabetic retinopathy [12]. Diabetic nephropathy was defined as urinary albumin excretion ≥ 30 mg/g creatinine or eGFR < 30 mL·min$^{-1}$·1.73 m$^{-2}$. The degree of diabetic nephropathy was graded according to the new classification of diabetic nephropathy of the Japanese Diabetes Society [13]. Prior history of cerebrovascular disease, cardiovascular disease, and peripheral vascular disease was recorded. HbA1c levels are expressed in accordance with the National Glycohemoglobin Standardization Program guidelines, as recommended by the Japanese Diabetes Society [14]. The eGFR was calculated using the following formula established by the working group of the Japanese Chronic Kidney Disease Initiative: eGFR (mL·min$^{-1}$·1.73 m$^{-2}$) = 194 × (serum creatinine) − 1.094 × (age) − 0.287 (× 0.739 for women) [15].

### Statistical analysis

We retrospectively compared HbA1c and GA levels at baseline (at the start of linagliptin treatment), 3 months, and 6 months. Changes in HbA1c and GA levels from baseline were analyzed by repeated-measures ANOVA; post hoc pairwise group comparisons were conducted using the Bonferroni test. Changes in hemoglobin levels were analyzed by the same method. ΔHbA1c was defined as HbA1c levels at 6 months − baseline HbA1c levels; likewise, ΔGA was defined as GA levels at 6 months − baseline GA levels. Correlations between ΔHbA1c and ΔGA, ΔHbA1c and baseline eGFR, and ΔGA and baseline eGFR were tested using Pearson's correlation coefficients. Linear regression analysis was used to identify independent predictors of ΔHbA1c and ΔGA. The following considered clinically meaningful variables were used as independent variables in the multivariate analyses: baseline CPR index, baseline eGFR, sex, age, BMI, diabetes duration, and baseline HbA1c levels for ΔHbA1c or baseline GA levels for ΔGA.

To evaluate the safety of linagliptin, several parameters were compared between baseline and 6 months after linagliptin administration. A paired *t*-test was used to compare normally distributed clinical parameters (body weight, hemoglobin, AST, ALT, TC, HDL cholesterol, LDL cholesterol, uric acid levels, and γ-GTP levels, CPR index, and eGFR). The Wilcoxon signed-rank test was used to compare non-normally distributed clinical parameters (i.e., triglycerides). These tests were performed for all patients ($n$ = 127) and those with diabetic nephropathy ($n$ = 69). Changes in the eGFR after linagliptin administration were analyzed using repeated-measures ANOVA in 3 patient categories stratified by baseline eGFR (<30, 30–60, and ≥ 60 mL·min$^{-1}$·1.73 m$^{-2}$).

All analyses were performed with SPSS version 19.0 (SPSS Inc, Chicago, IL, USA). Data are expressed as mean ± SD, and the level of significance was set at $P < 0.05$.

## Results

### Baseline patient demographic characteristics

The baseline demographic characteristics of the study subjects are shown in Table 1. The patients' mean eGFR was 54.2 mL·min$^{-1}$·1.73 m$^{-2}$, and 69 patients had diabetic nephropathy. Based on these findings, many of the study participants were likely to meet the chronic kidney disease criteria. Five patients were under erythropoietin therapy.

### Changes in hemoglobin A1c and glycoalbumin levels after linagliptin administration

Changes in HbA1c and GA levels are shown in Figure 1. In all patients (Figure 1a), HbA1c and GA levels decreased significantly at 3 and 6 months after the start of linagliptin administration (baseline → 3 months → 6 months: HbA1c 7.8 ± 1.5% → 7.3 ± 1.3 → 7.4 ± 1.4; GA 21.6 ± 6.2 → 19.9 ± 4.6% → 20.1 ± 5.2%; all $P < 0.001$ vs. baseline). In the 58 patients without diabetic nephropathy (Figure 1b), HbA1c and GA levels also decreased significantly at 3 and 6 months (HbA1c 7.5 ± 1.0% → 7.1 ± 1.0%, $P < 0.001$ vs. baseline → 7.1 ± 1.0%, $P < 0.001$ vs. baseline; GA 19.7 ± 3.4% → 18.7 ± 3.4, $P = 0.0048$ vs. baseline → 19.0 ± 3.4, $P = 0.043$ vs. baseline). In the 69 patients with diabetic nephropathy (Figure 1c), HbA1c and GA levels also decreased significantly at 3 and 6 months (HbA1c 8.2 ± 1.8% → 7.5 ± 1.5 → 7.6 ± 1.6 ; GA 23.1 ± 7.5% → 20.8 ± 5.3; → 21.2 ± 6.2; all $P < 0.001$ vs. baseline).

