Kidney Medicine

Case Report

Acute Kidney Injury Associated With Semaglutide

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Case reports of acute kidney injury in patients taking the glucagon-like peptide 1 (GLP-1) receptor agonists exenatide and liraglutide have been reported. We report 2 patients with chronic kidney disease due to diabetic kidney disease who experienced rapid worsening of kidney function and increased proteinuria after being prescribed the GLP-1 receptor agonist semaglutide. In 1 patient, kidney biopsy showed advanced diffuse and nodular glomerulosclerosis accompanied by interstitial lymphoplasmacytic and eosinophilic infiltrate and evidence of acute tubular injury. At this time, the long-term outcomes of patients who experience acute kidney injury associated with GLP-1 receptor agonists is not known. We recommend that caution be used with these agents in patients with moderate to severe chronic kidney disease due to limited kidney reserve in the event of an adverse kidney event. Because most adverse kidney events have occurred in patients who experience adverse gastrointestinal symptoms, such patients should have laboratory tests and discontinuation of the medication if there is acute worsening of kidney function.

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INTRODUCTION

In recent years, 2 new classes of drugs to treat type 2 diabetes mellitus (DM) have been introduced into clinical medicine: glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors. In a recent study in patients with type 2 DM and chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR], 30-<90 mL/min/1.73 m^2 and urinary albumin-creatinine ratio > 300 mg/g creatinine), the SGLT2 inhibitor canagliflozin was shown to improve kidney and cardiovascular outcomes.[1] GLP-1 receptor agonists have also been shown to have cardioprotective effects and have been suggested to also have renoprotective effects,[2] though there are few published data in patients with CKD.

There have been a number of postmarketing reports of acute kidney injury (AKI) and worsening CKD in patients taking the GLP-1 receptor agonist semaglutide.[3] Clinical details of these patients have not been published. We report 2 patients with CKD due to diabetic kidney disease who experienced rapid worsening of kidney function after being prescribed the GLP-1 receptor agonist semaglutide (Ozempic, Novo Nordisk, Inc., Bagsværd, Denmark).

CASE REPORTS

Case 1

A woman in her early 80s with DM, hypertension, and CKD was seen in the kidney clinic for increasing leg edema. Medications included amlodipine, insulin, metoprolol, and valsartan/hydrochlorothiazide. Five months before presentation, she had been prescribed weekly semaglutide injections. At that time, her serum creatinine level was 1.59 mg/dL (eGFR, 30 mL/min/1.73 m^2) and serum albumin level was 3.3 g/dL. Urinary protein-creatinine ratio (UPCR) was <1 g/g. The rate of decline in eGFR for the previous 6 years had been 1.5 mL/min/1.73 m^2 per year. The patient began weekly 0.25-mg injections in the 4 months before presentation. After increasing the dose to 0.5 mg, she experienced nausea and vomiting the day after the injection, so she was advised to stay on the 0.25-mg weekly dose and get laboratory studies (complete blood cell count and serum electrolytes, urea nitrogen, creatinine, glucose, amylase, and lipase). The patient did not have the laboratory studies done. A month before presentation, an increase in dose to 0.5 mg was again attempted by the patient but resulted again in nausea and vomiting, so she stopped the injections a few weeks later.

At the kidney clinic visit, the patient stated that she felt well other than the leg swelling. She had not had any illnesses or hospitalizations and had no new medications prescribed (other than semaglutide) or medication dose adjustments in the previous 5 months. She reported no use of nonsteroidal anti-inflammatory drugs (NSAIDs). Examination revealed her blood pressure to be 162/82 mm Hg and there was peripheral edema (3+). Serum creatinine level was 3.50 mg/dL (eGFR, 11 mL/min/1.73 m^2), serum albumin level was 2.9 g/dL, and UPCR was 4.9 g/g. The sudden decrease in eGFR after the previous slow decline in eGFR is shown in Fig 1. Urinalysis revealed protein (3+), glucose (2+), and 8 white blood cells and 1 red blood cell per high-power field. Urine culture was negative. Serologic studies to exclude glomerulonephritis and serum free light chains had normal results.

