# Comparative effect of dipeptidyl-peptidase 4 inhibitors on laboratory parameters in patients with diabetes mellitus

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## Abstract

**Background:** The purpose of this study was to evaluate and compare the effects on laboratory parameters among monotherapy with five DPP-4 inhibitors in patients with type 2 diabetes mellitus (DM).

**Methods:** We identified cohorts of new sitagliptin users ($n = 879$), vildagliptin users ($n = 253$), teneligliptin users ($n = 260$), alogliptin users ($n = 237$), and linagliptin users ($n = 180$) in patients with type 2 DM. We used a multivariate regression model to evaluate and compare the effects of the drugs on laboratory parameters including HbA1c concentration and serum concentrations of creatinine, estimated glomerular filtration rate, high density lipoprotein, total cholesterol, triglyceride, aspartate aminotransferase, and alanine aminotransferase among the five DPP-4 inhibitors up to 12 months.

**Results:** Our study showed a favorable effect on HbA1c concentration and a slightly unfavorable effect on serum creatinine concentration in users of the five DPP-4 inhibitors, a favorable effect on lipid metabolism in sitagliptin, vildagliptin, and alogliptin users, and a favorable effect on hepatic parameters in sitagliptin, alogliptin, and linagliptin users, in comparison of the baseline and exposure periods. However, there was no significant difference in mean change in the concentration of any laboratory parameter among the five groups of DPP-4 inhibitor users.

**Conclusions:** In this study, we showed the effect of five DPP-4 inhibitors on glycemic, renal, and lipid metabolism, and hepatic parameters. DPP-4 inhibitors are well-tolerated hypoglycemic drugs.

**Keywords:** Diabetes mellitus, Dipeptidyl-peptidase 4 inhibitor, Sitagliptin, Vildagliptin, Teneligliptin, Alogliptin, Linagliptin

## Background

Diabetes mellitus (DM) is a major risk factor for chronic kidney disease, cardiovascular disease, and chronic liver disease, including nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) [1–3]. In patients with type 2 DM, alteration of the lipid profile is an important factor in cardiovascular disease [4]. Therefore, it is important to understand the etiology of these

complications in patients with DM and to control laboratory parameters associated with renal function, lipoprotein metabolism, and liver function.

By blocking the dipeptidyl-peptidase 4 (DPP-4) enzyme, DPP-4 inhibitors increase insulin secretion by prevention of degradation of incretin hormones including glucagon-like peptide-1 (GLP-1) [2]. DPP-4 inhibitors exhibit different characteristics, including the duration of action, absorption, distribution, metabolism, and elimination. Sitagliptin is eliminated via the kidney, and is mainly excreted in urine as unchanged compound. Therefore, sitagliptin is contraindicated in patients with chronic renal failure [5, 6]. Vildagliptin is

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excreted by the kidney, but is rapidly converted to an inactive metabolite. Therefore, vildagliptin dosage does not have to be modified in patients with mild renal dysfunction [6]. Teneligliptin is mainly metabolized by cytochrome P450 (CYP) 3A4 and flavin monooxygenases, and approximately 34% is excreted in urine as unchanged compound. Teneligliptin is eliminated via dual hepatic and renal routes, and therefore can be used in patients with renal dysfunction without dose adjustment [7]. Alogliptin is mainly excreted in urine as unchanged compound, and 10% of alogliptin is metabolized by CYP2D6 and CYP3A4 [8]. Dose adjustment of alogliptin is not recommended in patients with mild renal dysfunction, but is recommended in patients with moderate to severe renal dysfunction [5, 8]. Linagliptin can be safely used in patients with renal impairment, because, differentiated from other DPP-4 inhibitors, linagliptin is primarily excreted unchanged via an entero-hepatic mechanism [6, 8].

Recently, the pleiotropic effects on several DPP-4 inhibitors have been reported. Sitagliptin administration for 12 weeks was effective in lowering blood pressure, triglyceride (TG), total cholesterol (TC), and alkaline phosphatase concentrations in patients with type 2 DM [9]. A meta-analysis of eight Phase III studies of linagliptin showed that therapy with linagliptin significantly lowered the risk of cardiovascular events versus a comparator. On the other hand, vildagliptin was associated with an increase in liver enzymes. Sitagliptin is contraindicated in patients with chronic kidney disease [5, 6].

Considering the association of DM and various diseases, including chronic kidney disease, cardiovascular disease, dyslipidemia, and chronic liver disease, it is important to investigate which DPP-4 inhibitors influence laboratory parameters other than parameters of glucose metabolism. The aim of this study was to evaluate and compare the effects on laboratory parameters, including renal parameters, lipid metabolism parameters, and hepatic parameters, among monotherapy with five DPP-4 inhibitors, sitagliptin, vildagliptin, teneligliptin, alogliptin, and linagliptin, in patients with type 2 DM.

## Methods
### Data source
This study was a retrospective cohort study utilizing data from the Nihon University School of Medicine (NUSM) Clinical Data Warehouse (CDW) between December 1, 2009 and December 31, 2018. NUSM's CDW centralizes an order entry database and a laboratory results database, from the hospital information systems at three hospitals affiliated with NUSM, and is described elsewhere [10]. In all databases in NUSM's CDW, patient identifiers are replaced by anonymized identifiers to protect patient privacy. The data in NUSM's CDW are mutually linked by anonymized identifiers, and the prescription data of over 0.7 million patients are longitudinally linked

with patient demographics, diagnosis, and laboratory data. Several epidemiological studies examining the effects of various drugs on laboratory parameters using NUSM's CDW have been published [11–13]. The experimental protocol was approved by the Ethical Committee of Nihon University School of Medicine, and the study was conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, Japan [14].

### Study populations
The subjects of this study were Japanese patients with type 2 DM aged over 20 years who had been newly treated with a DPP-4 inhibitor (sitagliptin, vildagliptin, teneligliptin, alogliptin or linagliptin) listed in Table 1, for at least three months. We identified 2753 patients with type 2 DM treated with sitagliptin (50 mg/day), 1442 with vildagliptin (100 mg/day), 1170 with teneligliptin (20 mg/day), 796 with alogliptin (25 mg/day), and 445 with linagliptin (5 mg/day). We excluded patients who met one of the following six criteria; 1. Patients with severe renal failure (estimated glomerular filtration rate, eGFR < 15), 2. Patients with acute renal failure (ICD10 code: N17), 3. Patients with acute hepatic failure (K72), 4. Patients on dialysis, and patients treated with GLP1 during the study period, 5. Patients who had been treated with other antidiabetic agents and/or lipid-lowering drugs during the exposure period, 6. Patients who had not received regular checks of hemoglobin A1c (HbA1c). After exclusion, the study population consisted of 879 for sitagliptin, 253 for vildagliptin, 260 for teneligliptin, 237 for alogliptin, and 180 for linagliptin (Table 1).

