

# World Journal of *Diabetes*

*World J Diabetes* 2018 October 15; 9(10): 165-179



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*World Journal of Diabetes* is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

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#### NAME OF JOURNAL

*World Journal of Diabetes*

#### ISSN

ISSN 1948-9358 (online)

#### LAUNCH DATE

June 15, 2010

#### FREQUENCY

Monthly

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#### PUBLISHER

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#### PUBLICATION DATE

October 15, 2018

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## Retrospective Cohort Study

# Efficacy of anagliptin as compared to linagliptin on metabolic parameters over 2 years of drug consumption: A retrospective cohort study

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**Author contributions:** Hamasaki H and Hamasaki Y equally contributed to study conception, data acquisition, data analysis, interpretation, and writing of article.

**Institutional review board statement:** This study protocol was reviewed and approved by the Japan Medical Association Ethical Review Board.

**Informed consent statement:** Study participants are assured that collected data will be used only for this study and will not be disclosed without the consent of the participants.

**Conflict-of-interest statement:** The authors declare no conflict of interest.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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**Manuscript source:** Invited manuscript

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Received: June 25, 2018

Peer-review started: June 25, 2018

First decision: July 9, 2018

Revised: July 12, 2018

Accepted: August 26, 2018

Article in press: August 26, 2018

Published online: October 15, 2018

## Abstract

### AIM

To evaluate the comparative effectiveness of anagliptin and linagliptin on the clinical parameters in patients with type 2 diabetes mellitus (T2DM).

### METHODS

A 2-year retrospective cohort study was conducted in patients with T2DM who received anagliptin and linagliptin. We enrolled 234 patients (anagliptin group, 117 patients; linagliptin group, 117 patients).

### RESULTS

The glycemic control considerably improved 3, 6, 12, and 24 mo after the administration of both dipeptidyl peptidase-4 (DPP-4) inhibitors. Following the administration of anagliptin, the diastolic blood pressure and serum total cholesterol levels decreased. However, serum high-density lipoprotein cholesterol levels increased and urinary albumin-creatinine ratio decreased following linagliptin administration. Furthermore, the liver function improved after the administration of linagliptin.

## CONCLUSION

These findings suggest that the efficacy of DPP-4 inhibitors on the blood pressure, lipid profile, and liver function differs between anagliptin and linagliptin.

**Key words:** Type 2 diabetes mellitus; Dipeptidyl peptidase-4 inhibitor; Anagliptin; Linagliptin; Cholesterol

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**Core tip:** Whether a substantial clinical difference exists in the effect of dipeptidyl peptidase-4 (DPP-4) inhibitors on metabolic parameters remains inconclusive. Although this study is a relatively small-scale, short duration, retrospective study, the findings of this study suggests that the efficacy of DPP-4 inhibitors on the blood pressure, lipid profile, and liver function differs between anagliptin and linagliptin.

Hamasaki H, Hamasaki Y. Efficacy of anagliptin as compared to linagliptin on metabolic parameters over 2 years of drug consumption: A retrospective cohort study. *World J Diabetes* 2018; 9(10): 165-171 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v9/i10/165.htm> DOI: <http://dx.doi.org/10.4239/wjd.v9.i10.165>

## INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors are extensively used in patients with type 2 diabetes mellitus (T2DM). As Asian patients with T2DM are typically characterized by  $\beta$ -cell dysfunction and exhibit less adiposity and insulin resistance than Caucasian patients with T2DM, DPP-4 inhibitors could be more effective in Asians<sup>[1]</sup>. Although DPP-4 inhibitors do not exert lower cardiovascular mortality compared with glucagon-like peptide I (GLP-1) receptor agonists and sodium-glucose cotransporter 2 inhibitors<sup>[2]</sup>, they exhibit good tolerability and safety in elderly people with renal impairment and liver disease<sup>[3]</sup>. Thus, DPP-4 inhibitors could be considered as one of the first/second preferences for treating T2DM<sup>[1,4]</sup>. In Japan, the following seven types of once- or twice-daily DPP-4 inhibitors are currently available: Sitagliptin, vildagliptin, alogliptin, linagliptin, teneligliptin, anagliptin, and saxagliptin. However, anagliptin is not commonly available in countries other than Japan<sup>[5]</sup>, and few studies have directly compared the efficacy of anagliptin with other gliptins for the management of patients with T2DM. Anagliptin is a unique DPP-4 inhibitor because it possibly reduces low-density lipoprotein cholesterol (LDL-C) levels<sup>[6,7]</sup>. However, it is unclear whether this effect is specific to anagliptin, and the reproducibility has not been substantially proven<sup>[8]</sup>. Thus, this study aims to assess the comparative effectiveness of anagliptin and linagliptin on the glycemic control, blood pressure, lipid profile, and liver and renal function in Japanese patients with T2DM.