ΔGA and ΔHbA1c were strongly correlated in all patient groups (total patients: $r = 0.832$, $P < 0.001$; patients without nephropathy: $r = 0.843$, $P < 0.001$; diabetic nephropathy patients: $r = 0.828$, $P < 0.001$; Figure 2). Neither ΔGA ($r = 0.111$, $P = 0.216$) nor ΔHbA1c ($r = 0.085$, $P = 0.343$) was significantly correlated with baseline eGFR.

Among the diabetic nephropathy patients whose hemoglobin level is less than 13 g/dL, HbA1c and GA levels decreased significantly at 3 and 6 months after the start of linagliptin administration (HbA1c 7.8 ± 1.8% → 6.8 ± 1.1%, $P < 0.001$ vs. baseline → 7.1 ± 1.2%, $P = 0.0069$ vs. baseline; GA 23.8 ± 8.3% → 20.2 ± 4.5%, $P < 0.001$ vs. baseline → 21.2 ± 5.9%, $P = 0.013$ vs. baseline). Otherwise, among the diabetic nephropathy patients whose hemoglobin level is 13 g/dL or above,

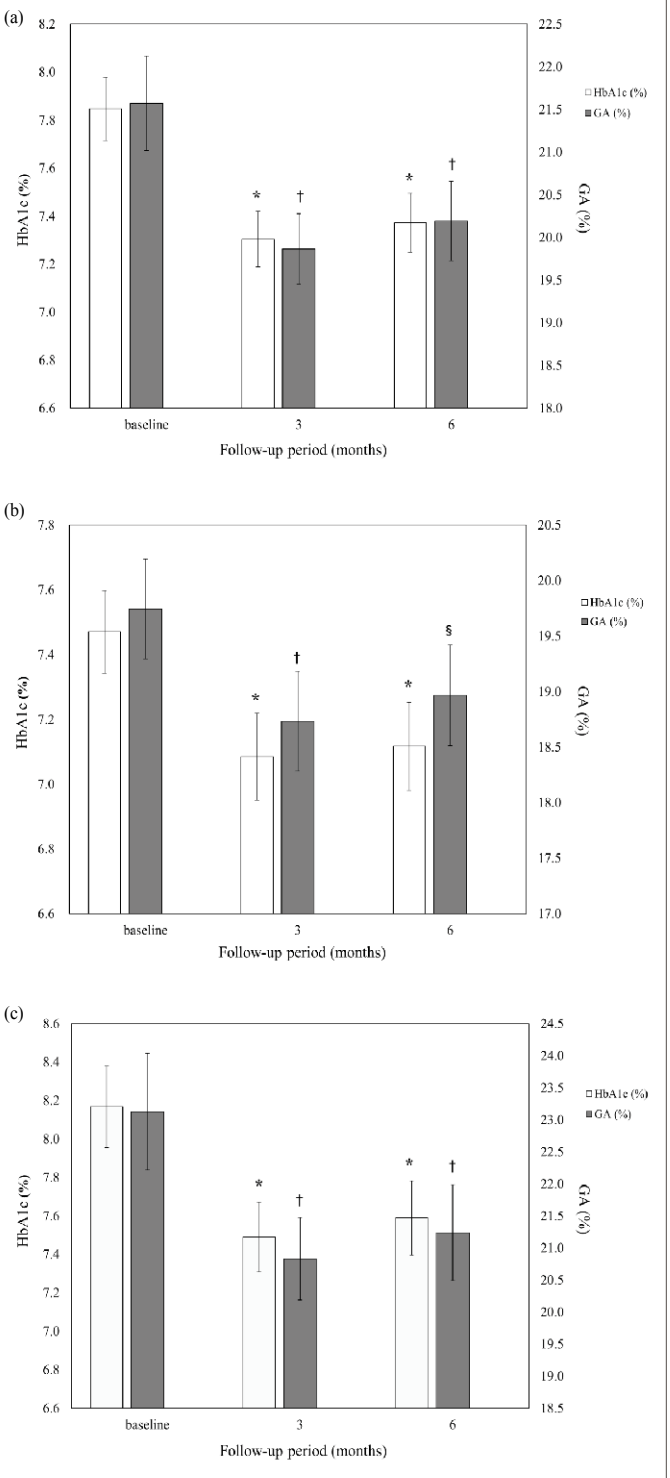
HbA1c level did not decrease significantly at 6 months and GA levels did not decrease significantly at both 3 and 6 months (HbA1c 8.7 ± 1.8% → 8.2 ± 1.7%, $P = 0.015$ vs. baseline → 8.3 ± 1.8%, $P = 0.055$ vs. baseline; GA 23.0 ± 7.3% → 21.5 ± 5.7%, $P = 0.080$ vs. baseline → 21.8 ± 6.6%, $P = 0.19$ vs. baseline).

