Semaglutide and Patients Receiving Hemodialysis: Case Reports of Unexpected Benefits for Hyperphosphatemia and Hyperkalemia

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INTRODUCTION

A high proportion of patients who receive intermittent hemodialysis (IHD) have type 2 diabetes mellitus, as diabetic nephropathy is the leading cause of end-stage renal disease in developed nations.[1] Managing diabetes for these patients is challenging because of their complex physiology, unpredictable pharmacokinetics, and a limited choice of pharmacological treatment options due to their marginal or absent renal function.[2] Given the dearth of evidence and guidance for treatment of type 2 diabetes in the setting of IHD, optimal management is unclear.[3,4]

Semaglutide is a glucagon-like peptide-1 receptor agonist that is frequently used for patients with type 2 diabetes. After metformin (which is typically avoided for patients receiving IHD), semaglutide is among the first add-on options for further glucose management.[2] For those with renal disease, a particularly desirable feature of this medication is that its pharmacokinetics are not affected to any clinically significant degree by end-stage renal disease or IHD.[5-8] In patients with diabetes who are not receiving IHD, semaglutide has been associated with clinically significant benefits in relation to weight loss,[9] major adverse cardiac events,[10] and all-cause mortality[11]; these benefits do not appear to be affected by the degree of renal function.[12]

Although there is currently insufficient evidence to recommend use of semaglutide for patients receiving dialysis,[13] clinical experience is increasing.[14-16] The following case reports add to these data and reveal some unexpected benefits seen when semaglutide was initiated for glucose management in 2 patients who were receiving IHD. These patients consented to a trial of semaglutide after discussion with their respective nephrology teams, and both provided informed consent for publication of their cases.

In addition, a comprehensive review of the existing literature on this topic was conducted. Systematic searches were performed in the MEDLINE (Ovid), Embase (Ovid), CENTRAL (Wiley), International Pharmaceutical Abstracts (Ovid), and Scopus databases, from inception to February 2, 2023, using the search terms "semaglutide" and "dialysis". All articles that provided clinical information on the use of semaglutide for patients receiving hemodialysis are included in the discussion of the 2 clinical scenarios below.

CASE REPORT 1: HYPERPHOSPHATEMIA

Case Description

A 67-year-old man with type 2 diabetes was receiving in-centre IHD 5 times per week. His home fasting blood glucose readings were elevated at 9 to 13 mmol/L (target range 5–7 mmol/L), and his hemoglobin A_{1c} (HbA_{1c}) was 7.2% (although this value was likely an underestimation due to the patient's anemia). The patient's diabetes treatment regimen consisted of insulin glargine 32 units subcutaneously at bedtime and linagliptin 5 mg orally once daily. The patient expressed a goal of weight loss, so in September 2021, the decision was made to switch from linagliptin to semaglutide 0.25 mg subcutaneously once weekly; an increase to 0.5 mg weekly occurred in October 2021.

This patient also struggled with persistent hyperphosphatemia. Whereas the target range for phosphate is 1.13 to 1.78 mmol/L, his average phosphate level had been 2.33 mmol/L over the preceding year, with only a single reading below 2 mmol/L. Phosphate levels did not improve despite multiple interventions by the renal dietitian and the use of calcium carbonate as a phosphate binder at a dose of 2500 mg (i.e., 1000 mg elemental calcium) taken 3 times daily.

In terms of other components of this patient's mineral and bone disorder, his serum calcium was always within the normal range. His hyperparathyroidism was poorly controlled, with persistently elevated parathyroid hormone readings in the range of 130 to 160 pmol/L (desired range 13.8–62.1 pmol/L). He took calcitriol 0.25 µg at bedtime,

3 times weekly; this dosage had not been increased further, as doing so would be expected to worsen hyperphosphatemia.

