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CASE REPORT

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Oral semaglutide in kidney transplant recipients with metabolic syndrome: three Japanese cases

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Abstract

Background Renal transplant recipients with chronic kidney disease often develop post-transplant diabetes mellitus or metabolic syndrome (MetS), which are poor prognostic factors after renal grafts. Although recent studies have reported the protective effects of glucagon-like peptide-1 receptor agonist (GLP-1RA) on the heart and kidneys, few have assessed its effects in renal transplant patients. Moreover, to our knowledge there have been no studies on the effects of oral GLP-1RA (semaglutide) in renal transplantation recipients in Japan.

Case presentation Case 1 was a 52-year-old male renal transplant recipient with MetS. Semaglutide was administered orally for 12 months, starting at 3 mg/day and titrating up to 14 mg/day. Over time, his HbA1c level decreased from 5.9 to 5.5% and weight from 100.6 to 96.3 kg. No adverse events were observed. Case 2 was a 62-year-old male renal transplant recipient with MetS. Oral semaglutide was started at 3 mg/day. However, the patient had severe nausea, and the dose was reduced to 1.5 mg/day and then gradually increased to 14 mg/day for 12 months. Over time, triglyceride decreased from 308 to 277 mg/dL and weight decreased from 75.4 to 63.2 kg. Case 3 was a 59-year-old male renal transplant recipient with MetS and fatty liver. Oral semaglutide was started at 3 mg/day and titrated up to 12 mg/day for 12 months. Over time, triglyceride decreased from 205 to 119 mg/dL and weight decreased from 79.1 to 76.4 kg. No adverse events were observed.

Conclusions In all three patients, oral semaglutide significantly reduced body weight and improved metabolic parameters. Additional studies are needed to further evaluate the efficacy of oral semaglutide and the incidence of associated adverse events in a large number of renal transplant recipients.

Trial registration: UMIN, UMIN000050853. Registered 14 April 2023—Retrospectively registered, https://center6.umin.ac.jp/cgi-bin/ctr/ctr_reg_rec.cgi

Keywords Renal transplant recipient, Oral semaglutide, Metabolic syndrome

Background

Obesity, metabolic syndrome (MetS) and post-transplant diabetes mellitus (PTDM) are frequent complications after kidney transplantation [1]. These three complications are associated with chronic allograft dysfunction, poor graft and patient survival [1–6]. The protective effects of an injectable glucagon-like peptide-1 receptor agonist (GLP-1RA) on the heart and kidneys were recently revealed in several large-scale clinical trials, the LEADER [7], SUSTAIN-6 [8], AWARD-7 [9] and

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EXSCEL trials [10]. Moreover, similar protective effects on the heart and kidneys have been reported with semaglutide, an oral GLP-1RA [11–15]. The American Diabetes Association lists metformin as the first-line drug in 2023 for children, adults and the elderly. For adults, sodium–glucose cotransporter (SGLT2) inhibitors and GLP-1RAs are also recommended in cases of cardiovascular disease, heart failure and CKD complications (or high risk) [16]. However, there are few reports of GLP-1RA administration to transplant recipients. This is because GLP-1RA decreases bowel motility, which may impact absorption of immunosuppressive agents. In addition, adverse events associated with GLP-1RA may include dehydration due to nausea and vomiting, which can lead to decreased renal function. [6]. In the present study, we report the favorable results obtained with administration of semaglutide to three transplant recipients with MetS.

Case presentation

Here we present the results from three patients treated with oral semaglutide for MetS following living donor kidney transplantation (Table 1). These are three of five cases we previously reported in which empagliflozin was administered for MetS after renal transplantation [17].