In both patients with and without nephropathy, hemoglobin levels did not change significantly from baseline during the follow-up period (with nephropathy: 12.7 ± 2.2 g/dL → 12.6 ± 2.1 g/dL → 12.7 ± 2.3 g/dL,

| Characteristic | | | |
|---|---|---|---|
| ***N*** | **127** | **Concomitant diabetic therapy, *n* (%)** | **96 (75.6)** |
| Male sex, *n* (%) | 79 (62.2) | SU, *n* (%) | 22 (17.3) |
| Age (years) | 67.2 ± 11.9 | BG, *n* (%) | 20 (15.7) |
| Diabetes duration (years) | 15.0 ± 9.8 | TZD, *n* (%) | 3 (2.4) |
| BMI (kg/m$^2$) | 25.2 ± 4.7 | αGI, *n* (%) | 36 (28.3) |
| CPR index | 1.4 ± 1.6 | Glinide, *n* (%) | 14 (11) |
| HbA1c, (%) | 7.9 ± 1.5 | Insulin, *n* (%) | 61 (48) |
| GA, (%) | 21.6 ± 6.2 | | |
| AST, (U/L) | 24.1 ± 15.5 | Hypolipidemic agents, *n* (%) | 63 (49.6) |
| ALT, (U/L) | 21.2 ± 18.1 | Statin, *n* (%) | 59 (46.5) |
| eGFR, (mL/min/1.73 m$^2$) | 54.2 ± 23.2 | Fibrate, *n* (%) | 2 (1.6) |
| Retinopathy, *n* (%) | 49 (39.8) | Ethyl icosapentate, *n* (%) | 4 (3.1) |
| NDR, *n* (%) | 74 (60.2) | Ezetimibe, *n* (%) | 1 (0.8) |
| SDR, *n* (%) | 20 (16.3) | Others, *n* (%) | 2 (1.6) |
| PPDR, *n* (%) | 7 (3.6) | | |
| PDR, *n* (%) | 22 (17.9) | Antihypertensive drugs, *n* (%) | 84 (66.1) |
| Nephropathy, *n* (%) | 69 (54.3) | CCB, *n* (%) | 51 (40.2) |
| Stage 1, *n* (%) | 58 (45.7) | ARB, *n* (%) | 68 (53.5) |
| Stage 2, *n* (%) | 28 (22.0) | ACEI, *n* (%) | 4 (3.1) |
| Stage 3, *n* (%) | 27 (21.3) | Diuretics, *n* (%) | 26 (20.5) |
| Stage 4, *n* (%) | 9 (7.1) | α-blockers, *n* (%) | 2 (1.6) |
| Stage 5, *n* (%) | 5 (3.9) | β-blockers, *n* (%) | 22 (17.3) |
| Hypertension, *n* (%) | 88 (69.3) | | |
| Dyslipidemia, *n* (%) | 80 (63.0) | Antihyperuricemia drugs, *n* (%) | 24 (18.9) |
| Macroangiopathy, *n* (%) | 42 (33.1) | Allopurinol, *n* (%) | 15 (11.8) |
| CAD, *n* (%) | 20 (15.7) | Febuxostat, *n* (%) | 7 (5.5) |
| CVD, *n* (%) | 27 (21.3) | Others, *n* (%) | 2 (1.6) |
| ASO, *n* (%) | 2 (1.6) | | |
| | | Anticoagulant agents, *n* (%) | 10 (7.9) |
| | | Warfarin, *n* (%) | 9 (7.1) |
| | | Dabigatran, *n* (%) | 1 (0.8) |
| | | | |
| | | Antiplatelet agents, *n* (%) | 38 (29.9) |
| | | Aspirin, *n* (%) | 28 (22) |
| | | Clopidogrel, *n* (%) | 10 (7.9) |
| | | Ticlopidine, *n* (%) | 2 (1.6) |
| | | Cilostazol, *n* (%) | 6 (4.7) |

