The renoprotective effect of once-weekly GLP-1 receptor agonist dulaglutide on progression of nephropathy in Japanese patients with type 2 diabetes and moderate to severe chronic kidney disease (JDDM67)

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Keywords
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ABSTRACT
Aims/Introduction: Few studies have investigated the renoprotective effect of glucagon-like peptide-1 (GLP-1) receptor in patients with chronic kidney disease (CKD). This study evaluated the effect of dulaglutide 0.75 mg on renal function in Japanese patients with type 2 diabetes and CKD stage 3 to 4.

Materials and Methods: Dulaglutide (group A) and non-dulaglutide (group B) were compared using data collected from a computerized diabetes care database. For group B, propensity score weighting based on propensity scores was performed. Evaluation items were a change from baseline in hemoglobin A1c (HbA1c), body weight, urine albumin-to-creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR), for 3 years.

Results: In total, the data obtained from 255 patients (125 and 130 patients for group A and B, respectively) were analyzed. Propensity score-adjusted patient background characteristics (group A vs B) were age 70.8 vs 69.4 years, body weight 70.2 vs 72.9 kg, body mass index 27.3 vs 28.1 kg/m2, HbA1c 8.4 vs 8.5%, eGFR 47.9 vs 47.7 mL/min/1.73 m2, and UACR 218 vs 251 mg/gCr. Although there were no statistically significant differences in the change from baseline between groups A and B at most time points in eGFR, a statistically significant eGFR decline in group B was observed in slope analysis for 3 years. This renoprotective effect was marked in patients with macro-albuminuria and/or concomitant SGLT2 inhibitor use.

Conclusions: Dulaglutide slowed the eGFR decline in patients with type 2 diabetes and CKD stage 3 to 4.

INTRODUCTION
In Japan, the number of diabetic patients is increasing due to changes in lifestyle and social environment, and this has become an issue in the aging society. Diabetes causes complications such as retinopathy, nephropathy, and neuropathy. Among them, diabetic nephropathy progresses and becomes renal failure, requiring renal replacement therapy. If renal replacement therapy is required, not only is the quality of life of the patient significantly lowered, but also the medical costs become a social burden, because the costs are covered by the public health insurance system in Japan. To improve this situation, the Ministry of Health, Labour, and Welfare developed a
diabetic nephropathy aggravation prevention program to identify high-risk patients and to provide active therapeutic intervention to prevent the transition to renal replacement therapy.10

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors are known as anti-diabetic drugs that suppress the progression of nephropathy. It had been reported that these drugs reduced the risk for renal composite endpoint including renal-replacement therapy, death due to renal disease, and new onset of persistent macro-albuminuria in the cardiovascular outcome trials.3–9. Although there are two studies including patients with moderate to severe renal dysfunction such as the CREDO-CKD study and the DAPA-CKD study, residual trials excluded patients with moderate to severe renal dysfunction, and the baseline estimated glomerular filtration rates (eGFR) were 74 to 85 mL/min/1.73 m² except 56 mL/min/1.73 m² in the CREDO study and 43 mL/min/1.73 m² in the DAPA-CKD study.

Dulaglutide is a long-acting GLP-1 receptor agonist approved for the treatment of type 2 diabetes. It is composed of two identical GLP-1 (7–37) analogs that are protected against dipeptidyl peptidase-4 (DPP-4) action and fused to a modified immunoglobulin G4 Fc fragment by a small peptide link.10 Dulaglutide is not cleared by the kidney, and administration to patients with mild-to-severe impairment of kidney function does not increase drug exposure, according to pharmacokinetic findings. Therefore, no dose adjustment for dulaglutide is recommended for patients with chronic kidney disease.

The efficacy and safety of dulaglutide, including a suppressing effect on the progression of nephropathy in patients with moderate to severe chronic kidney disease (CKD), were investigated in the AWARD-7 study.11 In that study, the baseline eGFR was 38 mL/min/1.73 m² and 30% of patients were CKD stage 4. Dulaglutide 0.75 mg and 1.5 mg were overall well tolerated in such severe patients, and suppressed the eGFR decline more effectively compared with insulin glargine. However, the AWARD-7 study included only 3% Asian patients, and no other study has evaluated Asian patients, including Japanese, so far. Therefore, we decided to conduct database research focusing on the suppressing effect on the progression of nephropathy of dulaglutide 0.75 mg using the computerized diabetes care (CoDiC) database provided by the Japan Diabetes Clinical Data Management Study Group (JDDM).

**MATERIALS AND METHODS**

**Participants and study procedures**

The JDDM is composed of Japanese diabetologists belonging to specialized facilities for diabetes treatment, and they established the CoDiC database in 2001.12 The basic patient data are published on the JDDM homepage as basic research reports, and the content is updated annually.13 The data of type 2 diabetes mellitus patients who visited JDDM facilities from 2015 to 2020 were extracted from the CoDiC database and analyzed cross-sectionally and retrospectively.