Case 1

In 2016, a 52-year-old male patient started hemodialysis due to chronic renal failure, probably due to chronic glomerulonephritis, and in 2017, he received a living donor kidney transplant from his sister. His pre-transplant weight was 87.0 kg, which gradually increased to 99.9 kg by March 2020. At that time, the patient was diagnosed with MetS and started empagliflozin 10 mg/day. The patient's weight temporarily decreased to 98.2 kg with this medication, but by November 2021, he weighed 99.9 kg, had an abdominal circumference of 112 cm, hemoglobin A1c (HbA1c) of 6.0% and triglyceride of 173 mg/dL. The patient was then started on oral semaglutide at 3 mg/day because this patient refused to use injectable GLP-1RA. His physical characteristics at the start of semaglutide administration were as follows: age, 53 years; height, 168.0 cm; BMI, 35.6 kg/m^2; blood pressure, 128/87 mmHg; pulse, 85 beats/min; and body temperature, 36.7 °C. No palpebral conjunctival anemia, ocular conjunctival yellow staining, abnormal breath sounds, heart murmurs or lower leg edema was present. There were also no neurological abnormalities. Evidence of the renal transplant surgery was observed in the right lower abdomen. For immunosuppression, the patient received prednisolone 5 mg/day, tacrolimus 3.5 mg/day, mizoribine 300 mg/day and everolimus 1.5 mg/day. He also received the following oral medications: mecobalamin 500 μg/day, fluvastatin sodium 30 μg/day, febuxostat 10 mg/day, empagliflozin 10 mg/day, ezetimibe 10 mg/day and lafutidine 20 mg/day. Urine protein was negative. Both urinary occult blood and urinary glucose were negative at the start of oral semaglutide administration. The urine albumin (Alb)–creatinine (Cr) ratio (UACR) was 73.4 mg/g Cr. His Cr level was 1.77 mg/dL, and his estimated glomerular filtration rate (eGFR) was 33.6 mL/min/1.73 m^2, indicating stage G3bA2 CKD. Other laboratory findings are listed in Table 1. The trough level for tacrolimus was 6.94 ng/mL. His body weight, systolic

Table 1 Clinical profiles of the patients before oral semaglutide administration

	Case 1	Case 3	Case 3
Gender	Male	Male	Male
Age (years)	52	62	59
Primary renal disease	CGN	IgAN	IgAN
Period after transplantation (years)	4.6	25.4	23.5
Waist circumference (cm)	114	91	102
Immunosuppressant	PSL, TAC, MZR, EVR	PSL, CyA, MMF, EVR	PSL, CyA, MZR, EVR
Concomitant drugs	Febuxostat Fluvastatin Ezetimibe	Febuxostat Fluvastatin Cilnidipine Valsartan	Febuxostat Fluvastatin Cilnidipine Valsartan, amlodipine
Complications	MetS, PTDM, HT Dyslipidemia C9 deficiency	MetS, HT, HU Dyslipidemia	MetS, HT,HU Fatty liver Dyslipidemia
Family history	DM(-) Renal disease(-)	DM(-) Renal disease(-)	DM(-) Renal disease(-)
Past history	Gastroduodenal ulcer	Hypouricemia	Hopes zoster

CGN Chronic glomerulonephritis, *CyA* cyclosporin A, *DM* diabetes mellitus, *EVR* everolimus, *HT* hypertension, *HU* hyperuricemia, *IgAN* IgA nephropathy, *MetS* metabolic syndrome, *MMF* mycophenolate mofetil, *MZR* mizoribine, *PsV* psoriasis vulgaris, *TAC* tacrolimus

blood pressure and HbA1c decreased by 4.3 kg, 7 mmHg and 4%, respectively, after oral semaglutide administration. Figure 1 shows the progress of patient 1. His eGFR prior to and 12 months after oral semaglutide administration were 36.6 and 41.3 mL/min/1.73 m^2, respectively. His UACR decreased slightly from 73.4 to 62.0 mg/g Cr. No adverse events related to oral semaglutide administration were observed. The trough value of tacrolimus was 6.94 ng/mL before oral semaglutide and ranged from 5.21 to 5.64/mL after oral semaglutide administration. The tacrolimus dose during this period was tacrolimus 3.5 mg/day throughout. The trough values before oral semaglutide administration also fluctuated in the 5 to 6 mg/mL range.