## MATERIALS AND METHODS

### Study design and patients

We conducted this retrospective cohort study in patients with T2DM who were treated at Hamasaki Clinic (diabetes-specialty clinic). We enrolled outpatients who were treated with anagliptin or linagliptin between April 2012 and September 2017. However, we excluded patients aged < 20 years, previously treated with DPP-4 inhibitors, changed the type of DPP-4 inhibitors, and discontinued treatment with DPP-4 inhibitors during the study period. We followed up all enrolled patients at 3, 6, 12, and 24 mo after initiation of DPP-4 inhibitors therapy. This study protocol was approved by the Japan Medical Association Ethical Review Board (Reference No. 29-6), and the study was performed in accordance with the Declaration of Helsinki.

### Medical history recording

We recorded patients' duration of diabetes, smoking history, drinking habit, and history of cardiovascular disease (CVD) before commencing the treatment with DPP-4 inhibitors. In addition, we confirmed the medication adherence of study patients at every medical examination.

### Anthropometric and physiological measurements

Patient height and weight were measured using a rigid stadiometer and calibrated scales, respectively. We calculated the body mass index (BMI) as body weight in kilograms divided by the square of body height in meters. In addition, the blood pressure was measured in a seated position using an automatic sphygmomanometer (KM-382; Kenzmedico Co., Ltd., Saitama, Japan).

### Blood and urinary examinations

We measured plasma glucose (PG), hemoglobin A1c (HbA1c; HLC-723G9, TOSOH Co., Ltd., Tokyo, Japan), serum total cholesterol (T-C; Determiner L TC II, Kyowa Medex Co., Ltd., Tokyo, Japan), triglycerides (TG; Determiner L TG II, Kyowa Medex Co., Ltd.), high-density lipoprotein cholesterol (HDL-C; Cholestest N HDL, Sekisui Medical Co., Ltd., Tokyo, Japan), and LDL-C (Cholestest LDL, Sekisui Medical Co., Ltd.). In addition, we measured aspartate transaminase (AST), alanine aminotransferase (ALT), creatinine (Cr), and the urinary albumin-Cr ratio (UACR; N-A TIA MicroALB, Nittobo Medical Co., Ltd., Tokyo, Japan) as a marker for diabetic nephropathy.

### Statistical analysis

All statistical analyses in this study were performed using SPSS version 24 (IBM Co., Ltd., Chicago, IL). Quantitative variables are presented as mean  $\pm$  SD and categorical variables are presented as numbers. We divided all participants into the anagliptin group and linagliptin group. We performed the Student's *t*-test (if normal data distribution), Mann-Whitney *U*-test (if non-normal