After the initiation of semaglutide, the patient's phosphate values dropped significantly, to an average of 1.73 mmol/L (Figure 1). By December 2021, his phosphate was so well controlled that it became possible to increase the calcitriol dose to optimize management of his hyperparathyroidism. The beneficial effect of semaglutide on his phosphate levels started within 1 month of initiation and was sustained until he received a kidney transplant in January 2022.

Semaglutide also improved the patient's glucose management, with fasting blood glucose in the range of 6.2 to 6.5 mmol/L and HbA_{1c} reduced to 6% (although again, this value was likely an underestimation because of anemia). The patient's insulin dose remained unchanged, and he did not experience any episodes of hypoglycemia. Other parameters such as potassium remained stable. The patient's weight steadily decreased, from 86 kg in September 2021 to 83.5 kg in January 2022.

The dose of semaglutide could have been increased further, but the patient declined further increases in dose given that he was experiencing a significant reduction in food cravings/appetite and was concerned about potential negative impacts on his nutritional status.

Other patients at this centre have exhibited improvements in phosphate levels after initiation of semaglutide, but this patient's case was the most compelling demonstration of this effect, given his long-standing history of hyperphosphatemia and the absence of other notable changes during his semaglutide treatment.

Discussion

Hyperphosphatemia is commonly encountered by patients receiving IHD due to reduced renal excretion of phosphate in chronic kidney disease.[17] Elevated phosphate causes arteriolar calcification, which in turn increases the risk of tissue necrosis, severe infection,[18,19] cardiovascular morbidity, and all-cause mortality.[20]

The phosphate target for patients receiving dialysis is controversial and based on weak evidence. The 2017 Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that phosphate be kept "toward the normal range" of 0.87 to 1.52 mmol/L.[21] However, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest a more attainable target of 1.13 to 1.78 mmol/L, given that phosphate levels above 1.78 mmol/L are most clearly associated with increased risk of mortality.[22]

Hemodialysis itself will help in managing hyperphosphatemia, because phosphate is removed from the bloodstream during dialysis. A standard IHD regimen of 4 hours 3 times weekly should remove more than half of a person's weekly dietary phosphate intake (assuming adherence to dietary restrictions).[23] Hence, it is important to ensure that dialysis is optimized for patients with hyperphosphatemia and that any reversible causes of inadequate dialysis (e.g., thrombotic occlusion of IHD access sites, poor adherence to dialysis schedule) are resolved. Of note, dialysis is not usually intensified solely for management of hyperphosphatemia because of time commitments, resource availability, and logistical issues[22]; however, intensification can be considered if the patient has other indications for this approach, such as hypervolemia. In this case, the patient was receiving dialysis 5 times weekly with shortened duration of 2.5 hours due to his inability to tolerate longer sessions (because of intradialytic hypotension and pain from sitting during longer sessions); this schedule was equivalent to a total weekly dialysis time of 12.5 hours, which is slightly longer than the standard weekly dialysis time of 12 hours. Although the adequacy of this patient's IHD was suboptimal in terms of percentage urea reduction during dialysis (53.5%) and K_t/V (0.93) over the preceding year, all of the easily reversible factors to improve dialysis adequacy had already been optimized.[24]

