Semaglutide and kidney function: friends or enemies?

Federica Giofrè,[1*] Vincenzo Trapanese,[1*] Maria Resilde Natale,[1] Clara Vatalaro,[1] Francesca Cosentino,[1] Melania Melina,[1] Maria Chiara Pelle,[1] Nazareno Carullo,[2] Maria Capria,[2] Franco Arturi[1,3]

[1]Internal Medicine Unit, Department of Medical and Surgical Sciences, "Magna Graecia" University of Catanzaro; [2]Renal Unit, "Renato Dulbecco" Hospital of Catanzaro; [3]Research Centre for the Prevention and Treatment of Metabolic Diseases (CR METDIS), "Magna Graecia" University of Catanzaro, Italy
*These authors have contributed equally.

ABSTRACT

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RAs) approved for the treatment of type 2 diabetes mellitus (T2DM) and chronic weight management in obesity. GLP-1RAs are being investigated to slow the decline of kidney function in type 2 diabetics with chronic kidney disease. These agents prevent renal complications and have proven beneficial effects on cardiac outcomes. We describe a rare case of semaglutide-induced acute kidney injury (AKI) in a young woman with obesity, T2DM, hypertensive cardiomyopathy, and no pre-existing chronic kidney disease (CKD). This case is relevant as GLP1-RAs is used frequently in patients with and without kidney disease. Currently, only 3 cases of AKI ascribed to semaglutide of which only 1 without CKD have been described. Only in this case, kidney function improves after semaglutide discontinuation. However, because GLP1-RAs will be prescribed more and more frequently, we sought to highlight this possible, serious adverse effect of semaglutide.

Correspondence: Vincenzo Trapanese, "Magna Graecia" University of Catanzaro, Viale Europa, Germaneto, Catanzaro, 88100, Italy.
Tel.: +39.0961-3647072.
Fax: +39.0961-3647192.
E-mail: vincenzo.trapanese@studenti.unicz.it

Key words: semaglutide; glucagon-like peptide-1 receptor agonist; type 2 diabetes; acute kidney injury; obesity.

Contributions: FG, VT, MC, FA, conceptualization; FG, VT, methodology; FG, VT, MC, CN, CV, FC, MM, MRN, MCP, FA, writing-original draft preparation; FG, VT, FA, writing-review and editing; FA, supervision. All the authors read and approved the final version to be published.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Availability of data and materials: all data underlying the findings are fully available.

Consent for publication: the patient gave her consent to use her personal data for the publication of this case report.

Received: 19 January 2024.
Accepted: 22 January 2024.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Licensee PAGEPress, Italy
Italian Journal of Medicine 2024; 18:1694
doi:10.4081/itjm.2024.1694

Introduction

Glucagon-like peptide-1 (GLP-1), a gut-derived hormone, belongs to the family of incretin hormones that are peptides released after food intake with the capacity to increase glucose-dependently insulin release.[1] GLP-1 identification and analysis triggered the idea that GLP-1 receptor stimulation is a suitable method of reducing plasma glucose in subjects with type 2 diabetes mellitus (T2DM) because of its three main mechanisms in reducing plasma glucose concentrations: glucose-dependent insulinotropic actions, suppression of glucagon hypersecretion except during hypoglycemia episodes and deceleration of gastric emptying.[2] Incidental discovery that the peptide exendin-4 from the saliva of a venomous lizard (*Heloderma suspectum*, the Gila monster) was homologous to mammalian GLP-1 and able to bind and activate GLP-1 receptors brought to the synthesis of Exenatide, the first GLP-1 receptor agonist approved to treat type 2 diabetes in 2005 in the USA.[3,4] After this other GLP-1 receptor agonists (GLP-1 RAs) were developed as lixisenatide, liraglutide, dulaglutide, and semaglutide. GLP-1 RAs have common pharmacodynamic effects: increase of hyperglycemia-induced insulin secretion, suppression of glucagon secretion during hyper- or euglycemia, deceleration of gastric emptying, reduction of calories intake, and body weight loss. Common side effects include: nausea, vomiting, diarrhea, and a worsening of diabetic retinopathy in patients with a pre-existing retinopathy. Several cardiovascular (CV) outcome studies have demonstrated that GLP-1 RAs can prevent CV events such as acute myocardial infarction or stroke and prevent renal complications. Guidelines recommend treatment with GLP-1 RAs in patients with pre-existing atherosclerotic vascular disease. Semaglutide is