**Table 1 Subject characteristics at baseline**

|                           | Anagliptin   | Linagliptin  | P-value |
|---------------------------|--------------|--------------|---------|
| Age (yr)                  | 63.5 (12.9)  | 62.7 (11.9)  | 0.63    |
| Men/women                 | 74/43        | 75/42        | 0.89    |
| Height (cm)               | 162.1 (10.4) | 162.5 (9.1)  | 0.77    |
| Weight (kg)               | 64.4 (16.1)  | 66.1 (14.7)  | 0.39    |
| BMI (kg/m <sup>2</sup> )  | 24.3 (4.7)   | 24.9 (4.3)   | 0.23    |
| Duration of diabetes (yr) | 11.9 (8.6)   | 10.5 (8.5)   | 0.21    |
| History of CVD (yes/no)   | 36/81        | 32/85        | 0.56    |
| Smoking habit (yes/no)    | 44/73        | 46/71        | 0.79    |
| Drinking habit (yes/no)   | 65/52        | 62/55        | 0.75    |
| SBP (mmHg)                | 130.4 (18.4) | 128.5 (18.7) | 0.43    |
| DBP (mmHg)                | 72.9 (14)    | 72.9 (11.4)  | 0.99    |
| AST (U/L)                 | 21.9 (9.3)   | 29.8 (26.7)  | 0.029   |
| ALT (U/L)                 | 24.9 (15)    | 33.1 (35.1)  | 0.069   |
| Cr (mg/dL)                | 0.71 (0.19)  | 0.79 (0.32)  | 0.03    |
| PG (mmol/L)               | 10.71 (4.49) | 12.06 (5.25) | 0.036   |
| HbA1c (mmol/L)            | 11.1 (2.8)   | 12 (3.3)     | 0.053   |
| T-C (mmol/L)              | 5.3 (0.88)   | 5.48 (1.02)  | 0.17    |
| TG (mmol/L)               | 1.63 (1.17)  | 2.07 (1.5)   | 0.009   |
| HDL-C (mmol/L)            | 1.36 (0.34)  | 1.33 (0.37)  | 0.55    |
| LDL-C (mmol/L)            | 3.19 (0.8)   | 3.19 (0.88)  | 0.95    |
| UACR (mg/gCr)             | 50.60 (78.4) | 47.6 (92)    | 0.65    |

BMI: Body mass index; CVD: Cardiovascular disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; AST: Aspartate transaminase; ALT: Alanine aminotransferase; Cr: Creatinine; PG: Plasma glucose; HbA1c: Hemoglobin A1c; T-C: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; UACR: Urinary albumin creatinine ratio.

data distribution), or  $\chi^2$  test to assess the difference in clinical parameters at the baseline between groups. The Friedman test was performed to evaluate the change in clinical parameters during the study period. Furthermore, we calculated the percentage change in clinical parameters (%change) from baseline to the end of study period to compare the effectiveness of anagliptin and linagliptin. Finally, we considered  $P < 0.05$  as statistically significant.

## RESULTS

We enrolled 234 patients in this study. Among 117 patients in the anagliptin group, 74 were male and 43 were female. Among 117 patients in the linagliptin group, 75 were male and 42 were female. The mean age of patients was  $63.5 \pm 12.9$  years and  $62.7 \pm 11.9$  years, and the mean BMI was  $24.3 \pm 4.7$  kg/m<sup>2</sup> and  $24.9 \pm 4.3$  kg/m<sup>2</sup> in the anagliptin and linagliptin groups, respectively. No significant differences were observed in the duration of diabetes, history of CVD, smoking and drinking habits, blood pressure, plasma HbA1c levels, serum T-C levels, HDL-C and LDL-C levels, and UACR; however, PG levels and serum AST, Cr, and TG levels were higher in the linagliptin group compared with the anagliptin group (Table 1). In total, 47 patients received 100-mg anagliptin once per day, and 70 received 100-mg anagliptin twice per day. In addition, we observed no significant differences in the number of patients receiving antihypertensive agents,

cholesterol-lowering agents, insulin therapy, and other oral hypoglycemic agents between both groups. During the study period, no differences were observed in the number of patients receiving additional treatment for hypertension, dyslipidemia, and diabetes between groups (Table 2).