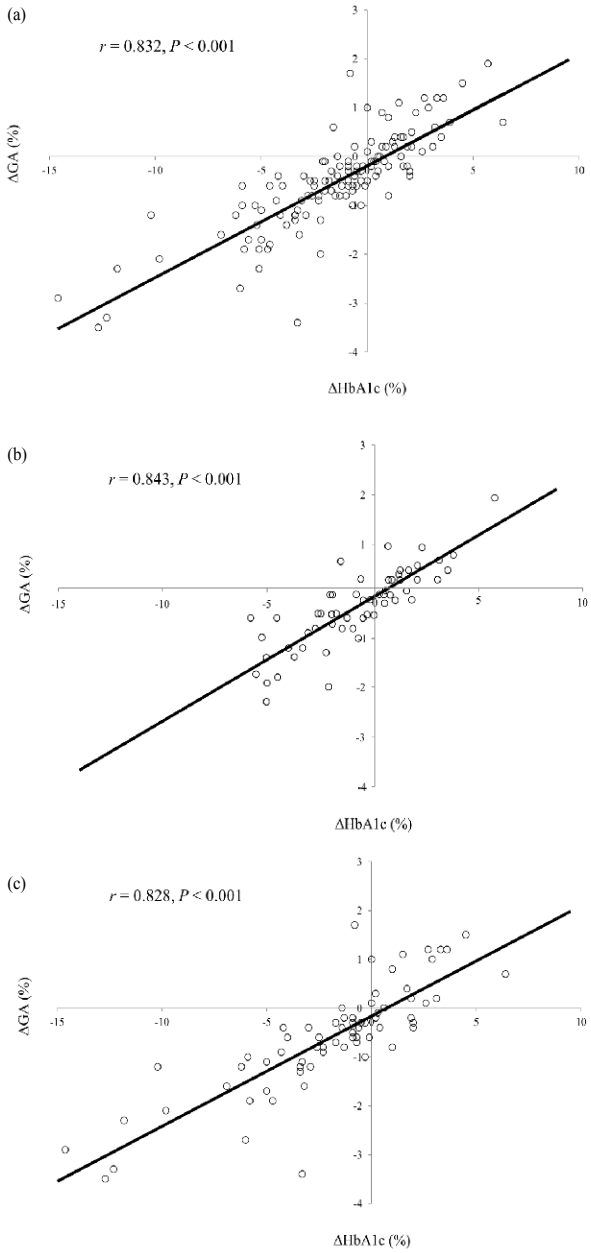
Values are expressed as number (%) or mean ± SD.
ACEI, angiotensin converting enzyme inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; ASO, arteriosclerosis obliterans; BG, biguanide; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CPR, C peptide immunoreactivity; CPR index = 100 × serum CPR (ng/mL) / blood glucose (mg/dL); CVD, cerebral vascular disease; GA, glycoalbumin; αGI, α-glucosidase inhibitor; HbA1c, hemoglobin A1c; NDR, no diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SDR, simple diabetic retinopathy; SU, sulfonylurea; TZD, thiazolidinedione

**Table 1:** Baseline patient characteristics.




*$P < 0.01$ vs. baseline for HbA1c
†$P < 0.01$ vs. baseline for GA
§$P < 0.05$ vs. baseline for GA
a) Total patients ($n = 127$)
b) Patients without diabetic nephropathy ($n = 58$)
c) Patients with diabetic nephropathy ($n = 69$)
GA, glycoalbumin; HbA1c, hemoglobin A1c

**Figure 1:** Changes in hemoglobin A1c and glycoalbumin levels after linagliptin administration.




ΔHbA1c = HbA1c at 6 months − baseline HbA1c; ΔGA = GA at 6 months − baseline GA
Horizontal axis shows ΔGA and the vertical axis ΔHbA1c.
a) Total patients (*n* = 127)
b) Patients without diabetic nephropathy (*n* = 58)
c) Patients with diabetic nephropathy (*n* = 69)
GA, glycoalbumin; HbA1c, hemoglobin A1c

**Figure 2:** Correlations between ΔHbA1c and ΔGA.

without nephropathy: 13.6 ± 1.2 g/dL → 13.6 ± 1.3 g/dL → 13.7 ± 1.2 g/dL; all $P = 1.00$ vs. baseline).