Case 2

In 1989, a 62-year-old male was started on continuous ambulatory peritoneal dialysis (CAPD). He received living kidney transplant in August 1996, with his mother as the donor. His medical history includes CAPD peritonitis in 1995. In March 2004, he was diagnosed with IgA nephropathy after a transplant kidney biopsy performed for proteinuria and microscopic hematuria. Based on the results of this biopsy, we performed a tonsillectomy and initiated steroid pulse therapy. In June 2015, we performed another transplant kidney biopsy because his renal function had declined. The biopsy showed chronic antibody-mediated rejection and calcineurin inhibitor nephropathy. The patient developed pseudogout in his cervical spine in February 2019, and he was subsequently diagnosed with MetS in June 2020, at which time his weight was 73.4 kg; abdominal circumference, 91 cm; blood pressure, 140/72 mmHg; and triglyceride, 248 mg/dL. We administered empagliflozin 10 mg/day. However, empagliflozin had no effect and was discontinued after about 18 months. In January 2022, the patient weighed 75.4 kg, and we started him on oral semaglutide at 3 mg/day. His physical characteristics at the start of the semaglutide administration were as follows: age, 62 years; height, 173.7 cm; BMI, 25.0 kg/m^2; abdominal circumference, 91 cm; blood pressure, 30/86 mmHg; pulse, 93 beats/min; and body temperature, 36.1 °C. No palpebral conjunctival anemia, ocular conjunctival yellow staining, abnormal breath sounds, heart murmurs or lower leg edema were observed. There were also no neurological abnormalities. Evidence of his renal transplant surgery was observed in the bilateral lower abdomen. For immunosuppression, the patient received prednisolone 5 mg/day, cyclosporin 50 mg/day, mycopheolate momofetil 1500 mg/day and everolimus 0.5 mg/day. He also received the following oral medications: daprodustat 4 mg/day, vonoprazan fumarate 10 mg/day, febuxostat 10 mg/day, fluvastatin 20 mg/day, cilnidipine 20 mg/day, valsartan 80 mg/day, alfacalcidol 0.75 μg/day, fluvastatin sodium 60 mg/day, montelukast sodium 10 mg/day and sodium picosulfate 10 mg/day. Urinary protein 2 plus, occult blood and glucose were negative at the start of semaglutide administration. The UPCR was 1.03 g/g Cr. His creatinine level was 2.54 mg/dL and his eGFR was 21.5 mL/min/1.73 m^2, indicating stage G4A3 CKD. Other laboratory data are listed in Table 1. The AUC0–4 for cyclosporin was 1,502 h·ng/mL, and the trough value for

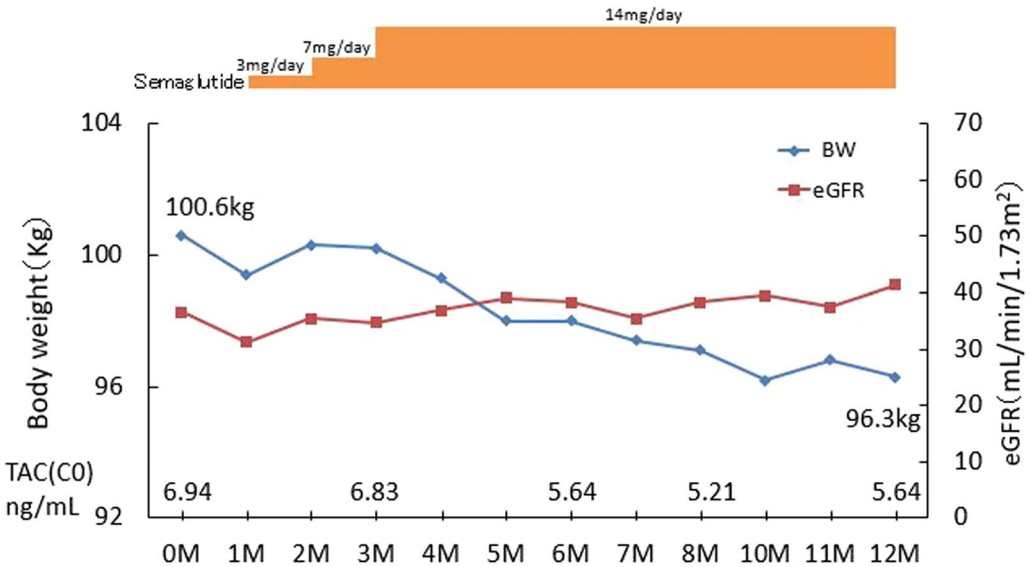

Fig. 1 Clinical course of patient 1. *Abbreviations* BW, body weight: C0, trough concentration; eGFR, estimated glomerular filtration rate; M, months after start of oral semaglutide administration; TAC, tacrolimus. *Legend section* Blue line indicates BW changes. Red line indicates eGFR changes

everolimus was 3.7 ng/mL, both of which were reasonable values for post-transplant patients. The patient was then started on oral semaglutide at 3 mg/day because this patient refused to use injectable GLP-1RA. After oral semaglutide administration, the patient experienced severe nausea, and the dose was reduced to 1.5 mg/day and then gradually increased to 14 mg/day for 12 months. His body weight markedly decreased from 75.4 to 63.2 kg, and his triglyceride deceased from 308 to 227 mg/dL. There were no changes in renal function during the observation period. His UPCR decreased slightly from 1.03 to 0.87 g/g Cr. Figure 2 shows the progress of patient 2. No adverse events other than the initial nausea were observed.