The glycemic control was markedly improved 3, 6, 12, and 24 mo after the administration of both DPP-4 inhibitors. HbA1c levels significantly decreased in both the anagliptin group (from  $11.1 \pm 2.8$  mmol/L to  $9.7 \pm 1.9$  mmol/L) and the linagliptin group (from  $12 \pm 3.3$  mmol/L to  $9.2 \pm 1.8$  mmol/L). However, the %change in HbA1c was lower in the anagliptin group than that in the linagliptin group ( $-5.6\%$  vs  $-17.4\%$ ,  $P = 0.004$ ). Notably, the diastolic blood pressure decreased 24 mo after the administration of anagliptin (from  $72.9 \pm 14$  mmHg to  $69.1 \pm 9.5$  mmHg); however, no change was observed in the blood pressure in the linagliptin group. The change in diastolic blood pressure was also larger in the anagliptin group than that in the linagliptin group ( $-9.7\%$  vs  $-4.9\%$ ,  $P = 0.044$ ). In addition, serum T-C levels declined 6 months after the administration of anagliptin (from  $5.3 \pm 0.88$  mmol/L to  $5.11 \pm 0.78$  mmol/L); however, serum HDL-C levels were elevated 24 mo after the administration of linagliptin (from  $1.33 \pm 0.37$  mmol/L to  $1.39 \pm 0.38$  mmol/L). There was also a significant difference in %change in HDL-C levels between groups ( $2.8\%$  vs  $5.6\%$ ,  $P = 0.037$ ). However, we observed no changes in LDL-C levels in both groups (from  $3.19 \pm 0.8$  mmol/L to  $2.96 \pm 0.53$  mmol/L and from  $3.19 \pm 0.88$  mmol/L to  $2.91 \pm 0.75$  mmol/L, respectively). Further, no changes were observed in the liver and renal function in the anagliptin group. Nevertheless, serum ALT levels decreased and Cr levels increased in the linagliptin group. We also found a significant difference in %change in Cr levels between groups ( $6.8\%$  vs  $22\%$ ,  $P = 0.038$ ); however, there was no significant difference in %change in ALT levels between groups ( $-2.2\%$  vs  $-15.2\%$ ,  $P = 0.088$ ). Although the UACR decreased in the linagliptin group (from  $47.6 \pm 92$  mg/gCr to  $23.8 \pm 34.9$  mg/gCr), it did not exhibit a substantial change in the anagliptin group (from  $50.6 \pm 78.4$  mg/gCr to  $40.7 \pm 76.8$  mg/gCr) (Table 3).

## DISCUSSION

This study illustrates that both anagliptin and linagliptin effectively improve long-term glycemic control; however, the efficacy of DPP-4 inhibitors on the blood pressure, lipid profile, and liver function may differ between anagliptin and linagliptin. Notably, anagliptin decreased the diastolic blood pressure, and linagliptin increased serum HDL-C levels 24 mo after the administration of each DPP-4 inhibitor. However, the efficacy of DPP-4 inhibitors on the blood pressure remains debatable. The elevation in GLP-1 levels accounts for the effects of DPP-4 enzyme inhibition on the cardiovascular function, which leads to cardiac remodeling, improvement of the

**Table 2 Medications in study subjects**

|   | Anagliptin             | Linagliptin | P-value |
|---|------------------------|-------------|---------|
| Dosage                                  | 100 mg; 47; 200 mg; 70 | 5 mg        | -       |
| Anti-hypertensive agents                | 42                     | 46          | 0.59    |
| ARB or ACE inhibitors                   | 31                     | 36          | 0.47    |
| Cholesterol-lowering agents             | 41                     | 37          | 0.58    |
| Insulin                                 | 7                      | 8           | 0.79    |
| Concomitant oral hypoglycemic agents    |                        |             |         |
| Metformin                               | 48                     | 42          | 0.42    |
| Sulfonylureas                           | 44                     | 40          | 0.59    |
| Glinides                                | 3                      | 4           | 0.70    |
| $\alpha$ -glucosidase inhibitors        | 4                      | 6           | 0.52    |
| Pioglitazone                            | 1                      | 2           | 0.56    |
| SGLT2 inhibitors                        | 1                      | 0           | 0.32    |
| No medication                           | 33                     | 37          | 0.57    |
| Additional medications for hypertension | 1                      | 2           | 0.56    |
| Additional medications for dyslipidemia | 3                      | 3           | 1.00    |
| Additional medications for diabetes     | 12                     | 16          | 0.42    |

ARB: Angiotensin II receptor blocker; ACE: Angiotensin converting enzyme; SGLT2: Sodium-glucose cotransporter 2.

