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Research Article

The Effect of Oral Semaglutide on Urinary Albumin to Creatinine Ratio in Patients with Type 2 Diabetes

Masahiro Yano*, Sadahiko Uchimoto, Masami Nishimura, Saori Yamaguchi

Department of Internal Medicine, Fujiidera Municipal Hospital, Fujiidera, Japan

ABSTRACT

Background: Oral semaglutide has been shown to have excellent effects such as reduction of HbA1c and weight loss. However, there are no reports of the effect of oral semaglutide on Urinary Albumin to Creatinine Ratio (UACR). In this study, we investigated the effect of oral semaglutide on UACR in patients with type 2 diabetes who switched from Dipeptidyl Peptidase-4 (DPP4) inhibitors to oral semaglutide.

Method: Thirty patients with type 2 diabetes (15 males, 15 females, average age 60.3 years old), whose UACR was measured before and after switching from DPP4 inhibitors to oral semaglutide, were investigated. It was compared between before and after 6.6 months on averages that body weight, systolic and diastolic blood pressure, HbA1c, Low-Density Lipoprotein Cholesterol (LDL-C), and UACR.

Result: After switching from DPP4 inhibitor to oral semaglutide, HbA1c decreased significantly (8.3 ± 1.1% before switching, 7.4 ± 0.9% after switching, $p<0.001$). Body weight (71.8 ± 13.7 kg before switching, 68.4 ± 12.6 kg after switching, $p<0.001$), systolic blood pressure (140.4 ± 17.0 mmHg before switching, 135.4 ± 13.8 mmHg after switching, $p<0.01$), LDL-C (111.1 ± 20.4 mg/dL before switching, 98.8 ± 21.5 mg/dL after switching mg/dL, $p<0.01$), and UACR (194.2 ± 311.8 mg/g・Cre before switching, 121.2 ± 224.3 mg/g・Cre after switching, $p<0.001$) were also significantly decreased.

Conclusion: Switching from DPP4 inhibitors to oral semaglutide resulted in reductions in HbA1c, body weight, systolic blood pressure, LDL-C, and UACR in patients with type 2 diabetes.

Keywords: Type 2 diabetes; Oral semagulutide; Urinary albumin to creatinine ratio; DPP4 inhibitors

INTRODUCTION

In the treatment of diabetes, it is important to prevent the onset and progression of complications. Typical complications include microvascular diseases such as retinopathy and nephropathy, and macrovascular disorders such as myocardial infarction and cerebrovascular disease. In order to prevent the onset and progression of these vascular complications, it is necessary to manage blood glucose, body weight, blood pressure, and lipids. Clinical studies such as Diabetes Control and Complications Trial, United Kingdom Prospective Diabetes Study and Kumamoto study have shown that strict glucose-control treatment policy suppresses the onset and progression of nephropathy and retinopathy in patients with type 2 diabetes [1-3]. In the ADVANCE Study and ACCORD Study, which set more intensive glucose-control treatment policy, though no cardiovascular events were suppressed, the onset and progression of nephropathy were suppressed, indicating the importance of glucose-control treatment in the treatment of nephropathy [4,5].

Patients with type 2 diabetes reduce blood glucose and body weight by using Glucagon like Peptide-1 Receptor Agonist (GLP-1RA). Thus, it is recommended as one of the treatment options for type 2 diabetes in many countries, including Japan. In addition, cardiovascular event suppression and renal protective effects were reported [6-8]. Thus, patients with type 2 diabetes, a history of cardiovascular events, a few cardiovascular risks, and Chronic Kidney Disease (CKD), are expected to be considered regardless of baseline Hemoglobin A1c (HbA1c) or individual HbA1c targets [9]. Conventional GLP-1RA was an injectable preparation, but oral GLP-1RA was developed for the first time in the world [10]. Efficient absorption of oral semaglutide is dependent on the presence of the absorption enhancer Sodium N-(8-(2-Hydroxybenzoyl) Aminocaprylate) (SNAC). Absorption of semaglutide takes place in the stomach, and requires co-formulation with SNAC. SNAC protects against enzymatic degradation *via* local buffering

Correspondence to: Masahiro Yano, Department of Internal Medicine, Fujiidera Municipal Hospital, Fujiidera, Japan; E-mail: yanomasa0802@gmail.com