The patient selection procedure for dulaglutide and non-dulaglutide groups is described in Figure 1. Patients in the dulaglutide group must have been treated with dulaglutide for more than 6 months without a prescription change. Patients in the non-dulaglutide group must have visited a hospital/clinic during October to December 2015 (reference visit), and must not have changed the prescription for 6 months after the reference visit.

Inclusion criteria were patients with type 2 diabetes aged ≥18 years, hemoglobin A1c (HbA1c) ≥ 7.0 and <10.5%, and CKD stage 3 to 4 (eGFR 15 to 59 mL/min/1.73 m²) at dulaglutide initiation or reference visit. Exclusion criteria were patients with renal replacement therapy and patients treated with a GLP-1 receptor agonist except dulaglutide.

The primary endpoint of this study was the slope in eGFR for 3 years. Other evaluation items were a change from baseline in HbA1c, body weight, urine albumin-to-creatinine ratio (UACR), and eGFR for 3 years. The UACR values was classified based on the albuminuria stage: normo-albuminuria (<30 mg/gCr), micro-albuminuria (30–299 mg/gCr), and macro-albuminuria (≥300 mg/gCr). The eGFR was estimated using the following equation provided by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m²) = 194 × serum Cr−1.094 × age−0.287 × 0.739 (if female).14 The eGFR values was classified based on CKD stage: stage 3a (≥45 and < 60 mL/min/1.73 m²), stage 3b (≥30 and < 45 mL/min/1.73 m²), and stage 4 (<30 mL/min/1.73 m²).

**Statistical analysis**

To adjust for differences in the baseline background characteristics between dulaglutide (group A) and non-dulaglutide (group B), inverse probability weighting using propensity scores was applied. Propensity scores were developed with age, gender, body weight, body mass index (BMI), blood pressure, HbA1c, eGFR, UACR, use of SGLT2 inhibitor, use of ACE inhibitor, and use of angiotensin receptor blocker. The background factors were summarized before and after adjustment by propensity score analysis. Differences between group A and group B were evaluated using the standardized mean difference (SMD), and values closer to zero indicated background difference was negligible.

We estimated the average treatment effect as treated, that is, the effect if the non-dulaglutide patients would have received dulaglutide. Changes from baseline to 3 years in HbA1c, body weight, UACR, and eGFR were determined at 0.5 year intervals, and the slope in eGFR was estimated. Also, the percentages of eGFR categories (45 or over, between 30 (inclusive) and 45 (exclusive), under 30 mL/min/1.73 m²) for each time point were summarized. In addition, subgroup analyses stratified by baseline UACR categories and the use of SGLT2 inhibitor were conducted. Confidence levels were set to 95% and all statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).
Patient background characteristics before propensity score weighting are also provided, in Table S1 for reference.

Changes in HbA1c, body weight, UACR, and eGFR for 3 years are shown in Figure 2. HbA1c was significantly reduced, and body weight was not significantly changed in group A or B. For UACR, there were no significant changes except for a transient increase at 2.5 years in group A. For eGFR, there was no significant change from baseline in group A and a decreasing tendency was observed in group B. When comparing groups A and B, statistically significant differences were observed in HbA1c and UACR at 0.5 years in group A, but there were no significant differences at other time points. In terms of the slope of eGFR, the mean (95%CI) in eGFR slope was 0.11 (−0.34, 0.56) mL/min/1.73 m² per year in group A and −1.29 (−1.64, −0.94) mL/min/1.73 m² per year in group B. The difference between groups was 1.40 (0.83, 1.97) mL/min/1.73 m² per year, and a statistically significant reduction was observed in group B (P < 0.0001). In the categorical analysis in eGFR, the percentage of stage 4 (<30 mL/min/1.73 m²) tended to be higher in group B (Figure 3).

In addition, subgroup analysis of eGFR stratified by the baseline albuminuria stage and use of SGLT2 inhibitor are shown in Figure 4 and Tables S2 and S3. In subgroup analysis stratified by the baseline albuminuria stage, differences between groups at 3 years were −3.07 (−8.14, 1.99) mL/min/1.73 m² in normo-albuminuria, 3.00 (−3.52, 9.53) mL/min/1.73 m² in micro-albuminuria, and 6.31 (−4.84, 17.45) mL/min/1.73 m² in macro-albuminuria, and the difference was greater for the higher degree of albuminuria. In subgroup analysis stratified by the use of SGLT2 inhibitor, differences between groups at 3 years were 3.31 (−4.10, 10.72) mL/min/1.73 m² in the use group, and 1.59 (−3.27, 6.44) mL/min/1.73 m² in the non-use group, and the difference was greater for the use of SGLT2 inhibitor.
Table 1 | Clinical characteristics of the patients