endothelial function, and lowering blood pressure<sup>[9-11]</sup>. In our study, we observed no differences in the use of antihypertensive agents, including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers between the anagliptin and linagliptin groups. Hence, the use of antihypertensive agents did not influence the effect of both DPP-4 inhibitors on blood pressure. Recently, Tahara *et al.*<sup>[12]</sup> reported that anagliptin could ameliorate arterial stiffness in association with the reduction of remnant-like particle cholesterol. Although we did not observe any substantial change in LDL-C levels in patients receiving anagliptin, T-C levels decreased after anagliptin administration. The reduction in the diastolic blood pressure in the anagliptin group could be attributed to the amelioration of arterial stiffness by the lipid profile improvement. A systematic review and meta-analysis reported that treatment with DPP-4 inhibitors correlated with a reduction in T-C levels by 7.0 mg/dL<sup>[13]</sup>. In addition, anagliptin was reported to improve the lipid profile in both fasting and postprandial conditions in men with T2DM<sup>[14]</sup>. Goto *et al.*<sup>[15]</sup> recently demonstrated that anagliptin decreased serum T-C and HDL-C levels in ApoE-deficient mice through DPP-4-dependent inhibition of intestinal cholesterol transport. The cholesterol-lowering effect of anagliptin could be attributed to the downregulation of hepatic cholesterol synthesis<sup>[16]</sup>. Furthermore, a 24-wk treatment with anagliptin reduced serum apoB-100 levels in patients with T2DM<sup>[7]</sup>, suggesting that the cholesterol-lowering effect of anagliptin is caused by a reduction in hepatic cholesterol synthesis as well as intestinal cholesterol absorption.

Reportedly, long-term treatment using exenatide, a GLP-1 receptor agonist, increases HDL-C levels by 0.05 mmol/L<sup>[17]</sup>; however, to our knowledge, no study to date has reported that DPP-4 inhibitors directly increase HDL-C levels in patients with T2DM. Individuals with metabolic syndrome have dyslipidemia, which is characterized by decreased HDL-C levels and dysfunctional HDL; such

impaired HDL-C metabolism is related to hepatic lipid deposition, such as nonalcoholic fatty liver disease through ApoI deficiency<sup>[18]</sup>. Notably, linagliptin has a xanthine-based structure, which could cause pharmacological differences compared with other DPP-4 inhibitors<sup>[19]</sup>. Although linagliptin is primarily eliminated by the nonrenal route, its efficacy and tolerability are not affected by hepatic impairment<sup>[19]</sup>. In fact, linagliptin could suppress xanthine oxidase activity in patients with T2DM<sup>[20]</sup>. In addition, an experimental animal study suggested that linagliptin suppressed adipose tissue inflammation, thus contributing to the reduction in the liver fat content and improvement of hepatic steatosis<sup>[21]</sup>. In our study, a decline in serum ALT levels in the linagliptin group suggests that linagliptin could improve fatty liver complicated with T2DM. Furthermore, linagliptin may have increased HDL-C levels because HDL-C metabolism was improved by a reduction in the hepatic fat deposition in this study.

In T2DM, both the blood pressure and renal impairment affect UACR. However, we observed no clinical changes in the blood pressure and serum Cr levels between the baseline and 3 mo following the administration of DPP-4 inhibitors. Reportedly, linagliptin has the potential to decrease albuminuria independent of the glycemic control because of the suppression of renal inflammatory responses mediated by the GLP-1 activity, inhibition of podocyte damage, and tumor necrosis factor- $\alpha$ <sup>[22]</sup>. While the renoprotective effect of linagliptin has been suggested, an increase in serum Cr levels 24 mo after the administration of linagliptin could be attributed to the time-dependent change in the renal function in patients with T2DM. In this study, linagliptin was administered to patients whose renal function was lower than that in patients receiving anagliptin at the baseline. Linagliptin could reduce the UACR but not improve the renal function. At present, randomized controlled clinical trials investigating the effects of linagliptin on CVD and renal function-the cardiovascular outcome study of linagliptin vs glimepiride in patients