Multivariate analysis of all patients showed that the factors contributing significantly to ΔHbA1c were baseline HbA1c levels ($P = 0.001$) and diabetes duration ($P = 0.007$). Similarly, the factors contributing significantly to ΔGA were baseline GA levels ($P < 0.001$) and diabetes duration ($P = 0.017$, Table 2a). In patients with diabetic nephropathy, baseline HbA1c levels ($P = 0.002$) and diabetes duration ($P = 0.043$) significantly contributed to ΔHbA1c, whereas only baseline GA levels ($P < 0.001$) contributed significantly to ΔGA (Table 2b).

## Safety of linagliptin

No significant changes in the eGFR after linagliptin administration were observed in the total patient group (Table 3a), in patients with diabetic nephropathy (Table 3b), or in those with reduced baseline eGFR (Figure 3). Moreover, clinical parameters did not change significantly after linagliptin administration in the total patient group (Table 3a). In patients with diabetic nephropathy, only triglyceride levels changed significantly after linagliptin administration (Table 3b).

(a) Total patients (*N* = 127)
ΔHbA1c

| | *β* | SE | *t* value | *p* value |
|---|---|---|---|---|
| Sex (male = 1, female = 0) | 0.045 | 0.202 | 0.22 | 0.826 |
| Age | −0.004 | 0.009 | −0.400 | 0.69 |
| Diabetes duration | 0.029 | 0.01 | 2.774 | 0.007* |
| BMI | 0.007 | 0.022 | 0.329 | 0.743 |
| CPR index | 0.043 | 0.069 | 0.622 | 0.535 |
| Baseline HbA1c | −0.265 | 0.079 | −3.359 | 0.001* |
| eGFR | 0.008 | 0.004 | 1.731 | 0.087 |

ΔGA

| | *β* | SE | *t* value | *p* value |
|---|---|---|---|---|
| Sex (male = 1, female = 0) | 0.056 | 0.681 | 0.082 | 0.935 |
| Age | 0.046 | 0.031 | 1.484 | 0.142 |
| Diabetes duration | 0.084 | 0.034 | 2.441 | 0.017* |
| BMI | −0.021 | 0.07 | −0.301 | 0.764 |
| CPR index | −0.045 | 0.23 | −0.197 | 0.844 |
| Baseline GA | −0.332 | 0.062 | −5.392 | <0.001* |
| eGFR | 0.008 | 0.015 | 0.525 | 0.601 |

(b) Patients with diabetic nephropathy (*n* = 69)
ΔHbA1c

| | *β* | SE | *t* value | *p* value |
|---|---|---|---|---|
| Sex (male = 1, female = 0) | 0.053 | 0.32 | 0.166 | 0.869 |
| Age | −0.008 | 0.014 | −0.550 | 0.585 |
| Diabetes duration | 0.03 | 0.015 | 2.082 | 0.043* |
| BMI | −0.007 | 0.034 | 0.194 | 0.847 |
| CPR index | 0.215 | 0.186 | 1.152 | 0.256 |
| Baseline HbA1c | −0.361 | 0.111 | −3.255 | 0.002* |
| eGFR | 0.003 | 0.008 | 0.384 | 0.703 |

ΔGA

| | *β* | SE | *t* value | *p* value |
|---|---|---|---|---|
| Sex (male = 1, female = 0) | 0.928 | 1.064 | 0.106 | 0.388 |
| Age | 0.09 | 0.049 | 0.261 | 0.071 |
| Diabetes duration | 0.062 | 0.048 | 0.169 | 0.204 |
| BMI | −0.080 | 0.107 | −0.101 | 0.460 |
| CPR index | −0.288 | 0.646 | −0.080 | 0.658 |
| Baseline GA | −0.353 | 0.088 | −0.632 | <0.001* |
| eGFR | 0.009 | 0.027 | −0.053 | 0.737 |