### Data elements
We collected the demographic data of age and sex, medical histories, and medication of each patients from database to use as a covariates for adjustment. Medical history included the following four diagnoses: 1) cerebrovascular disease (ICD-10 code; I60–69), 2) ischemic heart disease (I20-I25), 3) hyperlipidemia (E78.0-E78.5), and 4) hypertension (I10-I15) during the 365 days before the date of first use of each DPP-4 inhibitor. Medications during the 90 days before the first administration of each DPP-4 inhibitor included the following drugs: 1) oral hypoglycemic drugs, 2) lipid-lowering drugs, 3) antihypertensive drugs, 4) non-steroidal anti-inflammatory drugs (NSAIDs), and 5) steroids.

### Outcomes
The concentrations of HbA1c, serum creatinine, high density lipoprotein (HDL), TC, TG, aspartate aminotransferase

**Table 1** Numbers of cases of monotherapy with DPP-4 inhibitors

| Generic name | Trade name | Dose (daily) | Number of cases of monotherapy |
|---|---|---|---|
| Sitagliptin | Jauvia®, Glactive® | 50 mg | 879 |
| Vildagliptin | Equa® | 100 mg | 253 |
| Teneligliptin | Tenelia® | 20 mg | 260 |
| Alogliptin | Nesina® | 25 mg | 237 |
| Linagliptin | Trasenta® | 5 mg | 180 |

*DPP-4* dipeptidyl-peptidase 4

(AST), and alanine aminotransferase (ALT) were determined by routine laboratory testing at the hospital of the NUSM. eGFR was calculated using the formula for Japanese subjects specified by the Japanese Society of Nephrology (JSN): eGFR [JSN equation for Japanese] (mL/min/1.73 $m^2$) = $194*SCr^{-1.094}*Age^{-0.287}$ (*0.739 if female) [15]. We defined the baseline measurement period, the non-exposure period, as within 3 months before the start of administration of each DPP-4 inhibitor. We defined the exposure period, the outcome measurement period, as between 1 and 3 months (1-3 M) and between 3 and 12 months (3-12 M) after the start of administration of each DPP-4 inhibitor. Laboratory test data for outcome including HbA1c, serum creatinine, HDL, TC, TG, AST, and ALT were collected at the nearest date to the start of DPP-4 inhibitor administration in the baseline period, and at the dates nearest 3 months and 12 months after the start of DPP-4 inhibitor administration in the exposure period. The mean number of exposure days in the 1-3 M period was $56.2 \pm 0.5$ days for sitagliptin, $56.3 \pm 1.0$ for vildagliptin, $55.8 \pm 1.1$ for teneligliptin, $59.0 \pm 1.1$ for alogliptin, and $53.5 \pm 1.1$ for linagliptin. The mean number of exposure days in the 3-12 M period was $232.6 \pm 6.8$ days for sitagliptin, $230.0 \pm 12.5$ for vildagliptin, $221.7 \pm 10.3$ for teneligliptin, $224.0 \pm 12.6$ for alogliptin, and $242.4 \pm 13.1$ for linagliptin.

## Statistics

We applied a general linear model for continuous data (age and baseline values of laboratory parameters) and chi-squared test for categorical data for comparing the differences in baseline characteristics among the five DPP-4 inhibitors, sitagliptin, vildagliptin, teneligliptin, alogliptin, and linagliptin. We applied a mixed linear model, which was adjusted for age and sex, for the assessment of the differences in mean values of laboratory parameters between the baseline and exposure periods. A multiple-comparison test (Dunnett's post-hoc analysis) was used to analyze the differences in least square means between the baseline and exposure periods. This study was a retrospective observational study with repeated measures data of non-randomized subjects, which had inherent issues of selection bias and confounding factors. Therefore, we used an adjusted mixed linear model to assess the differences in mean changes

in values of laboratory parameters among the five DPP-4 inhibitors. To adjust the model for potential confounding factors, we used the following background variables which were unbalanced among the five DPP-4 inhibitors; time, age, sex, medical history in baseline period including ischemic heart disease and hypertension, medication in baseline period including hypoglycemic drugs and lipid-lowering drugs, and baseline concentration of HbA1c. In addition, the baseline concentrations of creatinine, HDL, AST and ALT were included in the covariates in each analysis of creatinine, HDL, AST and ALT, because differences in baseline values might influence these parameters. All reported *p*-values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

## Results

Table 2 shows the prevalence of treatment with antidiabetic drugs during the baseline period. The percentage of patients who had not received any therapy with antidiabetic drugs before the initiation of DPP-4 inhibitors was 28.6% for the sitagliptin group, 39.1% for vindagliptin, 55.8% for teneligliptin, 39.2% for alogliptin, and 49.4% for linagliptin.

Table 3 shows the baseline characteristics of each DPP-4 inhibitor group in our study. Mean age was $63.1 \pm 0.4$ in sitagliptin users, $64.2 \pm 0.8$ in vildagliptin, $66.0 \pm 0.8$ in teneligliptin, $63.5 \pm 0.8$ in alogliptin, and $67.2 \pm 0.9$ in linagliptin. The percentage of females was 317 (36.1%) in sitagliptin users, 79 (31.7%) in vildagliptin, 87 (33.5%) in teneligliptin, 72 (30.4%) in alogliptin, and 58 (32.2%) in linagliptin. There were significant differences in mean age and the proportions of patients with a medical history of ischemic heart disease and hypertension, and treatment with antidiabetic drugs and lipid-lowering drugs among the five groups of DPP-4 inhibitor users.

Table 4 shows the unadjusted and adjusted baseline concentrations of laboratory parameters. There were significant differences in the baseline concentrations of HbA1c, serum creatinine, HDL, AST, and ALT and eGFR among the five groups of DPP-4 inhibitor users.

Table 5 shows the least square mean concentrations of laboratory parameters during the study period. Compared

**Table 2** Antidiabetic drugs prior to administration of DPP-4 inhibitors

| Antidiabetic drugs | Sitagliptin | Vildagliptin | Teneligliptin | Alogliptin | Linagliptin |
|---|---|---|---|---|---|
| Insulin | 145 (16.5%) | 26 (10.3%) | 55 (21.2%) | 8 (3.4%) | 30 (16.7%) |
| Sulphonylurea | 333 (37.9%) | 69 (27.3%) | 36 (13.9%) | 71 (30%) | 30 (16.7%) |
| Biguanide | 275 (31.3%) | 63 (24.9%) | 36 (13.9%) | 49 (20.7%) | 34 (18.9%) |
| Alpha-glucosidase inhibitor | 189 (21.5%) | 43 (17%) | 22 (8.5%) | 46 (19.4%) | 15 (8.3%) |
| Thiazolidinedione | 102 (11.6%) | 21 (8.3%) | 7 (2.7%) | 51 (21.5%) | 4 (2.2%) |
| Glinide | 75 (8.5%) | 21 (8.3%) | 10 (3.9%) | 11 (4.6%) | 15 (8.3%) |
| SGLT2 inhibitor | 5 (0.6%) | 2 (0.8%) | 10 (3.9%) | 0 (0%) | 3 (1.7%) |
| Nothing | 251 (28.6%) | 99 (39.1%) | 145 (55.8%) | 93 (39.2%) | 89 (49.4%) |

*DPP-4* dipeptidyl-peptidase 4, *SGLT2* sodium glucose co-transporter 2

with baseline, HbA1c concentration was significantly decreased in the exposure period in all DPP-4 inhibitor users. Serum creatinine concentration was significantly increased in the exposure period in all DPP-4 inhibitor users. eGFR was significantly decreased in the exposure period in patients with sitagliptin, vildagliptin, teneligliptin, and linagliptin, and significantly decreased during 3 months in patients with alogliptin. Serum HDL concentration was significantly decreased in the exposure period in patients with sitagliptin and vildagliptin. Serum TC concentration was significantly decreased during 3 months in patients with sitagliptin, vildagliptin, and alogliptin. Serum TG concentration was significantly decreased during 3 months in patients with sitagliptin, vildagliptin, and alogliptin. Serum AST concentration was significantly decreased during 3 months in patients with alogliptin. Serum ALT concentration was significantly decreased in the exposure period in patients with sitagliptin, alogliptin, and linagliptin,

Table 6 shows the least square mean changes in laboratory parameters during the exposure period from baseline. After adjustment, there was no significant difference in mean changes in concentrations of laboratory parameters among the five groups of DPP-4 inhibitor users.