Case 3

In 1983, a 59-year-old male was diagnosed with IgA nephropathy; he started hemodialysis in 1990. He received his first living kidney transplant in 1991, with his father as the donor. He restarted hemodialysis in 2001 due to chronic rejection. In 2008, he received a second living kidney transplant, with his sister as the donor. His medical history includes herpes zoster on the right thigh diagnosed in 1991. In 2013, he became positive for anti-DQ antibodies and began receiving everolimus. In January 2019, he began treatment with empagliflozin due to elevated HbA1c, ALT and γ-GTP levels caused by fatty liver disease. His physical characteristics at the start of empagliflozin administration were as follows: age, 56 years; height, 164.2 cm; weight, 81.7 kg; BMI, 30.3 kg/m^2; abdominal circumference, 104 cm; blood pressure, 124/58 mmHg; pulse, 79 beats/min; and body temperature, 36.0 °C. After empagliflozin administration, the patient's body weight decreased by 1.2 kg and UACR decreased from 35.8 mg/g Cr to 18.4 mg/g Cr. In addition, transaminases normalized and his fatty liver showed improvement. But by January 2022, the patient's weight had rebounded to 79.1 kg and his abdominal circumference was 102 cm. For that reason, we began administering oral semaglutide 3 mg/day at that time. His other physical characteristics at the start of oral semaglutide administration were as follows: age, 59 years; height, 164.3 cm; BMI, 29.3 kg/m^2; blood pressure, 124/58 mmHg; pulse, 71 beats/min; and body temperature, 36.2 °C. No palpebral conjunctival anemia, ocular conjunctival yellow staining, abnormal breath sounds, heart murmurs or lower leg edema was observed. There were also no neurological abnormalities. Evidence of renal transplant surgery were observed in the lower right abdomen. For immunosuppression, the patient received prednisolone 5 mg/day, cyclosporin 50 mg/day, mizoribine 500 mg/day and everolimus 0.5 mg/day. He also received the following oral medications: empagliflozin 10 mg/day, cilnidipine 10 mg/day, amlodipine besilate 10 mg/day, valsartan 80 mg/day, febuxostat 40 mg/day, fluvastatin sodium 60 mg/day, ezetimibe 10 mg/day, alfacalcidol 0.5 μg/day and vonoprazan fumarate 10 mg/day. Urine protein was negative. Both urinary occult blood and urinary glucose were also negative at the start of semaglutide administration. His UACR was 73.4 mg/g Cr, creatinine level was 1.63 mg/dL, and eGFR was 35.3 mL/min/1.73 m^2, indicating stage G3bA2 CKD. Other laboratory findings are listed in