**Table 3** Changes in clinical parameters after starting the dipeptidyl peptidase-4 inhibitors therapy

|                | Anagliptin              |                          |                          |                          | Linagliptin              |                          |                          |                          |
|----------------|-------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                | 3 mo                    | 6 mo                     | 12 mo                    | 24 mo                    | 3 mo                     | 6 mo                     | 12 mo                    | 24 mo                    |
| Weight (kg)    | 64.5 (16.2)             | 65.4 (15.7)              | 64.7 (15.5)              | 63.7 (16.4)              | 66.1 (15.1)              | 66 (16.9)                | 67.3 (14.2)              | 66.4 (14.8)              |
| SBP (mmHg)     | 128.6 (17.2)            | 128.2 (14.8)             | 126.8 (16.6)             | 130.1 (16.6)             | 129.3 (17.7)             | 127.1 (16.4)             | 128.9 (19.1)             | 124.9 (16)               |
| DBP (mmHg)     | 70.7 (11.4)             | 70.9 (9.9)               | 69.4 (12.1)              | 69.1 (9.5) <sup>b</sup>  | 70.7 (11.4)              | 69.3 (10.8)              | 72.5 (11.2)              | 70.2 (8.6)               |
| AST (U/L)      | 22.5 (9.6)              | 22.4 (8.8)               | 22.3 (10)                | 23.8 (12.3)              | 22.7 (12.7)              | 24.9 (17.1)              | 23.2 (13.1)              | 23.7 (12.4)              |
| ALT (U/L)      | 23 (14.9) <sup>b</sup>  | 23 (14.8) <sup>a</sup>   | 22.6 (15.7) <sup>b</sup> | 25.5 (18)                | 23.5 (12.9)              | 24.8 (14.8)              | 24 (13.9)                | 23.7 (15.4)              |
| Cr (mg/dL)     | 0.74 (0.18)             | 0.77 (0.2)               | 0.77 (0.21)              | 0.77 (0.2)               | 0.85 (0.33)              | 0.86 (0.4)               | 0.9 (0.5)                | 0.84 (0.38) <sup>d</sup> |
| PG (mmol/L)    | 8.96 (3.4) <sup>a</sup> | 8.8 (2.9)                | 8.91 (3.16)              | 9.12 (4.19) <sup>b</sup> | 9.54 (3.82) <sup>d</sup> | 9.28 (3.85) <sup>d</sup> | 9.48 (3.28) <sup>d</sup> | 9.51 (3.5) <sup>b</sup>  |
| HbA1c (mmol/L) | 9.3 (2.3) <sup>d</sup>  | 9.4 (2.1) <sup>d</sup>   | 9.3 (1.8) <sup>b</sup>   | 9.7 (1.9) <sup>b</sup>   | 9.3 (2) <sup>b</sup>     | 9.1 (1.8) <sup>d</sup>   | 9.6 (2.2) <sup>d</sup>   | 9.2 (1.8) <sup>d</sup>   |
| T-C (mmol/L)   | 5.11 (0.87)             | 5.11 (0.78) <sup>b</sup> | 5.19 (0.69)              | 5.03 (0.64)              | 5.11 (0.86)              | 5.14 (0.89)              | 5.31 (0.97)              | 5.09 (0.81)              |
| TG (mmol/L)    | 1.83 (2.05)             | 1.73 (1.71)              | 1.64 (0.92)              | 1.51 (0.83)              | 2.1 (1.74)               | 1.85 (1.23)              | 2.11 (1.83)              | 1.76 (1.19)              |
| HDL-C (mmol/L) | 1.32 (0.3)              | 1.31 (0.32)              | 1.29 (0.27)              | 1.4 (0.37)               | 1.31 (0.37)              | 1.35 (0.42)              | 1.31 (0.34)              | 1.39 (0.38) <sup>a</sup> |
| LDL-C (mmol/L) | 3 (0.8)                 | 3.07 (0.78)              | 3.13 (0.7)               | 2.96 (0.53)              | 2.85 (0.86)              | 2.94 (0.83)              | 3.04 (0.86)              | 2.91 (0.75)              |
| UACR (mg/gCr)  | 40.7 (76.8)             | -                        | -                        | -                        | 23.8 (34.9)              | -                        | -                        | -                        |