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actions and transiently enhances absorption. By containing SNAC in the same tablet, oral administration became possible. The results of clinical trials have shown excellent effects such as reduction of HbA1c and weight loss [11]. On the other hand, in the LEADER study, in the liraglutide (one of GLP-1RA) group, risk of a composite renal microvascular outcome nephropathy (defined as the new onset of macroalbuminuria or a doubling of the serum creatinine level and an Estimated Glomerular Filtration Rate (eGFR) of ≤ 45 ml per minute per 1.73 m^2, the need for continuous renal-replacement therapy, or death from renal disease) decreased by 22%. In particular, the risk of new development of Urinary Albumin to Creatinine Ratio (UACR) was reduced by 12% and overt proteinuria by 26%. Subsequently, similar effects were reported in semaglutide and dulaglutide [7,8]. However, there are no reports of the effects of oral semaglutide on UACR. In this study, we investigated the effects of oral semaglutide on UACR in patients with type 2 diabetes who switched from Dipeptidyl Peptidase-4 (DPP4) inhibitors to oral semaglutide.

METHODOLOGY

Thirty patients with type 2 diabetes (15 males, 15 females, average age 60.3 years old) were investigated. After administration of oral semaglutide 3 mg, the dose was increased to 7 mg at intervals of at least 4 weeks, and to 14 mg in cases who it was necessary for blood glucose control. Ultimately, 3 mg was administered in 6 cases, 7 mg in 19 cases, and 14 mg in 5 cases according to the judgement of the attending physicians. It was compared between before and after 6 months on average that body weight, systolic and diastolic blood pressure, HbA1c, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma-Glutamyl Transferase (γ-GTP), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein (HDL-C), Triglyceride (TG), eGFR, and UACR. Blood samples were taken under fasting conditions, and LDL-C was measured by a direct method.

The present study was approved by the ethics committee of Fujiidera Municipal Hospital on Oct 5, 2022. The approval number was 4-1. Informed consent was obtained by the opt-out methods on the website of Fujiidera Municipal Hospital (https://www.city.fujiidera.lg.jp/hospital/oshirase/12593.html).

The data are presented as the number (percentage) or as the mean ± standard deviation. For comparisons before switching from DPP4 inhibitors to oral semaglutide, paired t test was used, and Wilcoxon signed rank test was used at TG and UACR. Pearson's correlation analysis was used at the relationship between the change of UACR and the change of each parameter. The significant level was set at 5%. Statistical analysis was performed using JMP14.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows the clinical background of all patients. The age, duration of diabetes, BMI, HbA1c level, LDL-C level, eGFR and UACR in all patients were 60.3 ± 13.5 years, 12.4 ± 8.3 years, 27.5 ± 4.7 kg/m^2, 8.3 ± 1.1%, 111.1 ± 20.4 mg/dL, 75.9 ± 21.4 ml/min/1.73m^2, and 194.2 ± 311.8 mg/g・Cre. Table 2 shows concomitant drugs as antidiabetic drugs, renin-angiotensin system inhibitors, β-blockers, and statins (Table 1 and 2).

Table 1: Clinical characteristics of the patients.

Clinical characteristics	Standard deviation
Age (y)	60.3 ± 13.5
Male sex, n (%)	15 (50.0)
Duration of diabetes (y)	12.4 ± 8.3
Smoking	13 (43.3)
Drinking	11 (36.7)
BMI (kg/m^2)	27.5 ± 4.7
HbA1c (%)	8.3 ± 1.1
AST (IU/L)	27.1 ± 17.0
ALT (IU/L)	33.2 ± 26.0
γ-GTP (IU/L)	43.1 ± 29.5
LDL-C (mg/dL)	111.1 ± 20.4
HDL-C (mg/dL)	56.5 ± 14.2
TG (mg/dL)	154.9 ± 55.0
eGFR (ml/min/1.73m^2)	75.9 ± 21.4
UACR (mg/g・Cre)	194.2 ± 311.8
Systolic blood pressure (mmHg)	140.4 ± 17.0
Diastolic blood pressure (mmHg)	77.2 ± 16.6
Presence of hypertension, n (%)	13 (43.3)
Presence of hyperlipidemia, n (%)	19 (63.3)
Presence of cardiovascular disease, n (%)	1 (3.3)

NOTE: The data are expressed as the n (%) or as the mean ± the standard deviation. BMI: Body Mass Index; HbA1c: Glycated Hemoglobin A1c; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; γ-GTP: Gamma-Glutamyl Transferase; LDL-C: Low-Density Lipoprotein; HDL-C: High-Density Lipoprotein; TG: Triglyceride; eGFR: Estimated Glomerular Filtration Rate; UACR: Urinary Albumin to Creatinine Ratio

Table 2: Antidiabetic drugs, renin-angiotensin system inhibitors, β-blockers, statin usage by the patients.