a GLP-1 RA with a subcutaneous administration once per week because of its long elimination half-life. Semaglutide has been approved since 2019 for the treatment of type 2 diabetes mellitus but its weight loss efficacy appears to be superior compared with the other once-weekly GLP-1 RAs, so it was recently approved for chronic weight management in people with overweight or obesity.[5,6] In agreement with the nephroprotective effects of semaglutide, a specific kidney outcome randomized controlled trial (the FLOW study, NCT03819153) is ongoing. In this study, the effects of weekly subcutaneous semaglutide on the occurrence of persistent estimated glomerular filtration rate (eGFR) decline of ≥50 percent from the trial start, reaching end-stage kidney disease, death from cardiovascular disease, or death from kidney disease, in patients with type 2 diabetes and chronic kidney disease (CKD) will be evaluated.[7] Generally, antibiotics, diuretics, nonsteroidal anti-inflammatory agents, and proton pump inhibitors are common causes of drug-induced acute kidney injury (AKI). The discontinuation of the offending agent is considered the mainstay of therapy. Our case is the rare case description of semaglutide-induced AKI in a patient with no pre-existing CKD.

Case report

A 29-year-old woman presented to our hospital for a recent history of malaise and severe nausea with an oliguric AKI. Her past medical history included severe obesity, type 2 diabetes with microangiopathy, and hypertensive cardiomyopathy. Her chronic medication had been: metoprolol, furosemide, nifedipine, and doxazosina mesilato. She had been prescribed weekly semaglutide injections 7 weeks before presenting, and the dose had increased from 0.25 mg to 0.5 mg 3 weeks prior. She reported no current or remote use of nonsteroidal anti-inflammatory drugs or other nephrotoxic medications. Clinical examination revealed her blood pressure to be 120/70 mmHg and there was peripheral edema. Serum creatinine level was 5.4 mg/dl (eGFR 10 ml/min/1.73 m^2), serum urea level was 112 mg/dl, serum uric acid level was 12.8 mg/dl and serum albumine level was 4,4 g/dl; no increase in proteinuria in 24h-urinalysis. Blood tests revealed the presence of hypochromic normocytic anemia. Her blood chemistry tests have been in range until a month ago before the dose increase of semaglutide. During hospitalization, the patient underwent an abdominal ultrasound with a negative result for renal morphological alterations. In the suspicion of autoimmune glomerulonephritis, the antibodies antinuclear antibody, perinuclear anti-neutrophil cytoplasmic antibodies, antineutrophil cytoplasmic antibodies, and serum-free light chains have been tested but they had normal results. According to the pharmacological history, an acute renal failure induced by semaglutide has been suspected, therapy has been stopped and the patient hydrated with 0.9% NaCl isotonic physiological solution in continuous infusion. In order to obtain a histological diagnosis, a kidney biopsy was suggested but the patient refused to perform it due to possible complications related to her body weight (body weight 170 Kg and body mass index 66 Kg/m^2). However, a rapid and continuous improvement in kidney function after stopping semaglutide therapy was observed: one week later, creatinine decreased (3.6 mg/dl; eGFR 16 ml/min/1.73 m^2) as well as urea (54 mg/dl) and uric acid (9.1 mg/dl). One month later serum creatinine level was 2.6 mg/dl (eGFR 24 ml/min/1.73 m^2). Three months later both serum creatinine level and eGFR were in the normal range (1.2 mg/dl and 63 ml/min/1.73 m^2 respectively). Acute renal failure induced by semaglutide was diagnosed.

