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Effects of Oral Semaglutide on Renal Function in Diabetic Kidney Disease: A Short-term Clinical Study

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Abstract. *Background/Aim: In the SUSTAIN-6 trial, semaglutide reduced the risk of worsening nephropathy in patients with type 2 diabetes. The objective of this retrospective study was to elucidate the effect and safety of oral semaglutide (Rybelsus®) in patients with diabetic kidney disease (DKD). Patients and Methods: Six patients with DKD received 3 mg/day semaglutide orally. The observation period was 9.0±5.0 months. Changes in estimated glomerular filtration rate (eGFR), urinary protein, fasting blood glucose, and hemoglobin A1c were studied from 6 months before the administration of oral semaglutide until 6 months after administration. Results: The change in eGFR over the 6 months prior to semaglutide administration was −1.2±1.6 ml/min/1.73 m^2, showing a trend for a decrease; although not statistically significant, the change at 6 months after oral semaglutide initiation showed improved eGFR (1-50.7±1.8 ml/min/1.73 m^2). Proteinuria was not reduced after treatment with oral semaglutide. No significant adverse effects (including retinopathy) were observed in any patient during the study. Conclusion: Despite the small sample size and short observation period, oral semaglutide was found to be a relatively well-tolerated drug for patients with DKD.*

Diabetic kidney disease (DKD), which is a major vascular complication of diabetes, is recognized as a global disease burden and the leading cause of end-stage renal disease (1, 2). Blood glucose control is fundamentally important for the treatment of DKD and the degree of glucose control is related to the development of DKD (3). The administration of renin-angiotensin-aldosterone inhibitors to manage blood pressure appears to offer protective effects against DKD (4, 5). Furthermore, recent large clinical trials clearly indicated that the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors delayed DKD progression (6-9). Despite significant advances, limited progress has been made regarding the prevention and treatment of DKD and residual risk still exists. Therefore, we recommended a combination of incretin-based therapeutic agents, SGLT2 inhibitors, renin-angiotensin-aldosterone inhibitors, and mineralocorticoid receptor antagonists, the 'DKD fantastic four', as a new standard DKD treatment (9, 10).

The rapid degradation of glucagon-like peptide-1 (GLP1) by dipeptidyl peptidase-4 inhibitors, commonly employed for treating type 2 diabetes, means these agents have the potential to serve as a viable treatment for DKD; GLP1 receptor agonists and dipeptidyl peptidase-4 inhibitors elicit vasotropic effects and reduce diabetes-induced inflammation and oxidative stress, ameliorating DKD (11-14).

Recently published, large clinical trials, LEADER (15) and SUSTAIN-6 (16), have attracted attention due to the renoprotective effects shown for the leading GLP1 receptor agonists. In the LEADER trial, liraglutide-treated patients had a 22% reduction in the risk of renal composite endpoints: new onset of proteinuria, doubling of serum creatinine, estimated glomerular filtration rate (eGFR)<45 ml/min/1.73 m^2 and continuous renal replacement therapy. In contrast to the renoprotective effects of SGLT2 inhibitors, no increase in serum creatinine doubling or eGFR reduction was demonstrated (15, 17). The SUSTAIN-6 study with semaglutide, a once-weekly formulation with a long half-life, also showed evidence of renoprotective effects. In addition to its potent hemoglobin A1c (HbA1c)- and weight-lowering effects, administration of semaglutide significantly reduced the primary outcome of cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) by 26%. Furthermore, the risk of new or worsening nephropathy

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(macroalbuminuria, serum creatinine doubling, renal replacement therapy, and death from renal failure) was reduced by 36% (16, 17). Therefore, semaglutide appears to be promising as a therapeutic agent to reduce residual risks related to DKD progression. However, no studies have yet been conducted specifically on the effects of oral semaglutide (Rybelsus®) on renal function in patients with DKD. This is the first study to examine the efficacy and safety of oral semaglutide in patients with DKD.