Due to lack of improvement in kidney function after stopping semaglutide therapy, a kidney biopsy was performed 5 weeks after presentation, which revealed advanced diffuse and nodular glomerulosclerosis; 23 of 36 glomeruli were globally sclerosed, with the remaining 13 glomeruli showing segmental mesangial expansion. There was interstitial lymphoplasmacytic and eosinophilic infiltrate and evidence of acute tubular injury. No immune complexes or light chain restriction were present (Fig 2). There has been no recovery of kidney function or decrease in proteinuria since semaglutide therapy was discontinued.

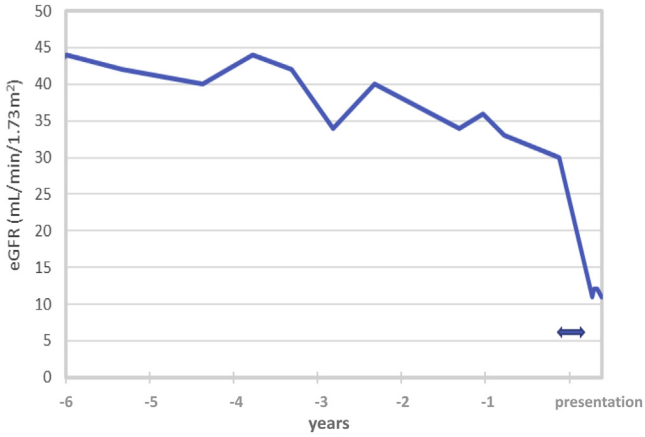

Figure 1. Time course of estimated glomerular filtration rate (eGFR) in patient 1. Before administration of semaglutide, there was a slow decline in eGFR of ~1.5 mL/min/1.73 m^2 per year over a 6-year period. There was a sudden decline in kidney function after administration of semaglutide (double arrow).

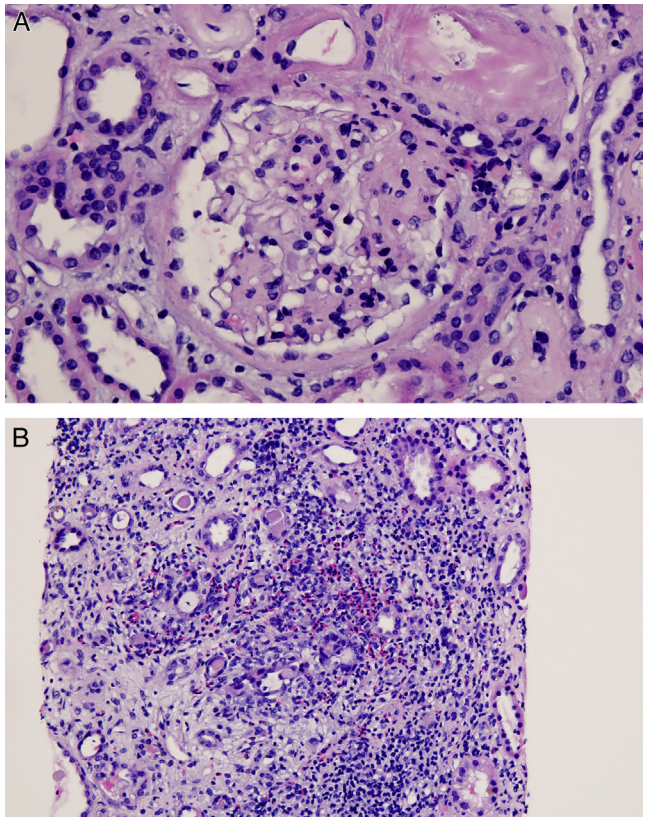

Figure 2. (A) Diffuse and nodular glomerulosclerosis and (B) lymphocytic and eosinophilic infiltrate from the kidney biopsy performed in patient 1.

