Pharmacodynamic Interaction Between Oral Semaglutide and Hydrochlorothiazide Resulting in Reproducible Hypotension: A Case Report

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly prescribed for type 2 diabetes mellitus (T2DM) and obesity, offering improvements in glycaemic control, weight reduction, and cardiovascular outcomes. Although these agents generally lower blood pressure modestly, clinically significant hypotension is rarely reported in either trial or real-world settings. We describe a 65-year-old man with long-standing T2DM, and well-controlled hypertension managed with olmesartan/hydrochlorothiazide who developed persistent dizziness two weeks after starting oral semaglutide 14 mg daily. Home blood-pressure readings averaged 95/60 mm Hg. Discontinuation of semaglutide led to rapid symptom resolution and blood-pressure rebound to 150/80 mm Hg. Upon rechallenge, hypotension recurred, fulfilling dechallenge-rechallenge criteria (Naranjo score = 7, probable). When hydrochlorothiazide was withdrawn but olmesartan and semaglutide were continued, blood pressure stabilized near 130/78 mm Hg and HbA1c improved from 7.4 % to 5.6 %. This reproducible pattern suggests a pharmacodynamic interaction between semaglutide and thiazide diuretics. Given that GLP-1 RAs promote natriuresis and mild diuresis through renal tubular pathways, concurrent diuretic use may potentiate volume depletion and precipitate symptomatic hypotension. Clinicians should monitor blood pressure closely when initiating GLP-1 RA therapy in patients receiving diuretics and adjust antihypertensive therapy as needed.

Keywords: Semaglutide; GLP-1 receptor agonists; Hypotension; Type 2 diabetes mellitus; Antihypertensive therapy; Diuretics.

INTRODUCTION

The introduction of glucagon-like peptide-1 receptor agonists, also known as GLP-1 RAs, has brought about a significant change in the management of type 2 diabetes and obesity. These medications have the ability to provide long-term control of blood glucose levels while also substantially lowering the risk of cardiovascular disease[1,2]. Additionally, a constant but relatively minor reduction in blood pressure has been reported, which is in addition to the metabolic benefits. The systolic pressure normally drops by 4-5 mm Hg, whereas the diastolic pressure drops by approximately 2-3 mm Hg[2,3]. This is the case throughout large randomized controlled trials and pooled analyses. Oral semaglutide has been shown to provide mean decreases of roughly 7 mm Hg[4], which is consistent with the data mentioned above.

Both weight reduction and enhanced endothelial function, as well as renal sodium management, are among the processes that are responsible for these outcomes. According to the findings of experiments, GLP-1 RAs tend to inhibit the sodium-hydrogen exchanger in the proximal tubule and induce natriuretic peptides, which ultimately leads to mild diuresis and a reduction in extracellular volume[5,6]. In most cases, these hemodynamic alterations are beneficial; yet, hypotension that is clinically significant continues to be unheard of.

However, there are no reports of repeatable symptomatic hypotension in the literature despite the fact that oral semaglutide, the first non-injectable GLP-1 RA, has made treatment more accessible. With the introduction of oral semaglutide, we describe a case of significant hypotension that was reversible in a hypertensive patient. The interaction with a thiazide diuretic appears to be the primary cause of this condition.

CASE PRESENTATION

A 65-year-old man (BMI 28.4 kg/m²) with a 23-year history of T2DM and long-standing hypertension presented with new-onset dizziness and mild headache two weeks after starting oral semaglutide 14 mg once daily. His medical history included hypothyroidism, hyperlipidemia, benign prostatic hyperplasia, and gastro-esophageal reflux disease.

Regular medications were empagliflozin/metformin (5/850 mg twice daily), rosuvastatin, levothyroxine, esomeprazole, alfuzosin, tadalafil, low-dose aspirin, and omega-3 supplements. Hypertension had been well controlled for years with olmesartan 20 mg plus hydrochlorothiazide 12.5 mg daily, maintaining home blood-pressure readings around 130/75 mm Hg.

In November 2024, laboratory results showed HbA1c 6.5 %, normal renal and hepatic function, and euthyroid status (TSH 2.6 µIU/mL, free T4 1.5 ng/dL). By February 2025, HbA1c had risen to 7.4 % with mild weight gain, prompting the addition of semaglutide (Table 1).