Patients and Methods

This study included a retrospective cohort of six cases who underwent outpatient care at the Department of Nephrology, Osaka Medical and Pharmaceutical University (Osaka, Japan). No changes were made to glucose-lowering agents other than semaglutide at study entry. Semaglutide was started at 3 mg once daily. Participants were evaluated for several parameters at baseline and 1 to 12 months after semaglutide administration. Therapy with angiotensin II receptor blockers and angiotensin receptor neprilysin inhibitor were also not changed during the study period. All procedures performed in studies involving human participants were in accordance with the ethical standards of the National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The requirement to obtain informed consent was waived, and ethical review was not performed by the Institutional Review Board rule because there were fewer than nine patients in the study. Blood and urine biochemical analyses were performed on a Hitachi Labospect 008 (Hitachi, Tokyo, Japan) autoanalyzer. Data on the levels of serum creatinine, fasting blood glucose, HbA1c, urinary protein-to-creatinine ratio, and patient characteristics (*e.g.,* medications, age, sex, and body mass index) were obtained and analyzed retrospectively using electronic medical records. The eGFR for each patient was calculated using the following formula: 194×(serum creatinine)$^{-1.094}$×(age)$^{-0.287}$×0.739 (if female) (18). The change in eGFR was assessed by the difference in values at 6 months prior to and 6 months after administration, from that at initiation of semaglutide administration and respectively.

Data analysis. Data are reported as the mean±standard deviation. Statistical significance for differences was determined by Wilcoxon test. All analyses were performed using StatView (SAS Institute, Cary, CA, USA) and Excel software (Microsoft, Redmond, WA, USA). Statistical significance was defined as $p<0.05$.

Results

Four male and two female patients were enrolled in the study. The average age at onset was 69.2±7.9 years. The mean observation period was 9.0±5.0 months. The duration of diabetes was 12.3±10.0 years. All patients were treated with oral semaglutide (Rybelsus®) at 3 mg/day. Concomitant medications for diabetes were as follows: Glinide in one, SGLT2 inhibitors in four, imeglimin in one and thiazolidine in one (Table I).

Table I. *Patient characteristics (n=6).*

Characteristic		Value
Sex, n	Male:female	4:2
Age, years	Mean±SD	69.2±7.9
BMI, kg/m^2	Mean±SD	27.8±5.7
Duration of diabetes, years	Mean±SD	12.3±10.0
Observation period, months	Mean±SD	9.0±5.0
Anti-diabetic agent, n		
	Glinide	1
	SGLT2 inhibitor	4
	Imeglimin	1
	Thiazolidine	1
Anti-hypertensive agent, n	ARBs	1
	ARNI	1
	Ca-Blockers	3
	α-Blockers	2
	β-Blockers	1
	αβ-Blockers	1
Anti-dyslipidemia agent, n	Statins	2
Anti-uric acid agent, n	Dotinurad	2

ARBs: Angiotensin II receptor blockers; ARNI: angiotensin receptor neprilysin inhibitor; BMI: body mass index; SD: standard deviation; SGLT2: sodium-glucose cotransporter 2.

Fasting blood glucose and HbA1c tended to decrease after oral semaglutide treatment compared with baseline, albeit without significance (Figure 1). Next, we analyzed the effect of oral semaglutide on renal function. Compared with pretreatment values, eGFR tended to be improved with the administration of oral semaglutide (pre *vs*. post semaglutide: −1.2±1.6 *vs*. 0.7±1.8 ml/min/1.73 m^2; $p=0.114$, Figure 2). However, there was no improvement in proteinuria with semaglutide treatment (Δ urinary protein-creatinine ratio: −0.6±2.4 *vs*. 0.0±2.4; $p=0.753$, Figure 3).

During the observation period, adverse events, such as hypoglycemia, diarrhea, nausea, vomiting, or worsening retinopathy complications were not recognized in all patients during the study.

Discussion

Due to the limited availability of real-world data on the use of oral semaglutide, this study was conducted to confirm its efficacy and safety for patients with DKD. Our results showed that oral semaglutide improved eGFR, although no significant differences were observed. Furthermore, no adverse events, including worsening of diabetic retinopathy, were observed during the study. Our results showed oral semaglutide reduced fasting blood glucose and HbA1c, although these differences were not statistically significant.