*$P < 0.05$
ΔHbA1c = HbA1c at 6 months − baseline HbA1c; ΔGA = GA at 6 months − baseline GA
BMI, body mass index; CPR, C peptide immunoreactivity; CPR index = 100 × serum CPR (ng/mL)/blood glucose (mg/dL); eGFR, estimated glomerular filtration rate; GA, glycoalbumin; HbA1c, hemoglobin A1c; SE, standard error

**Table 2:** Factors contributing to ΔHbA1c and ΔGA.

(a) Total patients (*N* = 127)

| | Before administration | 6 months after administration | *p* value |
|---|---|---|---|
| Body weight (kg) | 66.1 ± 13.2 | 65.9 ± 13.1 | 0.675 |
| AST (U/L) | 24.1 ± 15.6 | 25.7 ± 24.0 | 0.233 |
| ALT (U/L) | 20.9 ± 17.9 | 21.0 ± 18.7 | 0.876 |
| γ-GTP (U/L) | 52.4 ± 113.4 | 58.5 ± 173.5 | 0.549 |
| eGFR (mL/min/1.73 m$^2$) | 54.2 ± 23.2 | 53.9 ± 23.9 | 0.570 |
| LDL-C (mg/dL) | 104.5 ± 31.6 | 107.5 ± 30.5 | 0.134 |
| HDL-C (mg/dL) | 48.3 ± 12.9 | 49.4 ± 13.3 | 0.064 |
| TG (mg/dL) | 169.7 ± 138.3 | 150.1 ± 101.8 | 0.098 |
| TC (mg/dL) | 188.5 ± 45.3 | 187.8 ± 41.2 | 0.803 |
| UA (mg/dL) | 5.80 ± 1.53 | 5.87 ± 1.54 | 0.369 |
| Hb (g/dL) | 13.18 ± 1.81 | 13.19 ± 1.87 | 0.958 |

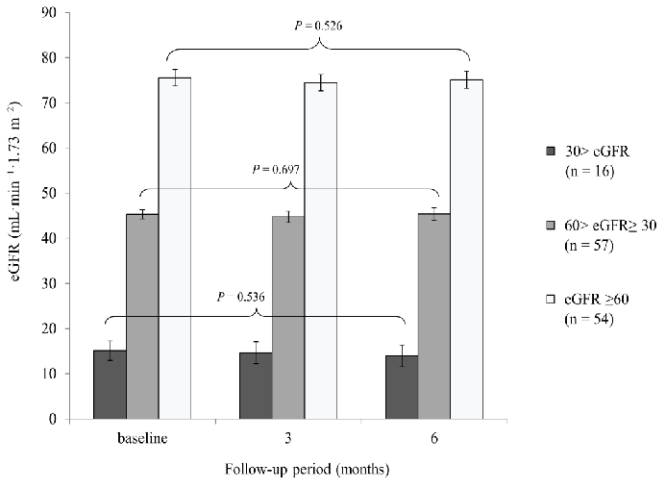
(b) Patients with diabetic nephropathy (*n* = 69)

| | Before administration | 6 months after administration | *p* value |
|---|---|---|---|
| Body weight (kg) | 66.4 ± 13.1 | 66.2 ± 13.0 | 0.674 |
| AST (U/L) | 23.8 ± 17.6 | 27.3 ± 31.5 | 0.123 |
| ALT (U/L) | 20.3 ± 21.0 | 20.7 ± 22.3 | 0.648 |
| γ-GTP (U/L) | 51.5 ± 115.5 | 72.9 ± 243.9 | 0.285 |
| eGFR (mL/min/1.73 m$^2$) | 45.1 ± 23.0 | 44.0 ± 24.1 | 0.220 |
| LDL-C (mg/dL) | 101.9 ± 34.6 | 105.7 ± 29.5 | 0.257 |
| HDL-C (mg/dL) | 46.8 ± 11.6 | 48.4 ± 11.9 | 0.059 |
| TG (mg/dL) | 182.6 ± 137.0 | 153.5 ± 108.6 | 0.014* |
| TC (mg/dL) | 185.8 ± 49.8 | 184.3 ± 42.5 | 0.715 |
| UA (mg/dL) | 6.11 ± 1.57 | 6.14 ± 1.54 | 0.749 |
| Hb (g/dL) | 12.75 ± 2.21 | 12.70 ± 2.28 | 0.685 |

*$P < 0.05$

ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, gamma-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UA, uric acid

**Table 3:** Safety of linagliptin.




eGFR was categorized as <30, 30–60, or ≥ 60 mL·min$^{-1}$·1.73 m$^{-2}$.
eGFR, estimated glomerular filtration rate