Values are from laboratory testing at three time points (November 2024, February 2025, and July 2025). Missing values (-) indicate parameters not measured at that visit. Laboratory testing was performed using standard automated analyzers at the same reference laboratory.

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Table 1. Laboratory results at three time points (November 2024, February 2025, and July 2025)

Parameter	Nov 2024	Feb 2025	Jul 2025	Reference range
Haemoglobin (g/dL)	13.2	14.0	14.7	11.5-16.5
BUN (mg/dL)	17	16	18	8-23
Creatinine (mg/dL)	1.3	1.1	1.3	0.6-1.2
eGFR (ml/min/1.73 m2)	57.6	69.7	57.6	>60
HbA1c (%)	6.5	7.4	5.6	4-5.6
TSH (uIU/mL)	2.6	0.9	0.4	0.27-4.8
FreeT4 (ng/dL)	1.5	_	1.6	0.93-1.7
Sodium (mmol/l)	136	_	139	135-145
Potassium (mmol/l)	4.5	_	4.3	3.5-5.0
Chloride (mmol/l)	98	_	99	98-107
Calcium (mg/dl)	10	_	_	8.6-10.2
Magnesium (mg/dl)	2.2	_	_	1.6-2.4
Cholesterol (mg/dl)	119	_	79	<200
Triglyceride (mg/dl)	–	–	133	<150
HDL (mg/dl)	–	–	33	>55
LDL (mg/dl)	–	–	32	<100

Two weeks after initiation, the patient reported continuous dizziness. Home blood-pressure readings averaged 95-100/55-65 mm Hg. Semaglutide was stopped, and within 24 hours symptoms resolved, and pressures rebounded to 150-160/78mm Hg. When semaglutide was restarted under the same antihypertensive regimen, hypotension recurred (Figure 1).

Ultimately, hydrochlorothiazide was discontinued while olmesartan and semaglutide were maintained. Blood pressure stabilized at 125-135/75-80 mm Hg and remained steady thereafter. Dizziness resolved completely, and the patient experienced improved energy and glycemic control (HbA1c 5.6 %). Renal and electrolyte values remained normal (Table 1). A detailed chronology of these events is summarized in Table 2.

No other medication changes occurred, and there was no evidence of infection, dehydration, or thyroid dysfunction. The causality was rated “probable” using both the Naranjo and WHO-UMC criteria. The case was managed in a private internal-medicine practice in Jeddah, Saudi Arabia, between November 2024 and July 2025. Written informed consent for publication was obtained, and institutional review board approval was granted (IRB No. 450-25).

DISCUSSION

In this case report, symptomatic hypotension that is reproducible after the administration of a GLP-1 receptor agonist in a patient is reported. The patient is also taking a thiazide diuretic, which is an example of a less common but clinically significant scenario. Because there is a strong argument for a causal pharmacodynamic interaction from the magnitude and rapidity of the drop in blood pressure, as well as its complete reversibility and recurrence upon rechallenge.

There are multiple ways in which GLP-1 receptor agonists have an effect on the physiology of the kidneys and the blood vessels. Due to the fact that they increase natriuresis and block the proximal tubular sodium-hydrogen exchanger (NHE3), they cause a moderate reduction of the intravascular volume[5,6]. Additionally, they inhibit the renin-angiotensin-aldosterone system and increase the bioavailability of endothelial nitric oxide, which leads to increased arterial compliance and a mild vasodilation[7]. These processes, when applied to the majority of patients, result in relatively minor and beneficial reductions in blood pressure, which are better for the cardiovascular system than they are detrimental[8].

The combination, on the other hand, may amplify sodium and volume loss beyond a compensatory threshold in patients who are already receiving diuretics, particularly thiazides[9]. As may be seen in this particular instance, the consequence can be symptomatic hypotension. The hemodynamic basis of this interaction is shown by the quick restoration of normal blood pressure that occurs after ceasing the use of hydrochlorothiazide while continuing to semaglutide.