The SUSTAIN-6 trial, a cardiovascular outcomes study which evaluated the use of semaglutide, demonstrated

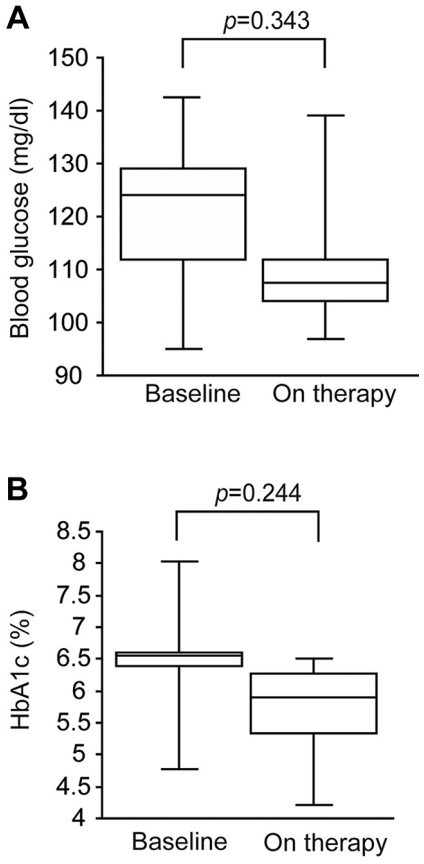

Figure 1. *Box plots showing fasting blood glucose (A) and glycosylated hemoglobin A1c (HbA1c) (B) before and after oral semaglutide treatment.*

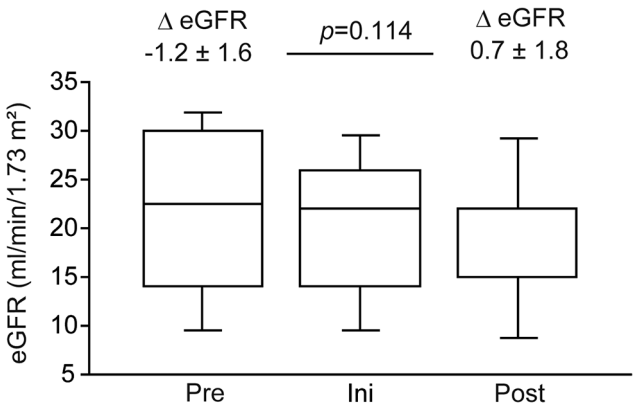

Figure 2. *Box plots showing estimated glomerular filtration (eGFR) rate 6 months before (Pre), at (Ini) and 6 months after (Post) oral semaglutide treatment. In the Post box the median value is 22, which coincides with the upper line of the box.*

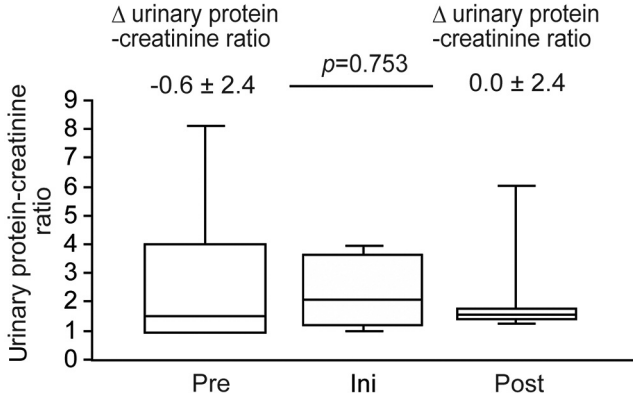

Figure 3. *Box plots showing urinary protein-creatinine ratio 6 months before (Pre), at (Ini) and 6 months after (Post) oral semaglutide treatment.*

favorable effects on renal function (hazard ratio=0.64, 95% confidence interval=0.46-0.89) and a significant reduction (46%) in the risk of developing macroalbuminuria (hazard ratio=0.64, 95% confidence interval=0.37-0.78) (16). The FLOW study aims to determine whether the administration of once-weekly semaglutide injection can effectively delay the progression of kidney disease and lower the risk of renal- and cardiovascular- related mortality in patients with DKD. This study is expected to conclude by late 2024 (19).