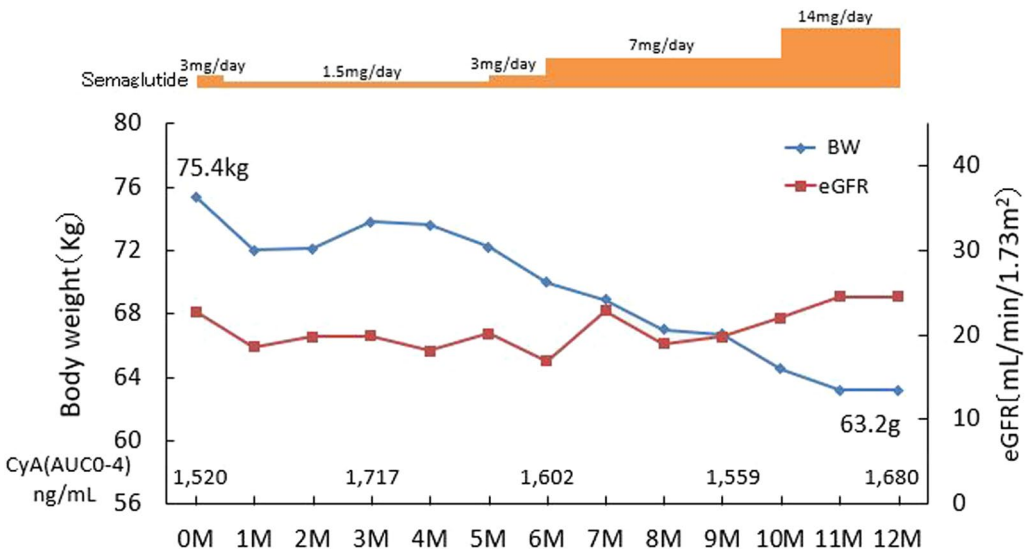

Fig. 2 Clinical course of patient 2. *Abbreviations* AUC0–4, Area Under the Curve 0–4 h; CyA, cyclosporine. *Legend section* Blue line indicates BW changes. Red line indicates eGFR changes

Table 1. The AUC0–4 for cyclosporine was 1,437 h ng/mL, and the trough value for everolimus was 5.8 ng/mL. The patient was then started on oral semaglutide at 3 mg/day because this patient refused to use injectable GLP-1RA. Oral semaglutide was gradually increased to 14 mg/day. After oral semaglutide administration, the patient's body weight, HbA1c and systolic blood pressure decreased by 2.7 kg, 2% and 86 mmHg, respectively. Figure 3 shows the progress of patient 3. The patient's eGFR did not change before or after oral semaglutide. No adverse events related to oral semaglutide administration were observed.

Table 2 summarizes the changes in physical and laboratory findings before and after oral semaglutide administration in the three patients. All three patients lost weight after receiving the drug, particularly patient 2, who lost 12.2 kg. In patients 1 and 3, HbA1c decreased, and in patients 2 and 3, triglyceride decreased. Patient 3 showed a decrease in UACR. Patients 1 and 3 experienced no adverse events, but patient 2 experienced severe nausea at the start of dosing, necessitating titration of the drug from a very low dose. All three patients received a final dose of 14 mg/day. All three patients lost weight and had no change in eGFR after treatment. Glycemic control improved in patient 1, where it was slightly poorer. Urinary Alb and proteinuria were little affected.

Two of the three patients were treated with empagliflozin and oral semaglutide, and the addition of empagliflozin and oral semaglutide resulted in further weight loss in these two patients, indicating a synergistic effect of the two drugs.

Table 2 Clinical course before and after oral semaglutide administration

	Case 1	Case 2	Case 3
Body weight (Kg)	100.6/96.3	75.4/63.2	79.1/76.4
BMI (Kg/m^2)	35.6/34.1	25.0/20.9	29.3/28.5
Abdominal circumference (cm)	114/110	91/80	102/99
SBP (mmHg)	128/121	140/133	124/128
DBP (mmHg)	87/72	72/93	58/63
Cr (mg/dL)	1.63/1.45	2.40/2.24	1.63/1.87
eGFR (ml/min/1.73^2)	36.6/41.3	22.8/24.4	35.2/30.2
UA (mg/dL)	4.8/4.9	4.1/3.2	3.6/3.8
ALT (IU/L)	30/18	8/6	18/26
γ-GTP (IU/L)	35/29	50/19	27/31
TG (mg/dL)	154/201	308/227	205/123
HbA1c (%)	5.9/5.6	N.A GA(%) 14.5/13.0	5.5/5.6
UACR (mg/gCr)	73.4/62.0	N.A UPCR (g/gCr) 1.82/0.89	21.5/36.3
Observation period (months)	12	12	12

Values show data before/after oral semaglutide administration

ALT Alanine aminotransferase, *Cr* creatinine, *γ-GTP* γ-glutamyl transpeptidase, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c, *N.A.* not available, *SBP* systolic blood pressure, *TG* triglyceride, *UA* uric acid, *UACR* urinary albumin-to-creatinine ratio, *UPCR* urinary protein-to-creatinine ratio

Discussion

GLP-1 inhibitors have been shown to be cardioprotective and renoprotective in several large trials. Obesity is a frequent and serious complication after renal