Case 2

A man in his 60s with DM, hypertension, and CKD was initially seen 8 years ago for CKD management. Blood pressure was well controlled and eGFR was stable in the 30- to 35-mL/min/1.73 m^2 range, with UPCR of 400 to 500 mg/g for the past 7 years. Urinalysis showed protein (2+) but was otherwise unremarkable. Medications included lisinopril/hydrochlorothiazide, carvedilol, and amlodipine. He reported no use of NSAIDs. In the 4 months before presentation, he was started on treatment with weekly semaglutide injections. He took 0.25 mg for 2 weeks, after which the dose was increased to 0.5 mg. He took 1 dose of 0.75 mg but then returned to the 0.5-mg dose. At presentation, eGFR was noted to have decreased to 24 mL/min/1.73 m^2, and treatment with lisinopril/hydrochlorothiazide was stopped. One week later, eGFR was 22 mL/min/1.73 m^2 accompanied by an increase in UPCR to 1,333 mg/g. The patient did not report gastrointestinal symptoms but described decreased appetite and fatigue and a 15-pound weight loss. Semaglutide therapy was stopped, with resolution of symptoms and an increase in body weight. However, there has been no improvement in kidney function or proteinuria.

DISCUSSION

In the patients described, the rapid decline in kidney function was temporally associated with semaglutide administration in the absence of another cause such as dehydration, hypotension, or use of NSAIDs or other nephrotoxic medications. In case 1, kidney biopsy showed evidence of diabetic kidney disease with superimposed interstitial nephritis and acute tubular injury. Case 2 experienced substantial weight loss (a known effect of semaglutide), which may have contributed to the decline in kidney function. According to the Naranjo scale,[4] both patients had a probable adverse drug reaction. In both patients, AKI was associated with an increase in proteinuria. Neither proteinuria nor kidney function improved in either patient after drug cessation.

In phase 3b trials with semaglutide, there were higher rates of AKI reported with semaglutide than with comparators (8 events with semaglutide vs 1 with dulaglutide and none with either placebo or canagliflozin).[5-7] There are published case reports of AKI in patients taking exenatide or liraglutide; of those who underwent kidney biopsy, both acute tubular injury and interstitial nephritis have been seen.[8] Affected patients typically had gastrointestinal symptoms (nausea, vomiting, and occasionally diarrhea). Only a minority had underlying CKD. Both our patients had underlying CKD and gastrointestinal adverse effects, although only case 1 experienced nausea and vomiting.

Both SGLT2 inhibitors and GLP-1 receptor agonists have been recommended as second-line agents after metformin and lifestyle modifications in patients with type 2 DM who are at increased cardiovascular risk.[9] In patients with CKD, GLP-1 receptor agonists are suggested for patients in whom SGLT2 inhibitors are not tolerated, are contraindicated, or eGFR is less than adequate.[9,10] However, there is a paucity of evidence for renoprotective effects of GLP-1 receptor agonists. In the Trial to Evaluate

Table 1. Risk of Acute Kidney Injury With Glucagon-Like Peptide 1 Receptor Agonists

Generic name	Semaglutide	Semaglutide	Exenatide	Exenatide	Exenatide	Lixisenatide	Liraglutide	Dulaglutide	Albiglutide	Liraglutide
Brand name	Rybelsus	Ozempic	Bydureon BCise	Bydureon	Byetta	Adlyxin	Saxenda	Trulicity	Tanzeum	Victoza
Cases		38	2	57	343	1	8	94	19	17
ROR		1.59	0.06	0.36	0.74	1.4	0.26	0.37	0.22	0.72
IC		0.83	−4.17	−1.59	−0.63	−0.08	−1.43	−1.03	−1.85	-0.03