## Discussion

In this study, we compared the long-term effect of monotherapy among five DPP-4 inhibitors, sitagliptin, vildagliptin, teneligliptin, alogliptin, and linagliptin, on laboratory parameters in patients with type 2 DM, during 12 months of treatment. Our results showed a favorable effect on HbA1c concentration in users of five DPP-4 inhibitors, a slightly unfavorable effect on serum creatinine concentration in users of five DPP-4 inhibitors, a favorable effect on lipid metabolism in sitagliptin, vildagliptin, and alogliptin users, and a favorable effect on hepatic parameters in sitagliptin, alogliptin, and

**Table 3** Baseline characteristics of users of DPP-4 inhibitors

| Variables | Sitagliptin | Vildagliptin | Teneligliptin | Alogliptin | Linagliptin | *p*-value |
|---|---|---|---|---|---|---|
| | *n* = 879 | *n* = 253 | *n* = 260 | *n* = 237 | *n* = 180 | |
| Age (years, mean ± SE) | 63.1 ± 0.4 | 64.2 ± 0.8 | 66 ± 0.8 | 63.5 ± 0.8 | 67.2 ± 0.9 | 0.0002* |
| Sex (female) | 317 (36.1%) | 79 (31.2%) | 87 (33.5%) | 72 (30.4%) | 58 (32.2%) | 0.3791 |
| **Medical History** | | | | | | |
| Cerebrovascular disease | 24 (50%) | 7 (14.6%) | 7 (14.6%) | 6 (12.5%) | 4 (8.3%) | 0.9963 |
| Ischemic heart disease | 74 (8.4%) | 29 (11.5%) | 14 (5.4%) | 29 (12.2%) | 20 (11.1%) | 0.038* |
| Dyslipidemia | 95 (10.8%) | 44 (17.4%) | 28 (10.8%) | 27 (11.4%) | 23 (12.8%) | 0.0688 |
| Hypertension | 78 (8.9%) | 34 (13.4%) | 38 (14.6%) | 26 (11%) | 34 (18.9%) | 0.0008* |
| **Medication** | | | | | | |
| Antidiabetic drug | 628 (71.4%) | 154 (60.9%) | 115 (44.2%) | 144 (60.8%) | 91 (50.6%) | <.0001* |
| Lipid-lowering drug | 377 (42.9%) | 115 (45.5%) | 101 (38.9%) | 127 (53.6%) | 76 (42.2%) | 0.0138* |
| Antihypertensive drug | 513 (58.4%) | 156 (61.7%) | 154 (59.2%) | 157 (66.2%) | 114 (63.3%) | 0.2087 |
| NASID | 177 (20.1%) | 44 (17.4%) | 54 (20.8%) | 45 (19%) | 33 (18.3%) | 0.8433 |
| Steroid | 67 (7.6%) | 21 (8.3%) | 33 (12.7%) | 22 (9.3%) | 22 (12.2%) | 0.0695 |

*DPP-4* dipeptidyl-peptidase 4, *SE* standard error, *NSAID* non-steroidal anti-inflammatory drug
*$p$ < 0.05 (among five DPP-4 inhibitors)

**Table 4** Baseline values of laboratory parameters

| Laboratory parameters | Sitagliptin mean (95%CI) | Vildagliptin mean (95%CI) | Teneligliptin mean (95%CI) | Alogliptin mean (95%CI) | Linagliptin mean (95%CI) | *p*-value |
|---|---|---|---|---|---|---|
| HbA1c (%) | 7.8 (7.7, 7.9) | 7.8 (7.6, 7.9) | 7.8 (7.7, 8) | 7.4 (7.2, 7.6) | 7.4 (7.3, 7.6) | <.0001* |
| Creatinine (mg/dL) | 0.8 (0.77, 0.82) | 0.89 (0.85, 0.93) | 0.94 (0.9, 0.98) | 0.82 (0.78, 0.87) | 1.04 (0.99, 1.09) | <.0001* |
| eGFR (mL/min/1.73m$^2$) | 74 (72.6, 75.5) | 70.3 (67.6, 73.1) | 66.3 (63.7, 68.9) | 72.5 (69.7, 75.3) | 61.8 (58.6, 65) | <.0001* |
| HDL (mg/dL) | 51.3 (50.3, 52.3) | 47.3 (45.4, 49.1) | 50.1 (48.3, 52) | 47.5 (45.6, 49.5) | 48.9 (46.7, 51.1) | 0.0002* |
| TC (mg/dL) | 192.3 (189.6, 194.9) | 188.7 (183.7, 193.7) | 190.1 (185.2, 194.9) | 188 (182.6, 193.4) | 189.3 (183.5, 195.1) | 0.5242 |
| TG (mg/dL) | 145 (139.1, 151) | 160.3 (148.9, 171.7) | 151.3 (140.5, 162) | 155 (143.3, 166.6) | 146.2 (133.2, 159.2) | 0.1483 |
| AST (U/L) | 27.8 (26.5, 29.1) | 30.3 (27.9, 32.7) | 29.8 (27.5, 32.2) | 29.9 (27.4, 32.4) | 24.7 (21.9, 27.5) | 0.0124* |
| ALT (U/L) | 30.4 (28.7, 32.1) | 32.3 (29.1, 35.6) | 30.2 (27.1, 33.3) | 34.7 (31.4, 38.1) | 26.2 (22.4, 29.9) | 0.0157* |

*$p < 0.05$ (among five DPP-4 inhibitors)
*HbA1c* hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *HDL* high density lipoprotein, *TC* total cholesterol, *TG* triglyceride, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CI* confidence interval

linagliptin users. However, there was no significant difference in the mean change in concentration of any laboratory parameter among the five groups of DPP-4 inhibitor users.

DPP-4 inhibitors are known to lower glycemic parameters in a glucose-dependent manner [2, 5, 6]. Compared with placebo, DPP-4 inhibitor monotherapy and combination with other agents significantly decreased HbA1c concentration at 24 weeks by 0.6% [5]. The mean reduction in HbA1c concentration was similar to that with DPP-4 inhibitors in patients with renal dysfunction [16]. In our study, the HbA1C concentration during the exposure period was significantly lower than that in the baseline period in all DPP-4 inhibitor users, and the mean change in HbA1c concentration showed no significant difference among the five groups of DPP-4 inhibitor users. These results confirmed that these five DPP-4 inhibitors are effective for glycemic control.