**Figure 3:** Changes in the estimated glomerular filtration rate.

## Discussion

Linagliptin treatment significantly decreased HbA1c and GA levels at 3 months, and this hypoglycemic effect was sustained for 6 months. It is suggested that GA is equivalent to HbA1c as a glycemic control indicator for two reasons. First, the changes in GA levels after linagliptin administration were similar to those in HbA1c in our study. Second, we observed strong correlations between ΔGA and ΔHbA1c in all patient group (all patients, patients without nephropathy, and patients with nephropathy). When the patients were divided into 2 groups according to their hemoglobin levels (less than 13 g/dL vs. 13 g/dL or above), HbA1c and GA changed in a similar manner. Both glycemic control indicators changed more significantly in patients with lower hemoglobin levels.

GA is expected to be a more useful indicator of glycemic control than HbA1c in patients with severe renal impairment. In our cohort, the number of the patients with severe renal impairment was small (9 patients with stage 4 and 5 with stage 5 diabetic nephropathy, Table 1). This might be why changes in GA and HbA1c over time were similar in this study. If a similar investigation would be conducted in a population including many patients with severe renal dysfunction, the results might be different.

The results of our multivariate analyses showed that higher baseline HbA1c and GA levels were associated with improvements in the patients' blood glucose control, regardless of the complication of diabetic nephropathy. In 79 randomized controlled trials, including 20,503 patients who were administered DPP-4 inhibitors (including vildagliptin, sitagliptin, saxagliptin, linagliptin, and alogliptin), higher baseline HbA1c level was a significant predictor of the HbA1c-lowering effect of DPP-4 inhibitor treatment [16]. These data are in agreement with our findings. On the other hand, baseline GA levels have been reported to be associated with the GA-lowering effect of a DPP-4 inhibitor only in one small study [17]. Our results suggest that both baseline GA and HbA1c levels can serve as predictors of blood glucose improvement after linagliptin administration, regardless of the presence of diabetic nephropathy.

The results of our multivariate analyses also showed that diabetes duration was significantly associated with both ΔGA and ΔHbA1c. Thus, shorter diabetes duration is likely indicative of a favorable hypoglycemic effect of linagliptin administration. As longer diabetes duration is associated with reduced β-cell function, our findings suggest that linagliptin is more effective in patients who maintain β-cell function.

Linagliptin treatment improved HbA1c and GA levels regardless of the baseline eGFR and did not change the eGFR in the study population. In particular, linagliptin did not decrease the eGFR in patients with a low baseline eGFR. Linagliptin has been reported to be effective and safe in diabetes patients with mild (eGFR = 60–90 mL·min$^{-1}$·1.73 m$^{-2}$), moderate (eGFR = 30–60 mL·min$^{-1}$·1.73 m$^{-2}$), and severe renal function impairment (eGFR < 30 mL·min$^{-1}$·1.73 m$^{-2}$) [18,19]. A pharmacokinetics study of linagliptin showed large overlaps in the steady-state area under the curve and $C_{max}$ values between subjects with normal renal function and those with renal function impairment [20]. Therefore, linagliptin is expected to be effective and safe in patients with a normal or low eGFR.

Our study has several limitations. First, patients not taking linagliptin were not included, i.e., we did not have a control group. Compensating for this shortcoming, we found an article reporting that linagliptin achieved consistent placebo-corrected HbA1c improvement across the three renal function categories; eGFR > 90 ml/min/1.73m$^2$: -0.63%, 60- < 90 ml/min/1.73m$^2$: -0.67%, and 30- < 60 ml/min/1.73 m$^2$: -0.53% [18]. Second, because of the retrospective design and

limited number of patients, the existence of biases and confounding factors cannot be ruled out. Third, the results may not be applicable to the general population or patients with type 2 diabetes in primary care settings, because the patients who attended the university hospital might be a distinct patient group. Therefore, further prospective studies with larger sample sizes are required to confirm the present findings.

## Conclusions

Linagliptin decreases HbA1c and GA levels regardless of the presence of diabetic nephropathy. HbA1c and GA levels are equivalent indicators of glycemic control during linagliptin treatment. High baseline HbA1c and GA levels might be good predictors of patients' responsiveness to linagliptin treatment regardless of the presence of diabetic nephropathy.

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