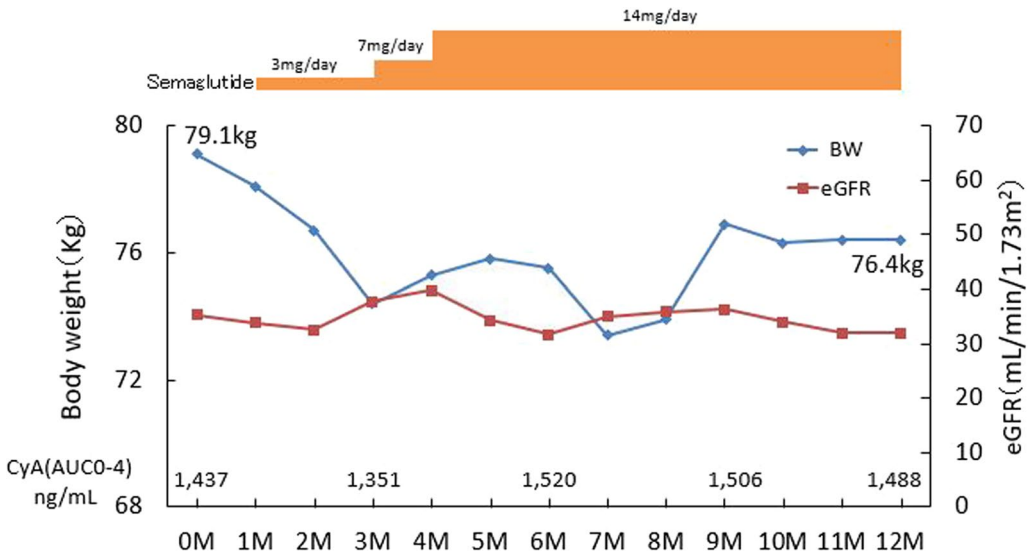

Fig. 3 Clinical course of patient 3. *Legend section* Blue line indicates BW changes. Red line indicates eGFR changes

transplantation [1]. Obesity is also a risk factor for MetS and PTDM [1–6]. Recently, SGLT-2 inhibitors were reported to be useful in the treatment of obesity, MetS and PTDM after renal transplants [17–20]. The main renoprotective effect of SGLT2 inhibitors is improvement of tubuloglomerular feedback [21]. On the other hand, GLP-1RA is reported to have several cardioprotective and renoprotective mechanisms, including vascular endothelial protection and anti-inflammatory, antioxidant and anti-atherosclerotic effects [22–25]. In their review, Almutairi et al. [22] reported that GLP-1 receptors are present on vascular endothelial cells and that administration of GLP-1RA has a salutary effect on vascular endothelium. In addition, Lee et al. [23] stated that GLP-1RAs bind to the GLP-1 receptor and block activation of PKC or NF-κB, which in turn inhibits NLRP3, IL-1, IL-6, VCAM-1, IFN-γ and MCP-1, thereby demonstrating anti-inflammatory properties. Ishibashi et al. [24] reported that GLP-1 decreased generation of reactive oxygen species and, in turn, reduced levels of vascular cell adhesion molecule-1 mRNA in human umbilical vein endothelial cells exposed to glycation end products. Arakawa et al. [25] demonstrated that GLP-1 receptor agonists reduce monocyte/macrophage accumulation in the arterial wall by inhibiting the inflammatory response of macrophages and that this effect may contribute to the attenuation of atherosclerotic lesions by exendin-4, a GLP-1RA. All three of our RTx recipients treated with oral semaglutide lost 2.7 to 12.2 kg of body weight during the 12-month observation period. Since there was no significant decrease in blood pressure and no change in eGFR during this period, this weight loss was considered to be a change in fat mass rather than due to dehydration. In all three cases, abdominal circumference decreased 3 to 11 cm before and after. Since abdominal circumference is said to reflect the amount of visceral fat, the weight loss in these three cases was considered to be a decrease in fat mass, not a decrease in body water. There have been only a few case reports and no randomized controlled trials examining the effects of GLP-1RA administration to recipients after RTx [26–30]. Liou et al. [26] reported that seven post-RTx PTMD patients with a once-daily subcutaneous injection of liraglutide showed decreases in HbA1c and weight and an improved eGFR. Four other groups also reported good results with a GLP-1RA in PTDM patients [27–30]. The main results of the available GLP-1RA studies in RTx recipients are summarized in Table 3. Currently, the most important immunosuppressive drug after RTx is calcineurin inhibitor. For this reason, the interaction between calcineurin inhibitor and drugs administered in PTDM is an important issue. Several references have shown that GLP-1RA has no effect on trough concentrations of tacrolimus [29–31]. Our three patients also showed no change in calcineurin inhibitor concentrations before or after oral semaglutide administration. Two of the three patients were treated with empagliflozin and oral semaglutide, and the addition of empagliflozin and oral semaglutide resulted in further weight loss in these two patients. There have been several reports of such synergistic effects in non-renal transplant patients [32–34], and we believe that two-drug combination therapy should be considered in the future. There are RTx recipients with Mets and DM with obesity and poor glycemic control who have difficulty improving their condition even with SGLT2 inhibitor therapy. Based on our experience with these three cases, we thought that oral semaglutide should be considered for patients who refuse semaglutide injections in the above cases.