Inhibitors	Standard deviation
Sodium glucose transporter 2 inhibitor	27 (90.0)
Biganide	24 (80.0)
Sulfonlyurea	12 (40.0)
Thiazolidine	7 (23.3)
Rapid-acting insulin secretagogue	1 (3.3)
α-Glucosidase inhibitor	4 (13.3)
Insulin	0 (0)
Renin-angiotensin system inhibitor	10 (33.3)
Statin	16 (53.3)

Note: The data are expressed as n(%).

Table 3 shows changes in each parameter. Body weight decreased significantly after switching from DPP4 inhibitors to oral semaglutide (71.8 ± 13.7 kg before switching, 68.4 ± 12.6 kg after switching, $p<0.001$). Systolic blood pressure decreased significantly after switching (140.4 ± 17.0 mmHg before switching, 135.4 ± 13.8 mmHg after switching, $p<0.01$), but no change was observed in diastolic blood pressure. HbA1c decreased significantly after switching (8.3 ± 1.1% before switching, 7.4 ± 0.9% after switching, $p<0.001$). No significant changes were observed in AST, ALT, γ-GTP, HDL-C, and TG, but LDL-C decreased significantly after switching (111.1 ± 20.4 mg/dL before switching, 98.8 ± 21.5 mg/dL after switching, $p<0.01$). Although eGFR did not change significantly, UACR decreased significantly after switching (194.2 ± 311.8 mg/g・Cre before switching, 121.2 ± 224.3 mg/g・Cre after switching, $p<0.001$) (Table 3).

Table 3: Changes in clinical parameters after switching DPP-4 inhibitors to oral semaglutide.

Inhibitors	Standard deviation	
Body weight (kg)	71.8 ± 13.7	68.4 ± 12.6**
Systolic blood pressure (mmHg)	140.4 ± 17.0	135.4 ± 13.8*
Diastolic blood pressure (mmHg)	77.2 ± 16.6	77.5 ± 11.7
HbA1c (%)	8.3 ± 1.1	7.4 ± 0.9**
AST (IU/L)	27.1 ± 17.0	24.7 ± 12.5
ALT (IU/L)	33.2 ± 26.0	30.8 ± 24.5
γ-GTP (IU/L)	43.1 ± 29.5	39.4 ± 23.3
LDL-C (mg/dL)	111.1 ± 20.4	98.8 ± 21.5*

HDL-C (mg/dL)	56.5 ± 14.2	54.6 ± 12.2
TG (mg/dL)	154.9 ± 55.0	148.1 ± 73.1
eGFR (ml/min/1.73m^2)	75.9 ± 21.4	79.6 ± 23.6
UACR (mg/g・Cre)	194.2 ± 311.8	121.2 ± 224.3**

Note: The data are expressed as the mean ± the standard deviation. *p<0.01, **p<0.001 *vs* baseline. HbA1c: Hemoglobin A1c, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase,γ-GTPGamma-Glutamyl Transferase, LDL-C: Low-Density Lipoprotein Cholesterol, HDL-C: High-Density Lipoprotein, TG: Triglyceride, eGFR: Estimated Glomerular Filtration Rate, UACR: Urinary Albumin to Creatinine Ratio.

Table 4 shows the relationship between the change of UACR and the change of body weight, SBP, DBP, HbA1c and LDL-C. There were no significant relationship between the change of UACR and the change of body weight, SBP, DBP, HbA1c and LDL-C (Table 4).

Table 4: The relationship between ΔUACR and each parameter.

	r^2	p
Δ BW	0.073	0.148
Δ SBP	0.098	0.091
Δ DBP	0.026	0.391
Δ HbA1c	0.013	0.556
Δ LDL-C	0.03	0.375

Note:Δ: The change from before to after switching; UACR: Urinary Albumin to Creatinine Ratio; BW: Body Weight; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HbA1c: Hemoglobin A1cLDL-C: Low-Density Lipoprotein Cholesterol