Serum creatinine concentration was increased during the exposure period compared with that in the baseline period in all DPP-4 inhibitor users. However, the mean change in creatinine concentration showed no significant difference among the five groups of DPP-4 inhibitor users. eGFR was significantly decreased in the exposure period in patients with sitagliptin, vildagliptin, teneligliptin, and linagliptin, and significantly decreased during 3 months in patients with alogliptin. However, the mean change in eGFR showed no significant difference among the five groups of DPP-4 inhibitor users. Sitagliptin has been reported to decrease eGFR in patients with diabetes mellitus with baseline eGFR > 60 up to 12 months [17]. The decrease in eGFR is explained by elimination of hyperfiltration. Treatment with GLP-1 has been reported to increase sodium excretion, and, via tubulo-glomerular feedback, decrease GFR in insulin-resistant obese men [18]. Therefore, our result of an increase in serum creatinine concentration in users of the five DPP-4 inhibitors might reflect the elimination of hyperfiltration, and

the effect may be small and may not be of clinical concern, consistent with previous reports.

Serum HDL concentration during the exposure period was significantly lower than that in the baseline period in sitagliptin and vildagliptin users. Serum TC and TG concentrations during the 3 M period were significantly lower than that in the baseline period in sitagliptin, vildagliptin, and alogliptin users. However, the mean changes in HDL, TC, and TG concentrations showed no significant difference among the five groups of DPP-4 inhibitor users. The results of DPP-4 inhibitors' effects on lipid metabolism parameters are diverse and inconclusive [2]. Park et al. reported a significant increase in HDL concentration in patients with 12-week administration of sitagliptin or linagliptin, and showed a decreasing trend in TC, TG, and LD in patients with 12-week administration of sitagliptin, vildagliptin, or linagliptin [19]. Kubota et al. reported that administration of sitagliptin significantly decreased TC and LDL concentrations, and tended to decrease HDL concentration in patients with type 2 DM, up to 12 weeks [9]. Takeda et al. reported that administration of alogliptin significantly decreased TC and LDL concentrations in patient with type 2 DM, up to 12 weeks [20]. In our results, HDL concentration was slightly decreased in the exposure period in sitagliptin and vildagliptin users. TC and TG concentrations were significantly decreased in the 3 M period in sitagliptin, vildagliptin, and alogliptin users. However, the mean changes in HDL, TC, and TG concentrations showed no significant difference among the five groups of DPP-4 inhibitor users. DPP-4 inhibitors might have a beneficial effect on lipid concentrations; however, further studies are needed to investigate the mechanism of the effect of DPP-4 inhibitors on lipid metabolism [2].

Of the hepatic parameters in our results, serum AST concentration during the 3 M period was significantly lower than that in the baseline period in alogliptin users. Serum ALT concentration during the exposure period

**Table 5** Relationship between treatment duration and laboratory parameters

| Laboratory parameters | Drugs | Time point | N | Unadjusted LS Mean (95%CI) | *p*-value | [a]Adjusted LS Mean (95%CI) | *p*-value |
|---|---|---|---|---|---|---|---|
| HbA1c (%) | Sitagliptin | | | | <.0001 | | <.0001 |
| | | baseline | 879 | 7.8 (7.7, 7.9) | reference | 7.8 (7.8, 7.9) | reference |
| | | 0-3 M | 835 | 7.4 (7.3, 7.4) | * | 7.4 (7.3, 7.5) | * |
| | | 3-12 M | 208 | 7.2 (7, 7.3) | * | 7.2 (7.1, 7.3) | * |
| | Vildagliptin | | | | <.0001 | | <.0001 |
| | | baseline | 253 | 7.8 (7.6, 7.9) | reference | 7.7 (7.6, 7.9) | reference |
| | | 0-3 M | 241 | 7.2 (7, 7.3) | * | 7.1 (7, 7.3) | * |
| | | 3-12 M | 64 | 7.1 (6.9, 7.3) | * | 7 (6.8, 7.2) | * |
| | Teneligliptin | | | | <.0001 | | <.0001 |
| | | baseline | 260 | 7.8 (7.7, 8) | reference | 7.9 (7.7, 8) | reference |
| | | 0-3 M | 237 | 7.2 (7.1, 7.4) | * | 7.2 (7.1, 7.4) | * |
| | | 3-12 M | 95 | 6.9 (6.7, 7.1) | * | 6.9 (6.7, 7.1) | * |
| | Alogliptin | | | | <.0001 | | <.0001 |
| | | baseline | 237 | 7.4 (7.3, 7.5) | reference | 7.4 (7.3, 7.6) | reference |
| | | 0-3 M | 216 | 7 (6.8, 7.1) | * | 7 (6.9, 7.1) | * |
| | | 3-12 M | 61 | 6.8 (6.6, 7) | * | 6.8 (6.6, 7) | * |
| | Linagliptin | | | | <.0001 | | <.0001 |
| | | baseline | 180 | 7.4 (7.3, 7.6) | reference | 7.4 (7.3, 7.6) | reference |
| | | 0-3 M | 176 | 7 (6.8, 7.1) | * | 6.9 (6.8, 7.1) | * |
| | | 3-12 M | 58 | 6.8 (6.6, 7) | * | 6.8 (6.6, 7) | * |
| creatinine (mg/dL) | Sitagliptin | | | | <.0001 | | <.0001 |
| | | baseline | 831 | 0.8 (0.78, 0.82) | reference | 0.76 (0.75, 0.78) | reference |
| | | 0-3 M | 795 | 0.82 (0.8, 0.84) | * | 0.79 (0.77, 0.8) | * |
| | | 3-12 M | 198 | 0.86 (0.83, 0.88) | * | 0.82 (0.8, 0.85) | * |
| | Vildagliptin | | | | 0.035 | | 0.0375 |
| | | baseline | 233 | 0.89 (0.84, 0.94) | reference | 0.84 (0.79, 0.89) | reference |
| | | 0-3 M | 222 | 0.91 (0.86, 0.97) | | 0.87 (0.81, 0.92) | |
| | | 3-12 M | 60 | 0.93 (0.87, 0.99) | | 0.88 (0.82, 0.94) | |
| | Teneligliptin | | | | <.0001 | | <.0001 |
| | | baseline | 259 | 0.94 (0.88, 1) | reference | 0.88 (0.82, 0.94) | reference |
| | | 0-3 M | 239 | 0.98 (0.91, 1.04) | * | 0.92 (0.86, 0.98) | * |
| | | 3-12 M | 98 | 1.05 (0.98, 1.12) | * | 0.99 (0.92, 1.06) | * |
| | Alogliptin | | | | 0.0001 | | 0.0001 |
| | | baseline | 226 | 0.82 (0.79, 0.86) | reference | 0.77 (0.74, 0.8) | reference |
| | | 0-3 M | 205 | 0.85 (0.82, 0.88) | * | 0.8 (0.77, 0.83) | * |
| | | 3-12 M | 62 | 0.86 (0.82, 0.9) | * | 0.81 (0.77, 0.85) | * |
| | Linagliptin | | | | 0.002 | | 0.0021 |
| | | baseline | 174 | 1.04 (0.95, 1.12) | reference | 0.99 (0.91, 1.08) | reference |
| | | 0-3 M | 169 | 1.08 (1, 1.16) | * | 1.03 (0.95, 1.12) | * |
| | | 3-12 M | 58 | 1.12 (1.03, 1.21) | * | 1.07 (0.98, 1.17) | * |
| eGFR (mL/min/1.73m$^2$) | Sitagliptin | | | | <.0001 | | <.0001 |
| | | baseline | 831 | 74 (72.7, 75.4) | reference | 74.4 (73.2, 75.5) | reference |
| | | 0-3 M | 795 | 72.1 (70.8, 73.5) | * | 72.4 (71.3, 73.6) | * |