|                        | Group A                                      | Group B                                      | SMD   |
|------------------------|----------------------------------------------|----------------------------------------------|-------|
| Age, years             | 70.8 ± 9.6                                   | 69.4 ± 10.0                                  | 0.1467|
| Male                   | 56.8%                                        | 59.4%                                        | -0.0529|
| Body weight, kg        | 70.2 ± 13.7                                  | 72.9 ± 15.3                                  | -0.1869|
| BMI, kg/m²             | 27.3 ± 4.9                                   | 28.1 ± 4.7                                   | -0.1535|
| HbA1c, %               | 8.4 ± 0.8                                    | 8.5 ± 1.0                                    | -0.0867|
| SBP, mmHg              | 127.7 ± 16.8                                 | 128.4 ± 15.0                                 | -0.0426|
| DBP, mmHg              | 69.3 ± 11.2                                  | 70.0 ± 11.9                                  | -0.0532|
| eGFR, mL/min/1.73 m²   | 47.9 ± 9.1                                   | 47.7 ± 10.2                                  | 0.0303|
| ≥45, <60               | 66.4%                                        | 66.7%                                        | -0.0067|
| ≥30, <45               | 27.2%                                        | 27.2%                                        | 0.0011 |
| <30                    | 6.4%                                         | 6.1%                                         | 0.011  |
| UACR, mg/gCr           | 218 ± 487                                    | 251 ± 532                                    | -0.0625|
| ≥30, <300              | 43.2%                                        | 45.2%                                        | -0.0407|
| ≥300                   | 41.6%                                        | 35.3%                                        | 0.1288 |
| Concomitant drug       |                                              |                                              |       |
| Sulfonylureas          | 57.6%                                        | 52.6%                                        | 0.1012 |
| Biguanides             | 56.8%                                        | 57.7%                                        | -0.0178|
| SGLT2 inhibitors       | 43.2%                                        | 39.3%                                        | 0.0790 |
| Thiazolidinedione      | 14.4%                                        | 10.8%                                        | 0.0860 |
| Glinides               | 12.8%                                        | 2.4%                                         | 0.3999 |
| α-Glucosidase inhibitors| 15.2%                                        | 11.1%                                        | 0.1215 |
| DPP-4 inhibitors       | 6.4%                                         | 68.6%                                        | -1.6782|
| Insulin                | 37.6%                                        | 48.5%                                        | -0.2214|
| GLP-1 receptor agonists| 100.0%                                       | 0.0%                                         | -      |
| ARB                    | 62.4%                                        | 59.5%                                        | 0.0588 |
| ACE inhibitor          | 1.6%                                         | 1.1%                                         | 0.04   |

Mean ± SD or proportion (%), ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ESS, effective sample size; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter-2; SMD, standardized mean difference; UACR, urine albumin-to-creatinine ratio.

DISCUSSION

In the current study, it was shown that dulaglutide slowed the eGFR decline for 3 years. In support of this finding, the following mechanisms of the renoprotective effects of GLP-1 receptor agonist have been reported\(^{16}\). GLP-1 receptor agonists have been shown to activate PKA and to increase the production of cyclic adenosine monophosphate (cAMP). As a consequence, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and NF-kB activity are inhibited, resulting in the attenuation of oxidative stress and inflammation. These favorable effects prevent podocyte loss as well as mesangial and endothelial dysfunction. GLP-1 receptor agonists inactivate NHE3 and promote atrial natriuretic peptide (ANP) secretion, thereby inducing natriuresis. Furthermore, GLP-1 receptor agonists inhibit tubular injury and subsequent tubulointerstitial fibrosis.

In the AWARD-7 study, which was the first study of dulaglutide in patients with type 2 diabetes and moderate to severe CKD, the baseline eGFR was 38 mL/min/1.73 m² and the percentage of patients with CKD stage 2 was 30%. On the other hand, the current study included milder patients compared with the AWARD-7 study, and the baseline eGFR was 48 to 49 mL/min/1.73 m² and the percentage of patients with CKD stage 2 was only 6%. Subgroup analysis stratified by CKD stage revealed a greater renoprotective effect in more severe patients in both studies, but it was clinically meaningful to show that dulaglutide slowed an eGFR decline in the moderate patients of the current study.

In a study on the renoprotective effects of GLP-1 receptor agonist except dulaglutide, Osono et al.\(^{17}\) reported liraglutide (maximum dose was 0.9 mg per day) slowed the eGFR decline in the 568 patients treated with liraglutide for more than 1 year. This study included normal and mild CKD, and the baseline eGFR was 61 mL/min/1.73 m². Subgroup analysis stratified by CKD stage showed greater renoprotective effects in the more severe patients, and this result was consistent with our study results.