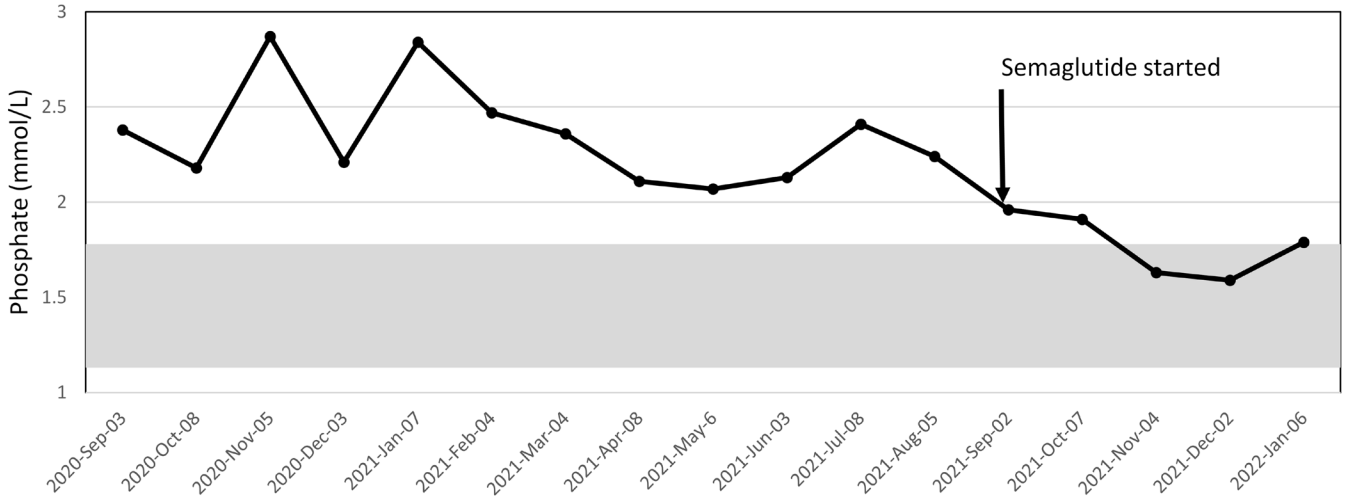

FIGURE 1. Phosphate levels over time for patient 1. The grey area represents the target phosphate range (1.13–1.78 mmol/L) for patients receiving intermittent hemodialysis, as per the 2003 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.[22]

If phosphate levels remain elevated despite IHD, a registered dietitian should be consulted.[25] Unfortunately, dietary restrictions are often logistically challenging and unbearable for patients, particularly given the other constraints often recommended in "renal diet" plans. There is also evidence that strict limitation of dietary phosphate may increase mortality among patients receiving IHD,[26] making this a difficult intervention to navigate. In this case, the patient's diet had already been adjusted to the extent he was able to manage.

If hyperphosphatemia is inadequately controlled with IHD and diet, phosphate binders can be started. Some observational evidence suggests that these agents may decrease mortality among patients with hyperphosphatemia who are receiving IHD.[27,28] The most common phosphate binder is calcium carbonate, and expert opinion suggests up to 1500 mg of elemental calcium per day for management of hyperphosphatemia. This patient was taking a higher-than-recommended dose totalling 3000 mg elemental calcium per day, and he was appropriately taking it with the first bite of each meal for maximum phosphate binding.[22] He did not qualify for coverage of the more costly alternatives to calcium-based phosphate binders (e.g., sevelamer, lanthanum), which can be used either alone or in combination with calcium carbonate.[29] Other phosphate binders, specifically those containing magnesium and aluminum, are not recommended for long-term use due to concerns regarding accumulation and toxicity.[22]

Vitamin D and/or its analogues are generally used to reduce parathyroid hormone in patients with hyperparathyroidism, but they also increase dietary phosphate absorption, especially if taken early in the day, before food.[30] If switching to nighttime administration of vitamin D does not improve phosphate levels, reducing or discontinuing calcitriol or vitamin D may help improve hyperphosphatemia.[31] Unfortunately, this patient's parathyroid hormone was already significantly above target, making it less desirable to reduce his calcitriol dose. Cinacalcet can also reduce parathyroid hormone but without increasing phosphate; unfortunately, this relatively costly medication was not covered under the Ontario provincial drug plan or the patient's private insurance.

As illustrated by this case, control of hyperphosphatemia is difficult to accomplish even with multiple management strategies. The addition of semaglutide resulted in a large improvement in this patient's phosphate by way of reductions in food cravings and appetite.