**Table 5** Relationship between treatment duration and laboratory parameters *(Continued)*

| Laboratory parameters | Drugs | Time point | N | Unadjusted LS Mean (95%CI) | *p*-value | [a]Adjusted LS Mean (95%CI) | *p*-value |
|---|---|---|---|---|---|---|---|
| | | 3-12 M | 198 | 70 (68.3, 71.7) | * | 70.4 (68.8, 71.9) | * |
| | Vildagliptin | | | | <.0001 | | <.0001 |
| | | baseline | 233 | 70.3 (67.3, 73.3) | reference | 70.6 (67.7, 73.6) | reference |
| | | 0-3 M | 222 | 67.5 (64.5, 70.6) | * | 67.8 (64.9, 70.8) | * |
| | | 3-12 M | 60 | 69 (65.6, 72.4) | | 69.3 (66, 72.7) | |
| | Teneligliptin | | | | <.0001 | | <.0001 |
| | | baseline | 259 | 66.3 (63.6, 69) | reference | 67 (64.4, 69.5) | reference |
| | | 0-3 M | 239 | 63.6 (60.8, 66.3) | * | 64.2 (61.7, 66.8) | * |
| | | 3-12 M | 98 | 63 (60, 66) | * | 63.7 (60.8, 66.5) | * |
| | Alogliptin | | | | 0.0009 | | 0.0009 |
| | | baseline | 226 | 72.5 (70, 75) | reference | 73.2 (70.8, 75.7) | reference |
| | | 0-3 M | 205 | 70.6 (68, 73.1) | * | 71.3 (68.8, 73.8) | * |
| | | 3-12 M | 62 | 70.4 (67.5, 73.3) | | 71.2 (68.3, 74.1) | |
| | Linagliptin | | | | 0.001 | | 0.001 |
| | | baseline | 174 | 61.8 (58, 65.7) | reference | 62.2 (58.3, 66.1) | reference |
| | | 0-3 M | 169 | 59.8 (56, 63.7) | * | 60.2 (56.3, 64.1) | * |
| | | 3-12 M | 58 | 59.5 (55.4, 63.6) | * | 59.9 (55.7, 64) | * |
| HDL (mg/dL) | Sitagliptin | | | | 0.0037 | | 0.0033 |
| | | baseline | 726 | 51.3 (50.3, 52.3) | reference | 52.2 (51.2, 53.2) | reference |
| | | 0-3 M | 685 | 50.5 (49.4, 51.5) | * | 51.4 (50.3, 52.4) | * |
| | | 3-12 M | 141 | 50 (48.6, 51.5) | | 50.9 (49.5, 52.3) | * |
| | Vildagliptin | | | | 0.0007 | | 0.0008 |
| | | baseline | 203 | 47.3 (45.6, 49) | reference | 48.6 (46.9, 50.3) | reference |
| | | 0-3 M | 194 | 46.1 (44.4, 47.8) | * | 47.4 (45.7, 49.1) | * |
| | | 3-12 M | 50 | 44.5 (42.3, 46.6) | * | 45.8 (43.7, 48) | * |
| | Teneligliptin | | | | 0.427 | | 0.4293 |
| | | baseline | 212 | 50.1 (48.3, 52) | reference | 51.8 (49.9, 53.6) | reference |
| | | 0-3 M | 188 | 50.2 (48.4, 52.1) | | 51.8 (50, 53.7) | |
| | | 3-12 M | 78 | 49.3 (47.1, 51.4) | | 50.9 (48.7, 53) | |
| | Alogliptin | | | | 0.5739 | | 0.5798 |
| | | baseline | 183 | 47.5 (45.6, 49.5) | reference | 48.6 (46.5, 50.7) | reference |
| | | 0-3 M | 163 | 47.1 (45.1, 49) | | 48.1 (46, 50.2) | |
| | | 3-12 M | 47 | 46.7 (44.2, 49.3) | | 47.8 (45.1, 50.4) | |
| | Linagliptin | | | | 0.3891 | | 0.3894 |
| | | baseline | 144 | 48.9 (46.8, 51) | reference | 49.7 (47.5, 51.9) | reference |
| | | 0-3 M | 140 | 48.3 (46.2, 50.4) | | 49.1 (46.9, 51.3) | |
| | | 3-12 M | 43 | 49.7 (47, 52.3) | | 50.4 (47.7, 53.2) | |
| TC (mg/dL) | Sitagliptin | | | | 0.0004 | | 0.0004 |
| | | baseline | 728 | 192.3 (189.8, 194.8) | reference | 194 (191.5, 196.5) | reference |
| | | 0-3 M | 682 | 188.9 (186.3, 191.4) | * | 190.6 (188, 193.2) | * |
| | | 3-12 M | 161 | 194.3 (190.4, 198.3) | | 196 (192.1, 200) | |
| | Vildagliptin | | | | 0.0071 | | 0.0024 |
| | | baseline | 204 | 188.7 (183.6, 193.8) | reference | 190.9 (185.6, 196.2) | reference |