Discussion

In our opinion, this case is relevant as GLP1-RAs is used more and more frequently in patients with and without kidney disease. Indeed, semaglutide, a long-acting glucagon-like peptide-1 receptor agonist can be prescribed to patients affected by T2DM, even if there's a CKD (excluding end-stage renal disease) or reduced liver function.[8] Furthermore, in agreement with nephroprotective effects, soon GLP1-RAs and semaglutide could also be used to slow the progression of diabetic kidney disease. AKI requiring dialysis is a possible rare adverse reaction during treatment with GLP-1 RA (usually occurring when GLP-1 RA induced nausea and vomiting with associated hypovolemia).[9] There are limited postmarketing reports of AKI and worsening CKD in patients taking the GLP-1 RAs semaglutide.[10] A pooled analysis of cardiovascular outcome trials showed that although multiple cases of AKI with GLP-1 RAs have been reported, GLP-1 RAs do not increase the risk of AKI.[11] Similarly, Shetty *et al.* developed a systematic review in which they analyzed 120 case reports of GLP-1 adverse reactions. They pointed out that liraglutide and exenatide induced the highest number of adverse drug reactions and that the most frequent adverse reactions were gastrointestinal disorders, followed by renal and immunologic reactions. Specifically, pancreatitis was the more frequent adverse gastrointestinal adverse event, followed by nausea and vomiting. AKI was the second most frequent adverse event in patients treated with GLP-1 RAs and it was reported in 23 patients, mostly with pre-existing kidney disease. However, only two cases of AKI were found in patients in treatment with semaglutide and both patients had a pre-existing renal disease. Authors tried to link this renal function worsening with different causes: first nausea and vomiting induced by GLP-1 and second the concomitant medications used such as angiotensin-converting enzyme inhibitors and diuretics; both causes can determine hypovolemia with a consequent renal injury, although authors pointed out that the mechanism is not still clear.[12] In the two cases of semaglutide-associated AKI, the GLP-1 RAs has been stopped with resolution of symptoms but there has been no improvement in proteinuria or kidney function.[13] More recently, another case of semaglutide-related AKI has been reported in a patient without CKD. In this case, discontinuation of semaglutide was able to induce an improvement of kidney function.[14] Our patient had no baseline CKD and the rapid decline in kidney function was temporally associated with initiation of semaglutide treatment and dose escalation in the absence of other causes. In this case, it was highly suggestive that AKI was due to therapy with semaglutide. Indeed, generally, drug-induced AKI typically occurs 7-10 days after drug exposure or at most after a few weeks or months.[15] Our patient was exposed to other treatments but at the same doses for at least 1 or 2 years. In addition, a rapid and continuous improvement in kidney function after stopping semaglutide therapy was observed, making this drug the only possible causative agent.

Conclusions

Although the association of AKI with semaglutide is not very frequent, it may have serious adverse outcomes and some patients may need hemodialysis for a short period. So, although semaglutide is an excellent drug, it's reasonable to use caution above all in patients with moderate to severe CKD due to limited kidney reserve in case of an adverse kidney and also in patients with adverse gastrointestinal symptoms due to subsequent dehydration that can worsen renal function. In our opinion, monitoring of kidney function should be performed in all patients during dose escalation of semaglutide.

References

1. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab 2021;46:101102.
2. Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab 2002;87:1239-46.
3. Eng J, Kleinman WA, Singh L, et al. Isolation and characterization of exendin-4, an exendin-3 analogue, from Heloderma suspectum venom. Further evidence for an exendin receptor on dispersed acini from Guinea pig pancreas. J Biol Chem 1992;267:7402-5.
4. Göke R, Fehmann HC, Linn T, et al. Exendin-4 is a high potency agonist and truncated exendin-(9-39)-amide an antagonist at the glucagon-like peptide 1-(7-36)-amide receptor of insulin-secreting beta-cells. J Biol Chem 1993;268:19650-5.
5. Amaro A, Sugimoto D, Wharton S. Efficacy and safety of semaglutide for weight management: evidence from the STEP program. Postgrad Med 2022;134:5-17.
6. Pratley RE, Aroda VR, Lingvay I, et al. SUSTAIN 7 investigators. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol 2018;6:275-86.
7. Rossing P, Baeres FMM, Bakris G, et al. The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. Nephrol Dial Transplant 2023;38:2041-51.
8. Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab 2017;19:1242-51.
9. Shetty R, Basheer FT, Poojari PG, et al. Adverse drug reactions of GLP-1 agonists: a systematic review of case reports. Diabetes Metab Syndr 2022;16:102427.
10. Advera Health Analytics. FAERS Adverse Event, Acute Kidney Injury, Glucagon-like peptide-1 (GLP-1) Analogues Classification Comparison Report. Evidex 2020.
11. Patoulias D, Boulmpou A, Papadopoulos CE, Doumas M. Glucagon-like peptide-1 receptor agonists and the risk of acute kidney injury: alarming, or not? Kidney Med 2021;3:674-5.
12. Shetty R, Basheer FT, Poojari PG, et al. Adverse drug reactions of GLP-1 agonists: A systematic review of case reports. Diabetes Metab Syndr 2022;16:102427.
13. Leehey DJ, Rahman MA, Borys E, et al. Acute Kidney Injury Associated With Semaglutide. Kidney Med 2021;3:282-5.
14. Borkum M, Lau W, Blanco P, Farah M. Semaglutide-Associated Acute Interstitial Nephritis: A Case Report. Kidney Med 2022;4:100561.
15. Perazella MA, Markowitz GS. Drug-induced acute interstitial nephritis. Nat Rev Nephrol 2010;6:461-70.