CASE REPORT 2: HYPERKALEMIA

Case Description

A 79-year-old man with type 2 diabetes was receiving in-centre IHD 3 times weekly. In September 2021, his HbA_{1c} level was 7.1% and rising; this value was likely an underestimation due to the patient's anemia. Random blood glucose readings done in-centre before dialysis sessions were above target, ranging from 10.0 to 14.6 mmol/L, and the patient declined to check blood glucose at home. His diabetes regimen consisted of linagliptin 5 mg orally once daily and insulin glargine 8 units subcutaneously at bedtime. One of the patient's main personal goals was weight loss, as obesity was contributing to significant back and knee pain. As such, the decision was made, in November 2021, to switch from linagliptin to semaglutide, with gradual titration to 1 mg subcutaneously once weekly by December 2021.

In addition to his diabetes, this patient was experiencing persistent, asymptomatic hyperkalemia. In the year preceding initiation of treatment with semaglutide, there had been only one potassium reading within the normal range of 3.5 to 5.0 mmol/L, and his average potassium level had been 5.8 mmol/L. Levels had been particularly elevated in the 5 months preceding initiation of semaglutide (average 6.1 [range 5.4–7.0] mmol/L). These elevated readings persisted despite intervention by the dietitian and use of the lowest possible concentration of potassium in his dialysate (i.e., a "K bath" of 1 mmol/L). The patient was adherent to his full dialysis treatment durations, and he had no relevant abnormalities on electrocardiograms obtained during this period.

In the 2 months after initiation of semaglutide, the patient's potassium level dropped to an average of 4.4 (range 4.1–4.6) mmol/L (Figure 2). Even before the dosage of semaglutide was increased to 1 mg once weekly, his potassium was so well controlled that it was possible to increase the potassium concentration of his dialysate to 2 mmol/L in December 2021. The patient's weight also improved, from 117.5 to 111.6 kg during this timeframe, which he attributed to a reduction in food cravings. His HbA_{1c} unexpectedly increased further to 7.4% in the context of stable hemoglobin readings, although random pre-dialysis blood glucose levels improved to a range of 8.9 to 9.9 mmol/L. The patient's insulin dose remained unchanged, and he did not experience any known episodes of hypoglycemia. Other parameters such as phosphate remained unchanged.

Discussion

Because 99% of potassium is excreted by the kidneys, stage 5 chronic kidney disease is the most common risk factor for development of hyperkalemia.[32] As a result, chronic hyperkalemia (i.e., potassium greater than 5.0 mmol/L) is an exceedingly frequent problem for patients receiving IHD.[24,32] Although this condition can be asymptomatic, it can have serious sequelae, including muscle paralysis, cardiac conduction abnormalities or arrhythmias, and death, particularly if potassium is 7 mmol/L or higher; appropriate management is therefore paramount.[24,33]

This patient's potassium levels frequently exceeded 6.5 mmol/L (i.e., "severe hyperkalemia"), which would usually necessitate acute management; however, this approach would

have been impractical in this case because of the chronicity of the hyperkalemia. For example, checking the patient's potassium levels at every IHD session, administering acute treatments such as IV insulin and calcium, and performing continuous cardiac monitoring would not have been realistic. In addition, some have suggested higher thresholds for classification of hyperkalemia in patients receiving IHD,[34] according to which this patient was categorized as having "moderate hyperkalemia". As such, he was treated as having non-emergency hyperkalemia.

The first step in management of non-emergency hyperkalemia is to exclude pseudohyperkalemia (i.e., false elevations of potassium levels due to issues such as hemolysis).[35] Once the potassium result is determined to be reliable (through repeat measurement and/or discussion with laboratory staff), any modifiable factors should be identified, which generally includes a review of dialysis adequacy, diet, and medications. Of note, pseudohyperkalemia was not present in the patient described here.