**Table 5** Relationship between treatment duration and laboratory parameters *(Continued)*

| Laboratory parameters | Drugs | Time point | N | Unadjusted LS Mean (95%CI) | *p*-value | [a]Adjusted LS Mean (95%CI) | *p*-value |
|---|---|---|---|---|---|---|---|
| | | 0-3 M | 194 | 183.4 (178.2, 188.6) | * | 185.5 (180.2, 190.9) | * |
| | | 3-12 M | 50 | 183.7 (176.5, 190.9) | | 186 (178.7, 193.4) | |
| | Teneligliptin | | | | 0.0668 | | 0.0764 |
| | | baseline | 217 | 190.1 (185.2, 195) | reference | 193.6 (188.7, 198.5) | reference |
| | | 0-3 M | 196 | 186.5 (181.5, 191.5) | | 189.9 (184.9, 194.9) | |
| | | 3-12 M | 76 | 185 (178.5, 191.4) | | 188.9 (182.4, 195.3) | |
| | Alogliptin | | | | 0.043* | | 0.0372 |
| | | baseline | 176 | 188 (182.5, 193.5) | reference | 189.5 (183.6, 195.4) | reference |
| | | 0-3 M | 153 | 183.4 (177.8, 189) | * | 184.8 (178.8, 190.8) | * |
| | | 3-12 M | 48 | 188.4 (180.9, 195.9) | | 190.1 (182.3, 197.9) | |
| | Linagliptin | | | | 0.1222 | | 0.1105 |
| | | baseline | 151 | 189.3 (183.1, 195.5) | reference | 191.6 (185.2, 198) | |
| | | 0-3 M | 146 | 186.3 (180.1, 192.5) | | 188.6 (182.2, 195) | |
| | | 3-12 M | 50 | 191.4 (183.8, 198.9) | | 193.8 (186.1, 201.6) | |
| TG (mg/dL) | Sitagliptin | | | | 0.0473 | | 0.0469 |
| | | baseline | 755 | 145.1 (139.4, 150.7) | reference | 142.9 (137.1, 148.8) | reference |
| | | 0-3 M | 712 | 139.1 (133.3, 144.8) | * | 136.9 (131, 142.8) | * |
| | | 3-12 M | 160 | 141.9 (132.4, 151.4) | | 140 (130.4, 149.6) | |
| | Vildagliptin | | | | 0.0203 | | 0.0072 |
| | | baseline | 206 | 160.3 (148.9, 171.7) | reference | 190.9 (185.6, 196.2) | reference |
| | | 0-3 M | 195 | 148.2 (136.6, 159.7) | * | 185.5 (180.2, 190.9) | * |
| | | 3-12 M | 54 | 144.4 (126.8, 162) | | 186 (178.7, 193.4) | |
| | Teneligliptin | | | | 0.1054 | | 0.1204 |
| | | baseline | 233 | 151.3 (140.7, 161.9) | reference | 149.4 (138.6, 160.3) | reference |
| | | 0-3 M | 209 | 145.2 (134.2, 156.1) | | 143.1 (132, 154.3) | |
| | | 3-12 M | 85 | 136.4 (121.3, 151.4) | | 135.2 (120, 150.4) | |
| | Alogliptin | | | | 0.0086 | | 0.0077 |
| | | baseline | 197 | 155 (143.6, 166.3) | reference | 155.3 (143.1, 167.5) | reference |
| | | 0-3 M | 174 | 140.3 (128.6, 152) | * | 140.5 (128, 153) | * |
| | | 3-12 M | 51 | 152.2 (135, 169.5) | | 153 (135.1, 170.9) | |
| | Linagliptin | | | | 0.9511 | | 0.9521 |
| | | baseline | 159 | 146.2 (134, 158.5) | reference | 146.8 (134, 159.6) | reference |
| | | 0-3 M | 154 | 144.5 (132.2, 156.9) | | 145.1 (132.1, 158) | |
| | | 3-12 M | 49 | 144.6 (126.1, 163) | | 145.4 (126.5, 164.4) | |
| AST (U/L) | Sitagliptin | | | | 0.0879 | | 0.0856 |
| | | baseline | 830 | 27.8 (26.6, 29) | reference | 27.5 (26.3, 28.7) | reference |
| | | 0-3 M | 794 | 26.8 (25.6, 28.1) | | 26.5 (25.3, 27.8) | |
| | | 3-12 M | 199 | 28 (26.2, 29.8) | | 27.7 (25.9, 29.5) | |
| | Vildagliptin | | | | 0.3947 | | 0.3942 |
| | | baseline | 232 | 30.3 (27.1, 33.5) | reference | 30.5 (27.1, 33.9) | reference |
| | | 0-3 M | 222 | 31.2 (28, 34.4) | | 31.4 (28, 34.8) | |
| | | 3-12 M | 57 | 32.6 (28.2, 37) | | 32.8 (28.2, 37.4) | |
| | Teneligliptin | | | | 0.7444 | | 0.7366 |

**Table 5** Relationship between treatment duration and laboratory parameters *(Continued)*

| Laboratory parameters | Drugs | Time point | N | Unadjusted LS Mean (95%CI) | p-value | aAdjusted LS Mean (95%CI) | p-value |
|---|---|---|---|---|---|---|---|
| | | baseline | 256 | 29.8 (26.9, 32.8) | reference | 30.6 (27.5, 33.6) | reference |
| | | 0-3 M | 236 | 28.5 (25.5, 31.6) | | 29.2 (26.1, 32.4) | |
| | | 3-12 M | 97 | 29.4 (24.9, 33.9) | | 30.2 (25.7, 34.8) | |
| | Alogliptin | | | | 0.0056 | | 0.0056 |
| | | baseline | 221 | 29.9 (27.3, 32.4) | reference | 29.5 (26.7, 32.3) | Reference |
| | | 0-3 M | 200 | 26.8 (24.2, 29.4) | * | 26.4 (23.6, 29.2) | * |
| | | 3-12 M | 61 | 28.4 (24.8, 32) | | 28 (24.3, 31.8) | |
| | Linagliptin | | | | 0.3101 | | 0.3365 |
| | | baseline | 176 | 24.7 (22.7, 26.7) | reference | 25.1 (23.1, 27.1) | reference |
| | | 0-3 M | 171 | 24.2 (22.2, 26.2) | | 24.6 (22.6, 26.7) | |
| | | 3-12 M | 58 | 23.3 (20.9, 25.7) | | 23.8 (21.3, 26.3) | |
| ALT (U/L) | Sitagliptin | | | | <.0001 | | <.0001 |
| | | baseline | 830 | 30.4 (28.8, 32) | reference | 29.8 (28.3, 31.4) | reference |
| | | 0-3 M | 794 | 28.1 (26.5, 29.7) | * | 27.5 (25.9, 29.1) | * |
| | | 3-12 M | 199 | 27.8 (25.5, 30.1) | * | 27.2 (25, 29.5) | * |
| | Vildagliptin | | | | 0.1288 | | 0.1286 |
| | | baseline | 233 | 32.3 (29.1, 35.6) | reference | 32 (28.7, 35.2) | reference |
| | | 0-3 M | 223 | 30.2 (27, 33.5) | | 29.8 (26.5, 33.2) | |
| | | 3-12 M | 58 | 31.6 (27.2, 36) | | 31.1 (26.7, 35.6) | |
| | Teneligliptin | | | | 0.0824 | | 0.089 |
| | | baseline | 256 | 30.2 (27, 33.4) | reference | 30.6 (27.3, 33.9) | reference |
| | | 0-3 M | 236 | 27.5 (24.2, 30.8) | | 27.9 (24.5, 31.3) | |
| | | 3-12 M | 97 | 25.5 (20.9, 30.2) | | 26 (21.3, 30.8) | |
| | Alogliptin | | | | <.0001 | | <.0001 |
| | | baseline | 223 | 34.7 (31.1, 38.3) | reference | 34.1 (30.3, 37.9) | reference |
| | | 0-3 M | 202 | 29 (25.4, 32.6) | * | 28.4 (24.5, 32.2) | * |
| | | 3-12 M | 61 | 29.6 (24.8, 34.5) | * | 29.1 (24, 34.1) | * |
| | Linagliptin | | | | <.0001 | | <.0001 |
| | | baseline | 176 | 26.2 (22.6, 29.8) | reference | 26.5 (23.2, 29.9) | reference |
| | | 0-3 M | 171 | 23.4 (19.8, 26.9) | * | 23.7 (20.3, 27.1) | * |
| | | 3-12 M | 58 | 22.4 (18.4, 26.3) | * | 22.8 (19, 26.6) | * |