In the current study, we performed subgroup analysis stratified by the use of SGLT2 inhibitor, and eGFR in the SGLT2 inhibitor use group was greater than that in the SGLT2 inhibitor non-use group. In a subgroup analysis of the AMPLITUDE-O Trial, which was the cardiovascular outcome trial for epeglenatide and started after the launch of the SGLT2 inhibitor, the hazard ratio of renal composite endpoint was numerically lower in patients with the use of SGLT2, and it was suggested that the mechanisms of renoprotective effects of GLP-1 receptor agonist and SGLT2 inhibitor were different\(^{18}\). Based on these results, additive and/or synergistic renoprotective effect by GLP-1 receptor agonist and SGLT2 inhibitor might be expected.

There are some limitations in the current study. First, the observation period of the dulaglutide group was shorter than that in the non-dulaglutide group. The percentage of patients with eGFR data was 88% at 1 year, 73% at 2 years, and 77% at 3 years in the non-dulaglutide group, and 90% at 1 year, 53% at 2 years, 27% at 3 years in the dulaglutide group. As a result, the variability of the results became large when the number of cases was small. Second, we performed propensity score weighting in the current study, but it was difficult to match exactly, and the standardized mean differences in some items exceeded 0.1. Third, this was not a prospective randomized control trial, so there might have been a patient selection bias by physicians. Fourth, the approved dose of dulaglutide is 0.75 mg in Japan and this is half the global dose of 1.5 mg.
In conclusion, dulaglutide slowed the eGFR decline in patients with type 2 diabetes and CKD stage 3 to 4. This effect was marked in patients with macro-albuminuria and/or concomitant SGLT2 inhibitor use.

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Figure 2 | Change of (a) HbA1c, (b) Body weight, (c) UACR, (d) eGFR in continuous measures for 3 years. Data are shown as mean ± SD, eGFR, estimated glomerular filtration rate; ESS, effective sample size; HbA1c, hemoglobin A1c; UACR, urine albumin-to-creatinine ratio.
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REFERENCES
1. Ministry of Health, Labour and Welfare. National Health and Nutrition Examination Survey 2016 (Japanese). Available from: https://www.mhlw.go.jp/bunya/kenkou/eiyou/h28-houkoku.html Accessed March 8, 2022.

2. Japan Medical Association, Ministry of Health, Labour and Welfare. Diabetic nephropathy aggravation prevention program (Japanese). Available from: https://www.mhlw.go.jp/content/12401000/program.pdf. Accessed March 8, 2022.

3. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. LEADER steering committee and investigators. liraglutide and renal outcomes in type 2 diabetes. N Engl J Med 2017; 377: 839–848.

4. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016; 375: 1834–1844.

5. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet 2019; 394: 131–138.

6. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016; 375: 323–334.

7. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol 2019; 7: 606–617.

8. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019; 380: 2295–2306.

9. Heerspink HJJ, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020; 383: 1436–1446.

10. Glaesener W, Vick AM, Millican R, et al. Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an Fc fusion protein. Diabetes Metab Res Rev 2010; 26: 287–296.

11. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol 2018; 6: 605–617.

12. Kobayashi M, Yamaizaki K, Hirao K, et al. The status of diabetes control and antidiabetic drug therapy in Japan—a cross-sectional survey of 17,000 patients with diabetes mellitus (JDDM 1). Diabetes Res Clin Pract 2006; 73: 198–204.

13. Japan Diabetes Clinical Data Management Study Group [Japanese]. Available from: http://jddm.jp/ Accessed March 8, 2022.

14. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53: 982–992.

15. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011; 46: 399–424.

16. Kawanami D, Takashi Y. GLP-1 receptor agonists in diabetic kidney disease: from clinical outcomes to mechanisms. Front Pharmacol 2020; 11: 967.

17. Osono T, Saito M, Osono Y, et al. Liraglutide improves estimated glomerular filtration rate slopes in patients with chronic kidney disease and type 2 diabetes: a 7-year retrospective analysis. Diabetes Technol Ther 2020; 22: 828–834.

18. Lam CSP, Ramasundarahettige C, Branch KRH, et al. Efpeglenatide and clinical outcomes with and without concomitant sodium-glucose co-transporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O trial. Circulation 2021; 145: 565–574.
SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Clinical characteristics of the patients before propensity score weighting
Table S2 | Average and change from baseline in eGFR at each time point (stratified by UACR class).
Table S3 | Average and change from baseline in eGFR at each time point (stratified by use of SGLT2 inhibitor).