Because potassium is readily removed by IHD, dialysis itself is a major component of hyperkalemia management; as with management of hyperphosphatemia, the adequacy of dialysis should be assessed for patients with hyperkalemia. In particular, blood and dialysate flow rates should be assessed, given their significant impact on potassium removal, and these rates can be increased as tolerated if more potassium removal is needed.[36] For this patient, dialysis was adequate during the period described, in terms of percentage urea reduction (67.9%) and K_t/V (1.31).[24]

Unlike phosphate, the concentration of potassium in the patient's dialysate can be lowered to increase the gradient between plasma and dialysate; the larger the gradient, the more potassium is removed from the blood. At this centre, "K baths" are available as 1 mmol/L, 2 mmol/L, and 3 mmol/L (known as K1, K2, and K3 baths, respectively), with a K1 bath causing the largest reduction in serum potassium. However, dialysate solutions containing less than 2 mmol/L of potassium have been associated with an increase in morbidity and mortality, possibly due to arrhythmias secondary to rapid shifts in serum potassium.[37-40] As such, K1 baths are not widely used, although a K1 bath had been used for this patient for many years due to his persistent hyperkalemia.

Dietitians should be consulted to review and assist with limiting dietary potassium sources. However, this can be challenging for patients receiving IHD, who are often already following a restrictive diet.

Hyperkalemia can also be worsened by medications, so patients should be evaluated for drugs that can increase potassium (e.g., potassium supplements, digoxin, nonsteroidal anti-inflammatory drugs, potassium-sparing diuretics), especially renin–angiotensin–aldosterone inhibitors.[38] Of particular importance, renin–angiotensin–aldosterone inhibitors are frequently taken by patients receiving IHD for blood pressure, heart failure, and/or preservation of residual renal function.[41] Discontinuation of these medications has been linked to increases in cardiovascular events and mortality, so ideally these treatments should be continued at optimized doses.[42,43] This patient was not receiving any such medications.

Various other medications can be used to decrease potassium. For those with residual renal function, diuretics such as furosemide can increase potassium excretion through the urine and may be considered for patients with concurrent hypervolemia.[44] Unfortunately, this patient's residual renal function was minimal, as indicated by minimal urine output, which limited the utility of this option.

For patients with redistributive hyperkalemia secondary to uncontrolled hyperglycemia, insulin can be used to shift potassium from the extracellular fluid back into