Superscripts indicate statistically significant changes from baseline: <sup>a</sup> $P < 0.05$ ; <sup>b</sup> $P < 0.01$ ; <sup>d</sup> $P < 0.001$ . SBP: Systolic blood pressure; DBP: Diastolic blood pressure; AST: Aspartate transaminase; ALT: Alanine aminotransferase; Cr: Creatinine; PG: Plasma glucose; HbA1c: Hemoglobin A1c; T-C: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; UACR: Urinary albumin creatinine ratio.

with type 2 diabetes (CAROLINA) and cardiovascular safety and renal microvascular outcome study with linagliptin (CARMELINA) trials<sup>[23,24]</sup> - are ongoing. Hence, further evidence is expected.

This study has several limitations. First, we could not adjust confounding factors, such as dietary intake and physical activity, because of the retrospective nature of this study. Second, the liver and renal function were lower in the linagliptin group than in the anagliptin group at the baseline, which may have affected the difference of serum ALT levels and UACR changes between groups. However, at the baseline, no substantial differences in serum ALT levels and UACR were observed between groups, suggesting that the study results are not because of the difference in patients' characteristics. Third, although we confirmed the medication adherence at every medical examination, we could not ensure whether the study participants kept medication adherence during the study period. Finally, we did not perform blood and urinary tests under constant conditions, which may have decreased the precision of the results, including PG and serum TG levels. Despite these limitations, this study demonstrated that anagliptin and linagliptin could have different effects on metabolic parameters in patients with T2DM.

In conclusion, this study demonstrated that anagliptin decreased diastolic blood pressure and T-C levels, and linagliptin increased HDL-C levels and decreased ALT levels and UACR beside improvement of the glycemic control in Japanese patients with T2DM. This study supports the hypothesis that there could be a drug-specific effect of DPP-4 inhibitors on metabolic parameters beyond their class effect. Thus, we cannot describe the utility of these drugs in clinical practice separately. However, a multicenter, randomized, open-label, parallel-group trial has been conducted to assess the comparative effectiveness of anagliptin and sitagliptin on LDL-C in patients with T2DM and atherosclerosis<sup>[25]</sup>.

Nevertheless, further investigations are warranted to validate the findings of this study.

## ACKNOWLEDGMENTS

The authors appreciate the support of Masayo Yoshidome who collected the data.

## ARTICLE HIGHLIGHTS

### Research background

Dipeptidyl peptidase-4 (DPP-4) inhibitors are extensively used in patients with type 2 diabetes mellitus (T2DM). DPP-4 inhibitors can improve dyslipidemia and hypertension in addition to glycemic control.

### Research motivation

Anagliptin is a unique DPP-4 inhibitor that possibly reduces the low-density lipoprotein cholesterol levels; however, it is not commonly available outside Japan. Few studies have directly compared the efficacy of anagliptin with other gliptins in the management of T2DM.

### Research objectives

To assess the comparative effectiveness of anagliptin and linagliptin on the glycemic control, blood pressure, lipid profile, and liver and renal function in Japanese patients with T2DM.

### Research methods

A 2-year retrospective cohort study in a diabetes-specialty clinic.

### Research results

Both anagliptin and linagliptin effectively improved glycemic control for 2 years. Interestingly, diastolic blood pressure was reduced following the administration of anagliptin, and serum high-density lipoprotein cholesterol levels were increased following the administration of linagliptin. However, no significant changes in serum low-density lipoprotein cholesterol levels were observed in both the anagliptin group and the linagliptin group.

### Research conclusions

This study adds to the current literature supporting that the efficacy of DPP-4 inhibitors on metabolic parameters may differ between anagliptin and linagliptin. Both DPP-4 inhibitors may have a unique effect beyond the class effect of



DPP-4 inhibitors. However, whether a substantial clinical difference exists in the effect of DPP-4 inhibitors on metabolic parameters is still inconclusive because this study is a retrospective cohort study.

## Research perspectives

We suggest the need for well-designed, large-scale studies to elucidate the effect of DPP-4 inhibitors on metabolic parameters beyond the glucose-lowering effect. Furthermore, comparative efficacy of DPP-4 inhibitors for arterial stiffness should also be investigated in the future.

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