DISCUSSION

It is known that UACR and reduced eGFR are continuous risk factors for cardiovascular events, and a reduction of UACR is an integrated indicator for renal and cardiovascular risk reduction in patients with type 2 diabetes [12,13]. GLP-1RA, such as liraglutide, semaglutide, and dulaglutide, has been approved for the treatment of type 2 diabetes, and its efficacy in lowering glucose levels has been established. Furthermore, protective effects on renal function have been reported and received attention. At a point of protective effects on renal function of DPP4 inhibitors, it is known that UACR was reduced for a median of 2.1 years in SAVOR-TIMI53 [14]. Systematic review and meta-analysis demonstrated that SGLT2 inhibitors might be more effective than DPP4 inhibitors in reducing UACR. However, DPP4 inhibitors had beneficial renal effects by reducing the risk of development or progression of albuminuria compared with placebo [15]. We examined the influence to UACR by switching from DPP4 inhibitors to oral semaglutide during a 6.6-month follow-up in a single-center. The results showed that oral semaglutide significantly reduced UACR by switching from DPP-4 inhibitors to oral semaglutide. This study first proved that oral semaglutide reduced UACR in patients with type 2 diabetes. Some studies reported liraglutide, dulaglutide, and semaglutide in subcutaneous injection could reduce UACR [6-8]. Plasma levels of semaglutide achieved with oral semaglutide overlapped substantially with those detected after subcutaneous semaglutide administration [16]. Although the route of administration differed, it is thought that the effect was similar to that of semaglutide by subcutaneous injection. The causes of reduction of UACR by oral semaglutide were speculated some mechanisms. First, broad arrays of renoprotective properties, the risk factors of CKD such as decreased blood glucose, blood pressure, and weight loss, have been reported from GLP-1 therapies [17]. Steno-2 study has reported to reduce the onset and progression of diabetic nephropathy by 61% on multifactorial intervention such as blood glucose control, blood pressure control, lipid management compared with conventional therapy [18]. In our study, oral semaglutide not only improved blood glucose but also decreased systolic blood pressure and LDL-C, so reduced UACR by acting in a complex manner. On the other hand, there were not significant relationships between the change of UACR and the change of body weight, SBP, DBP, Hba1c and LDL-C was not seen. GLP-1 receptors have been shown to be expressed not only in the pancreas but also in various organs. Fujita demonstrated that GLP-1R mRNA transcripts were localized in glomerular capillary walls and throughout vascular walls, but not in tubules and collecting ducts, in the mouse kidney [19]. As GLP-1RA administration inhibits Na+/H+-Exchanger Type-3 (NHE3)-activity in the proximal tubule, GLP-1RA causes natriuresis [20]. It may contribute in part to protective effects on renal function. It is thought that the effects, such as anti-inflammatory effects, antioxidant effect and vasodilator effect, play a key role in this mechanism, but the detailed mechanism is still unknown [21-23]. The detailed mechanism is considered to be a future research topic.

LIMITATIONS

First of all, our study is a single-center study and the number of cases is as small as 30. More prospective studies are needed in the future. Second, this is a single arm study. All patients switched from DPP4 inhibitors to oral semaglutide, not placebo with oral semaglutide. DPP4 inhibitors tend to reduce UACR compared to UACR based on meta-analysis with placebo and other hypoglycemic drugs except SGLT2 inhibitors. Since switching from DPP-4 inhibitors to oral semaglutide reduced UACR, oral semaglutide can be expected to reduce UACR. Third, this study was a retrospective observational study, and the average duration of oral semaglutide administration was 6.6 months, which was a short observation period. However, we consider this to be an important study of the effect of oral semaglutide on UACR.

CONCLUSION

Although DPP4 inhibitors are useful hypoglycemic agents, switching from DPP4 inhibitors to oral semaglutide resulted in reductions in HbA1c, body weight, systolic blood pressure, LDL-C, and UACR in patients with type 2 diabetes. Oral semaglutide is a powerful hypoglycemic drug and also improves cardiovascular risk factors. Moreover, oral semaglutide has a renal protective effect. Oral semaglutide is one of the leading options for patients with type 2 diabetes.

It belongs to the class of Glucagon-Like Peptide-1 (GLP-1) receptor agonists, which stimulate insulin secretion and lower blood glucose levels. Unlike other GLP-1 receptor agonists, which are injected subcutaneously, oral semaglutide can be taken as a tablet once a day. Several clinical trials have shown that oral semaglutide is effective in lowering Hemoglobin A1c (HbA1c), a marker of long-term blood glucose control, in patients with type 2 diabetes. Moreover, oral semaglutide has additional benefits on other aspects of metabolic health, such as body weight, blood pressure, cholesterol levels, and kidney function. Compared to Dipeptidyl Peptidase-4 (DPP4) inhibitors, another class of oral hypoglycemic agents, oral semaglutide resulted in greater reductions in HbA1c, body weight, systolic blood pressure, Low-Density Lipoprotein Cholesterol (LDL-C), and Urinary Albumin-To-Creatinine Ratio (UACR) in patients with type 2 diabetes. Therefore, oral semaglutide is a promising option for patients with type 2 diabetes who need better glycemic control and cardiovascular risk reduction.

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