*$p < 0.05$ (compared with baseline period, multiple-comparison test: Dunnett's post-hoc analysis), aAdjusted for age and sex
*LS mean* least square mean, *CI* confidence interval, *HbA1c* hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *HDL* high density lipoprotein, *TC* total cholesterol, *TG* triglyceride, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

was significantly lower than that in the baseline period in sitagliptin, alogliptin, and linagliptin users. However, the mean changes in AST and ALT concentrations showed no significant difference among the five groups of DPP-4 inhibitor users. Kusunoki et al. previously reported that serum AST, ALT, and γ-GT concentrations were significantly decreased in patients with 6-month administration of combination therapy with a DPP-4 inhibitor and a sodium glucose co-transporter 2 (SGLT2) inhibitor [21]. Aoki et al. previously reported that serum ALT and γ-GT concentrations were significantly decreased in patients with 16-week administration of combination therapy with alogliptin and pioglitazone compared with those with monotherapy [22]. Twelve-month treatment with alogliptin was previously reported to decrease NAFLD score [23]. Considering these results, some DPP-4 inhibitors might have a beneficial effect on hepatic metabolism; however, further studies are needed to investigate the mechanism of the effect of DPP-4 inhibitors on hepatic parameters.

**Table 6** Comparison of mean changes in laboratory parameters from baseline during exposure periods among five DPP-4 inhibitors

| Laboratory parameters | Drugs | Unadjusted LS mean (95%CI) | | p-value | [b]Adjusted LS mean (95%CI) | | p-value |
|---|---|---|---|---|---|---|---|
| | | 3 M | 12 M | | 3 M | 12 M | |
| [a]HbA1c (%) | | | | 0.001 | | | 0.0668 |
| | Sitagliptin | −0.46 (−0.52, − 0.4) | − 0.55 (− 0.65, −0.45) | | − 0.46 (− 0.53, − 0.38) | − 0.6 (− 0.71, −0.49) | |
| | Vildagliptin | − 0.61 (− 0.72, − 0.5) | −0.69 (− 0.87, − 0.51) | | −0.6 (− 0.7, − 0.5) | −0.64 (− 0.81, − 0.47) | |
| | Teneligliptin | − 0.64 (− 0.75, − 0.53) | − 0.9 (− 1.05, − 0.74) | | − 0.54 (− 0.64, − 0.43) | − 0.76 (− 0.91, − 0.62) | |
| | Alogliptin | − 0.43 (− 0.55, − 0.32) | − 0.58 (− 0.77, − 0.39) | | − 0.57 (− 0.68, − 0.47) | −0.74 (− 0.91, − 0.56) | |
| | Linagliptin | − 0.49 (− 0.62, − 0.36) | −0.59 (− 0.78, − 0.4) | | −0.58 (− 0.7, − 0.46) | −0.69 (− 0.87, − 0.51) | |
| [a]creatinine (mg/dL) | | | | 0.0259 | | | 0.1505 |
| | Sitagliptin | 0.02 (0.01, 0.03) | 0.06 (0.04, 0.08) | | 0.04 (0.02, 0.06) | 0.08 (0.05, 0.11) | |
| | Vildagliptin | 0.02 (0, 0.05) | 0.04 (0, 0.08) | | 0.04 (0.01, 0.06) | 0.06 (0.02, 0.1) | |
| | Teneligliptin | 0.04 (0.02, 0.06) | 0.11 (0.08, 0.14) | | 0.05 (0.02, 0.07) | 0.12 (0.08, 0.15) | |
| | Alogliptin | 0.03 (0, 0.05) | 0.04 (0, 0.08) | | 0.04 (0.02, 0.07) | 0.05 (0.01, 0.1) | |
| | Linagliptin | 0.04 (0.02, 0.07) | 0.07 (0.03, 0.12) | | 0.05 (0.02, 0.08) | 0.07 (0.03, 0.12) | |
| [a]eGFR (mL/min/1.73m$^2$) | | | | 0.4528 | | | 0.4143 |
| | Sitagliptin | − 1.92 (− 2.55, − 1.29) | −4.13 (− 5.27, − 2.98) | | − 2.9 (− 3.86, − 1.93) | − 4.9 (− 6.25, − 3.54) | |
| | Vildagliptin | − 2.79 (− 3.98, − 1.6) | − 1.33 (− 3.42, 0.76) | | − 3.97 (− 5.31, − 2.64) | − 2.36 (− 4.54, − 0.18) | |
| | Teneligliptin | − 2.73 (− 3.88, − 1.59) | − 3.22 (− 4.88, − 1.56) | | − 4.23 (− 5.57, − 2.89) | −4.68 (− 6.48, − 2.87) | |
| | Alogliptin | − 1.99 (− 3.23, − 0.76) | −1.94 (− 4.03, 0.14) | | − 2.96 (− 4.35, − 1.57) | − 3.01 (− 5.17, − 0.84) | |
| | Linagliptin | − 2 (− 3.36, − 0.63) | −2.24 (− 4.37, − 0.1) | | − 3.85 (− 5.35, − 2.35) | − 4.13 (− 6.35, − 1.9) | |
| [a]HDL (mg/dL) | | | | 0.1268 | | | 0.0613 |
| | Sitagliptin | − 0.87 (− 1.42, − 0.31) | −1.33 (− 2.45, − 0.21) | | − 0.8 (− 1.65, 0.05) | −1.37 (− 2.65, − 0.09) | |
| | Vildagliptin | − 1.15 (− 2.19, − 0.1) | −2.9 (− 4.78, − 1.03) | | −1.67 (− 2.85, − 0.49) | −3.29 (− 5.23, − 1.35) | |
| | Teneligliptin | 0.1 (− 0.95, 1.15) | − 0.9 (− 2.44, 0.63) | | 0.1 (−1.12, 1.31) | − 0.93 (− 2.58, 0.71) | |
| | Alogliptin | − 0.46 (− 1.59, 0.67) | − 0.89 (− 2.86, 1.08) | | − 0.93 (− 2.2, 0.33) | −1.33 (− 3.36, 0.7) | |
| | Linagliptin | −0.57 (−1.8, 0.66) | 0.84 (− 1.18, 2.86) | | − 0.87 (− 2.2, 0.46) | 0.36 (− 1.71, 2.43) | |
| [a]TC (mg/dL) | | | | 0.1469 | | | 0.3631 |
| | Sitagliptin | − 3.4 (− 5.3, −1.51) | 1.3 (− 2.1, 4.7) | | − 3.14 (− 6.14, −0.14) | 1.06 (− 3.05, 5.16) | |
| | Vildagliptin | − 5.22 (− 8.79, − 1.65) | − 6.57 (− 12.63, − 0.5) | | −4.67 (− 8.81, − 0.53) | − 6.05 (− 12.51, 0.42) | |
| | Teneligliptin | −3.22 (− 6.74, 0.3) | − 6.56 (− 11.63, − 1.49) | | − 1.71 (− 5.89, 2.48) | − 5 (− 10.57, 0.57) | |
| | Alogliptin | −4.58 (− 8.56, − 0.6) | −0.18 (− 6.63, 6.27) | | −4.32 (− 8.84, 0.19) | −0.36 (− 7.17, 6.46) | |
| | Linagliptin | −2.91 (− 7.03, 1.21) | 1.21 (− 4.92, 7.33) | | − 2.76 (− 7.35, 1.83) | 1.12 (− 5.38, 7.62) | |
| [a]TG (mg/dL) | | | | 0.4256 | | | 0.536 |
| | Sitagliptin | −5.96 (− 10.95, −0.97) | − 3.1 (− 12.32, 6.13) | | − 1.49 (− 9.42, 6.43) | 0.92 (− 10.15, 12) | |
| | Vildagliptin | −12.01 (−21.55, − 2.47) | −15.02 (− 30.92, 0.89) | | − 7.39 (− 18.46, 3.68) | − 10.3 (− 27.3, 6.69) | |
| | Teneligliptin | − 6.32 (− 15.46, 2.82) | − 12.27 (− 25.28, 0.74) | | 0.5 (− 10.55, 11.55) | − 5.66 (− 20.13, 8.8) | |
| | Alogliptin | −14.92 (− 24.95, − 4.9) | −2.56 (− 19.42, 14.29) | | −10.28 (− 21.97, 1.41) | 1.49 (− 16.39, 19.36) | |
| | Linagliptin | −1.78 (− 12.55, 8.99) | 1.45 (− 15.24, 18.14) | | 2.27 (− 9.79, 14.34) | 5.12 (− 12.56, 22.8) | |
| [a]AST (U/L) | | | | 0.1086 | | | |
| | Sitagliptin | −0.97 (−2.06, 0.13) | − 0.27 (− 2.41, 1.86) | | −2.65 (− 4.25, −1.06) | −2.02 (− 4.45, 0.4) | 0.105 |
| | Vildagliptin | 0.91 (−1.16, 2.98) | 3.11 (− 0.89, 7.1) | | 0.05 (−2.2, 2.29) | 0.57 (− 3.47, 4.62) | |
| | Teneligliptin | −1.43 (− 3.44, 0.57) | − 0.41 (− 3.48, 2.67) | | − 2.32 (− 4.58, − 0.07) | −1.44 (− 4.66, 1.77) | |
| | Alogliptin | − 2.87 (− 5.04, − 0.69) | −2.24 (− 6.11, 1.64) | | − 4.23 (− 6.6, − 1.86) | −2.73 (− 6.64, 1.17) | |
| | Linagliptin | −0.49 (−2.84, 1.87) | − 1.23 (− 5.19, 2.73) | | − 2.99 (− 5.48, − 0.5) | −3.93 (− 7.94, 0.09) | |
| [a]ALT (U/L) | | | | 0.1576 | | | 0.2768 |