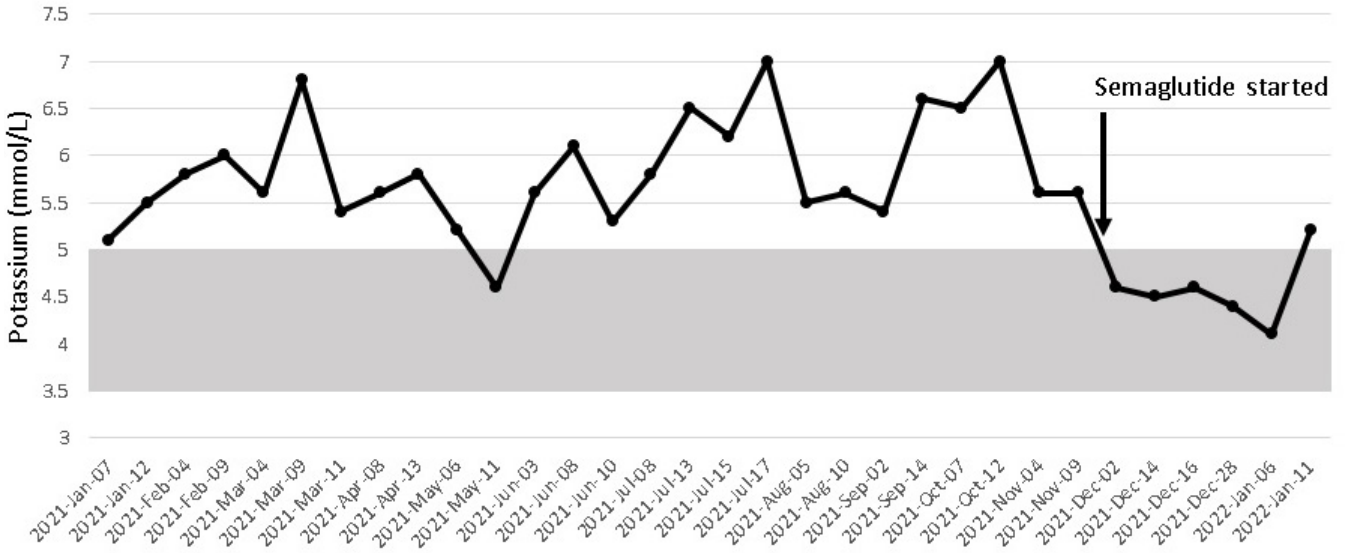

FIGURE 2. Potassium levels over time for patient 2. The grey area represents the normal range for potassium (3.5–5.0 mmol/L).

intracellular spaces, thereby reducing serum potassium. The ability to intensify insulin therapy for this patient was limited because he declined to check blood glucose at home or use continuous glucose monitoring, which meant the risk of hypoglycemia would have been difficult to identify and manage.

Potassium binders are ion-exchange resins that exchange cations (e.g., sodium) for potassium ions in the intestines, thereby increasing fecal potassium excretion; this potentially allows patients to continue their renin–angiotensin–aldosterone inhibitors.[45,46] Historically, the most commonly used potassium binder is sodium polystyrene sulfonate (SPS), which has gained widespread use despite safety concerns. The sodium contribution of SPS is substantial, with each 15-g dose contributing 1.5 g of sodium, which can lead to fluid retention (already a frequent problem for patients receiving IHD).[47] Calcium polystyrene sulfonate is an alternative to SPS; unlike SPS, it does not contribute sodium, but it can result in hypercalcemia due to its calcium contribution, and it is less widely available than SPS.[48] Both of these older-generation binders lack compelling efficacy data, are unpalatable, and are associated with gastrointestinal side effects; of these, minor effects include nausea and constipation, whereas serious effects include colonic ulceration, obstruction, perforation, and necrosis.[48-51]

The newer-generation potassium binders currently available in Canada are sodium zirconium cyclosilicate and patiromer.[52] Sodium zirconium cyclosilicate exchanges sodium and hydrogen for potassium and ammonium, whereas patiromer exchanges calcium.[47,53] Both of these agents have been investigated in well-conducted trials demonstrating the ability to lower potassium within a few hours and to maintain normokalemia for up to 12 months in patients with chronic kidney disease, including those who are receiving IHD, without an increase in the rates of serious adverse effects.[47,54-61] Of note, each 5-g dose of sodium zirconium cyclosilicate contains 0.4 g of sodium, which theoretically could contribute to sodium retention and edema.[62]

In contrast to the older-generation binders, the newer potassium binders have established efficacy data, their palatability is substantially improved, and their clinical trials have not thus far demonstrated any significant safety concerns (e.g., none of the serious gastrointestinal side effects seen with the older-generation potassium binders). For these reasons, use of newer-generation binders is increasing.[52] While widespread use has been limited by the significant cost of these medications, combined with a lack of public funding, some jurisdictions have been able to incorporate them into practice through a combination of private insurance plans and manufacturers' samples. Because of a lack of local nephrologist experience for use in the setting of IHD at the time and a lack of private drug coverage for these costly medications, they were not used for the patient described here.

As illustrated in this case, hyperkalemia in patients who are receiving IHD can be difficult to manage. The addition of semaglutide made a large contribution to normalizing potassium for this patient.

CONCLUSIONS AND FUTURE DIRECTIONS

Although use of semaglutide in patients receiving IHD is still in its infancy, there is growing experience and comfort with use of this medication. Patients receiving IHD face challenges with managing hyperphosphatemia and hyperkalemia. These 2 case reports illustrate that semaglutide may provide benefit in managing these issues, in addition to its known benefits for blood glucose control and weight loss.

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