Advera Health Analytics (Evidex) definitions: Cases, number of case reports in which the drug was listed as the primary suspect associated with the adverse reaction; IC, information component, a measure of the disproportionality between the observed and expected reporting of a drug–adverse drug reporting pair (a positive IC value indicates that a particular drug–adverse drug reporting pair is reported more often than expected, based on all the reports in the database); ROR, reporting odds ratio, relative occurrence of the adverse event with the drug compared with this adverse event's relative occurrence with all other drugs in the database (ROR > 1 indicates increased frequency of reporting; <1, decreased reporting). https://www.who-umc.org/media/164041/measures-of-disproportionate-reporting_2016.pdf

Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), although semaglutide had a marked benefit on the composite kidney outcome including macroalbuminuria, there was no benefit on worsening of kidney function.[11] A recent meta-analysis of large cardiovascular outcome trials with GLP-1 receptor agonists demonstrated improvement in both cardiovascular and kidney outcomes, but the kidney benefits were mainly due to a reduction in urinary albumin excretion. Worsening of kidney function outcome was only slightly and not significantly reduced.[2] This is in contradistinction to a much larger and highly significant 45% reduction in kidney disease progression in a pooled analysis of the 3 large broadly inclusive cardiovascular outcome trials of SGLT2 inhibitors.[12] Adverse kidney events were not discussed in these meta-analyses with either GLP-1 receptor agonists or SGLT2 inhibitors.[2,12] However, in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, the risk for AKI was not increased by the SGLT2 inhibitor canagliflozin.[1]

The only clinical trial with GLP-1 receptor agonists specifically in type 2 DM with CKD is the Dulaglutide versus Insulin Glargine in Patients with Type 2 Diabetes and Moderate-to-severe Chronic Kidney Disease (AWARD-7) trial.[13] In this multicenter open-label trial, patients with type 2 DM and stage 3-4 CKD were randomly assigned to treatment with either dulaglutide or insulin glargine. Secondary outcomes included eGFR and urinary albumin-creatinine ratio. Change from baseline in eGFR was significantly greater in the insulin than the dulaglutide groups in patients with macroalbuminuria. Adjudicated kidney events (increase in serum creatinine from baseline of ≥30%) were not different between dulaglutide and insulin. Those events, thought to be due to an intrinsic kidney cause, occurred in 2% of the dulaglutide groups and 1% of the insulin group. Higher rates of nausea and diarrhea were seen with dulaglutide.

In the absence of information from the literature, we did a search of Evidex (Advera Health) looking for AKI associated with the use of semaglutide and other GLP-1 receptor agonists.[3] As shown in Table 1, semaglutide is associated with a higher reporting odds ratio (ROR) and information component (IC) for AKI than other GLP-1 receptor agonists. However, because RORs and ICs are calculated from spontaneously reported information that has not been scientifically or otherwise verified as to a cause-and-effect relationship, they cannot be used to estimate incidence or relative risk. Comparisons between drugs, even within the same class, also cannot be made from these data. Therefore, we cannot state whether semaglutide is more commonly associated with AKI compared with other GLP-1 receptor agonists. However, there is cause for concern because more than 1 signal detection metric indicates a higher than average reporting rate for AKI with semaglutide (ROR interval > 1 and IC is positive).[14]

The association of AKI with GLP-1 receptor agonists and particularly semaglutide is not necessarily causative. However, it is concerning that AKI events associated with GLP-1 agonists may have serious adverse outcomes, including in some cases the need for hemodialysis.[15] The long-term outcomes of patients who experience AKI associated with GLP-1 receptor agonists are also not known. We recommend that caution be used with these agents in patients with moderate to severe CKD due to limited kidney reserve in the event of an adverse kidney event. Because most cases of AKI have occurred in patients who experience adverse gastrointestinal symptoms, such patients should have laboratory tests and discontinuation of the medication if there is acute worsening of kidney function.

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