**Table 6** Comparison of mean changes in laboratory parameters from baseline during exposure periods among five DPP-4 inhibitors *(Continued)*

| Laboratory parameters | Drugs | Unadjusted LS mean (95%CI) | | p-value | [b]Adjusted LS mean (95%CI) | | p-value |
|---|---|---|---|---|---|---|---|
| | | 3 M | 12 M | | 3 M | 12 M | |
| | Sitagliptin | −2.33 (−3.56, −1.11) | −1.92 (−3.99, 0.16) | | −4.08 (−5.82, −2.34) | −3.74 (−6.15, −1.32) | |
| | Vildagliptin | -2.05 (-4.36, 0.26) | −0.25 (−4.1, 3.6) | | −2.88 (−5.29, −0.47) | −1.81 (−5.75, 2.12) | |
| | Teneligliptin | −2.74 (−4.97, −0.51) | −3.69 (−6.77, −0.6) | | −3.73 (−6.14, −1.31) | −3.42 (−7.28, 0.44) | |
| | Alogliptin | −5.69 (−8.1, −3.28) | −5.08 (−8.94, −1.23) | | −6.13 (−8.66, −3.6) | −4.86 (−8.76, −0.97) | |
| | Linagliptin | −2.83 (−5.47, −0.18) | −3.68 (−7.57, 0.22) | | −5.15 (−7.82, −2.48) | −6.19 (−10.13, −2.24) | |

[a]indicates change in laboratory parameter during exposure period from baseline
*HbA1c* hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *HDL* high density lipoprotein, *TC* total cholesterol, *TG* triglyceride, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LS mean* least square mean, *CI* confidence interval, p value: p value among five DPP-4 inhibitors (multiple-comparison test)
[b]Adjusted for time, age, sex, medical history in baseline period including ischemic heart disease and hypertension, medication in baseline period including hypoglycemic drugs and lipid-lowering drugs, baseline concentration of HbA1c, and baseline concentration of each parameter

## Limitations

There are several limitations of our study. First, there is a possibility of selection bias and confounding factors because this study was a retrospective study using non-randomized data. We applied a multivariate regression model, which enabled us to control for potential confounding variables among the five DPP-4 inhibitor groups; however, their ability to control for differences was limited to available or measurable variables. Second, we did not exclude patients who had received other antidiabetic drugs before the initiation of DPP-4 inhibitors, because DPP-4 inhibitors are relatively new drugs and many patients (about 44 to 71%) were then treated with other antidiabetic drugs, including insulin and oral hypoglycemic drugs. Sulphonylureas and thiazolidine-diones are known to be associated with an increase in body weight [24]. Metformin, one of the biguanides, is reported to improve liver enzymes in patients with NASH [25]. We used rigorous statistical methods to control for differences in prior treatment among the five DPP-4 inhibitor groups; however, we would like to study patients firstly treated with antidiabetic drugs when a sufficient sample has been collected. Third, the standard dose of sitagliptin in Japan is 50 mg, which is half the world standard dose; this is because, in Japanese cases, it has been reported that there are no statistically significant differences in HbA1c, fasting plasma glucose, and 2 h postprandial glucose concentration among doses of sitagliptin of 50, 100, and 200 mg [26]. Therefore, the adverse effects of sitagliptin might have been mitigated at this dose. Fourth, the number of sitagliptin users was larger than those of the other DPP-4 inhibitors. Because sitagliptin was the first entrant and is the dominant DPP-4 inhibitor in Japan, this unbalanced sample size might have reflected the market share of sitagliptin in Japan, suggesting that this study is a good reflection of clinical practice. We used a mixed linear model, which is a rigorous statistical model that enables adjustment for unbalanced sample sizes. The findings of our study are relevant to clinical practice in real world settings, and have sufficient reliability based on a sophisticated statistical method, however, further studies such as randomized clinical trials will be needed for confirmation.

## Conclusion

In this study, we showed the effect among five DPP-4 inhibitors on glycemic, renal, and lipid metabolism, and hepatic parameters. DPP-4 inhibitors are well-tolerated hypoglycemic drugs; however, physicians should monitor laboratory parameters for at least 12 months after their initiation.

using anonymized archived data from a clinical database and did not compromise anonymity or confidentiality.

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