Table 3 Summary of reports on GLP-1RA use in transplant patients

Number of cases	Number of cases of RTx	Age (years) mean ± SD or (Me and range)	Sex male/female	eGFR (ml/min/1.73 m^2) Baseline changes after GLP-1RA	HbA1c (%) Baseline changes after GLP-1RA	Body weight (kg) Baseline changes after GLP-1RA	References
7	7	N.A	N.A	67.7 ± 18.7 73.9 ± 20.2	8.1 ± 0.8	78.0 ± 7.8 77.7 ± 9.1	[26]
63	51	58 (30–74)	43/20	M 47.1 M 42.4	M 7.6 M 7.6	M 98.7 M 99.5	[27]
L 63 D 25	L 51 D 21	L 58 (30–74) D 57 (35–76)	N.A	L/DMe 48.0/42.5 L/DMe 55.2/39.1	L/D Me 7.5/7.5 L/D Me 6.9/7.7	L/D Me 98.9/112.6 L/D Me 93.8/111.6	[28]
14	14	51.8 (40.4–62.2)	11/3	53 (40.2–60) 56 (44.7–67)	7.7 (6.8–8.1) 7.1 (6.2–7.8)	106.6 (98.5–125.2) 97.2 (95.2–119.7)	[29]
19	7	62 (48–71)	12/7	Change from baseline to 12 months +1.08	Change from baseline to 12 months −0.75	Change from baseline to 12 months −4.86	[30]

D Dulaglutide, *L* iraglutide, *M* mean, *Me* median, *N.A.* not available

Conclusion

In this study, oral semaglutide was administered to three Japanese patients with MetS after RTx with favorable results. All patients showed weight loss. Two patients showed decreases in HbA1c and triglyceride, and one showed a decrease in UACR. Further studies involving larger patient populations will be required to clarify the efficacy and safety of oral semaglutide in patients with MetS after renal transplantation.

Abbreviations

ADA	American Diabetes Association
Alb	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC0–4	Area under the curve 0–4 h
BW	Body weight
CAMR	Chronic antibody-mediated rejection
CAPD	Continuous ambulatory peritoneal dialysis
CGN	Chronic glomerulonephritis
CKD	Chronic kidney disease
CNI	Calcineurin inhibitor
Cr	Creatinine
CyA	Cyclosporin A
C0	Trough concentration
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
EVR	Everolimus
γ-GTP	Gamma-glutamyl transpeptidase
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Hemoglobin A1c
HT	Hypertension
HU	Hyperuricemia
IgAN	IgA nephropathy
MetS	Metabolic syndrome
MMF	Mycophenolate mofetil
MZR	Mizoribine
PsV	Psoriasis vulgaris
PSL	Prednisolone
PTDM	Post-transplant diabetes mellitus
RCTs	Randomized controlled trials
RTx	Renal transplantation
SGLT2	Sodium–glucose cotransporter
TAC	Tacrolimus
TG	Triglyceride
TGF	Tubuloglomerular feedback
UA	Uric acid
UACR	Urine albumin–creatinine ratio
UPCR	Urine protein–creatinine ratio

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Author contributions

RM and KM took care of patients and participated in decisions regarding treatment. RM prepared the manuscript. Both authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Consent for publication

We obtained written informed consent for publication from all patients.

Ethics approval and consent to participate

After local ethics committee approval, we obtained written informed consent from all patients. The number of Ethics Committee approvals is five.

Competing interests

The authors declare that they have no competing interests.

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