Unlike other GLP1 receptor agonists currently available, semaglutide offers the convenience of oral administration. The oral administration of peptide agonists has been challenging in the past due to the specific physicochemical properties of peptides, such as high molecular weight, enzymatic instability, increased hydrophilicity, and low permeability. Oral semaglutide possesses the distinctive characteristic of undergoing gastric absorption, setting it apart from most oral drugs that are typically absorbed in the gut. The enzymatic degradation of peptides in the gastrointestinal tract often plays a major role in impeding absorption and reducing bioavailability, thus presenting challenges in delivering peptides *via* the oral route (20).

The PIONEER-5 study showed the effectiveness and safety of oral semaglutide in patients with DKD with moderate renal impairment (eGFR: 30-59 ml/min/1.73 m^2); renal function remained unchanged during the study period in both the oral semaglutide and placebo groups, while the albumin-to-creatinine ratio decreased in the oral semaglutide group when compared to placebo (21). As a result of these favorable findings, oral semaglutide became the first oral GLP1 receptor agonist to receive U.S. Food and Drug Administration (https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-glp-1-treatment-type-2-diabetes) approval in 2019.

In glomerular endothelial cells, GLP1 has the ability to suppress the expression of tumor necrosis factor-α and vascular cell adhesion molecule-1. It has been observed that GLP1 stimulates the production of nitric oxide, potentially enhancing glomerular endothelial function (12). Additionally, GLP1 has been shown to ameliorate glomerular injury in rodents (11). However, so far, the exact mechanism through which GLP1 protects glomerular endothelial cells remains unknown. Recently, we reported that the activation of GLP1 receptor agonists was able to trigger the cyclic AMP/protein kinase A (PKA) pathway, increasing phosphor-c-RAF (Ser259), which in turn inhibits phosphor-c-RAF (Ser338)/plasminogen activator inhibitor type 1 signaling activated by protein kinase C (PKC)b and angiotensin II (10, 11).

The induction of inflammation and oxidative stress by hyperglycemia and dyslipidemia plays a significant role in developing DKD (22). The increase of inflammatory cytokines and reactive oxygen species have also been recognized in DKD (14). Our previous study clearly showed that GLP1 reduced expression of inflammatory cytokines, such as CD68 and CXCL2 (11). Interestingly, GLP1 receptor expression was observed in the glomeruli, but not in the tubules. The Medalist Program and Study at Joslin Diabetes Center at Harvard University studying people who have been living with type 1 diabetes for more than 50 years has revealed they experience decreases in GLP1 receptor expression in the renal cortex (Mima A and King GL, unpublished data). Furthermore, we have shown that diabetes-induced PKCb activation reduced GLP1 receptor by ubiquitination (11). Thus, GLP1 receptor agonists may be better used from the early stage of diabetes stage.

Our study has several limitations. Firstly, it was conducted as a single-center cohort study. Secondly, it included only a small number of patients. Lastly, the follow-up period was relatively short.

In summary, the results of our study suggest that eGFR decline tended to be reduced after the administration of oral semaglutide in patients with DKD. Hence, administration of oral semaglutide may be useful to improve the prognosis of patients with DKD.

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Conflicts of Interest

Akira Mima received a speaker honorarium from Otsuka, Kyowa Kirin, Mitsubishi Tanabe, Torii, Kowa, Bayer, Eli Lilly, Mochida, Sumitomo Pharma, Novo Nordisk and Boehringer Ingelheim.

Authors' Contributions

Akira Mima: Conceptualization, methodology, software, data curation, writing – original draft, preparation, writing – review and editing. Rina Lee, Ami Murakami, Hidemasa Gotoda, Sayumi Kidooka: Visualization, investigation, writing – review and editing. Rina Lee, Takahiro Nakamoto, Suguru Kido: Visualization, investigation, software and validation. Shinji Lee: Supervision. All Authors named meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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