There have been reports of synergistic effects that are comparable to those caused by other incretin-based medications[10]. A dual GIP/GLP-1 receptor agonist, tirzepatide, for instance, has been linked to episodes of dizziness and low blood pressure in individuals who are also taking antihypertensive medication at the same time[11,12]. Rather than being an individual reaction to semaglutide, these results point to the possibility of a class effect[13].It is likely that cumulative volume depletion occurs as a result of the overlap between thiazide-induced natriuresis and GLP-1-mediated sodium excretion. This is a pathophysiological finding. It is possible that the adaptive baroreflex response is not adequate to maintain perfusion pressure in individuals who are older or who are on a stable antihypertensive treatment[14].This not only explains the symptoms that the patient is experiencing, but it also explains how the event can be repeated.

Under certain treatment combinations, "beneficial" hemodynamic effects can become deleterious. This example also serves as an important clinical reminder of this fact. Clinicians should be aware of these nuances, particularly when patients are already on multimodal antihypertensive therapy, as the use of GLP-1 RAs increases beyond the treatment of diabetes to include the prevention of cardiovascular disease and obesity[15].

This report has intrinsic limitations, despite the fact that the time sequence and reproducible dechallenge-rechallenge reaction render the causal link to be plausible. Because it is a single instance, it is not possible to determine the incidence or estimate the danger. It was not possible to carry out objective hemodynamic tests, which would have shed light on the underlying mechanism. These measurements could have included plasma renin activity, aldosterone, or direct volume assessment. However, the fact that the physiologic response remains the same over a number of different drug exposures is convincing circumstantial evidence.

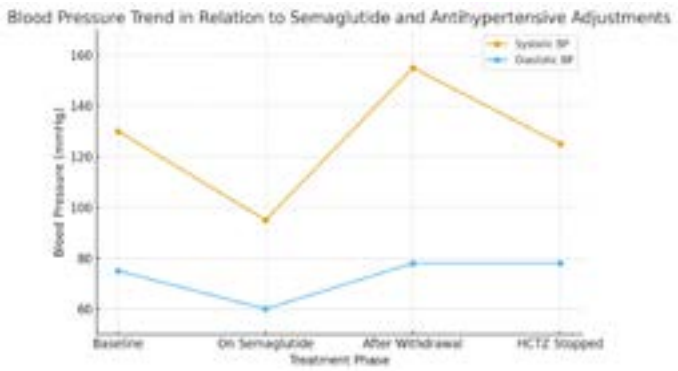

Figure 1. Timeline showing blood-pressure trend and therapeutic adjustments.

Table 2. Timeline of clinical events, medication changes, and corresponding symptoms described in the case report.

Date / Timepoint	Event	Medication Change	Symptoms
February 2025	HbA1c had risen to 7.4% with mild weight gain, prompting the addition of semaglutide.	Semaglutide 14 mg once daily started.	
Two weeks after initiation	Patient reported continuous dizziness. Home BP readings averaged 95–100/55–65 mm Hg.		Continuous dizziness; low home BP readings.
After dizziness onset	Semaglutide was stopped; within 24 hours symptoms resolved and blood pressure rebounded to 150–160/78 mm Hg.	Semaglutide discontinued.	Symptoms resolved within 24 hours.
Rechallenge period	When semaglutide was restarted under the same antihypertensive regimen, hypotension recurred.	Semaglutide restarted.	Hypotension recurred.
Following recurrent hypotension	Hydrochlorothiazide was discontinued while olmesartan and semaglutide were maintained.	Hydrochlorothiazide discontinued; olmesartan and semaglutide continued.	
After HCTZ withdrawal	Blood pressure stabilized at 125–135/75–80 mm Hg and remained steady thereafter. Dizziness resolved completely; HbA1c improved to 5.6%.		Dizziness resolved; stable blood pressure.

The following are some of the things that doctors should do before starting a GLP-1 RA in a patient who is already taking a diuretic, particularly thiazide or loop types:

- Pay special attention to the patient's blood pressure throughout the first few weeks of treatment.
- In the event that hypotensive symptoms show up, decreasing or temporarily stopping the diuretics should be a consideration.

It is important to provide patients with guidance on how to identify symptoms of excessive volume loss, including dizziness, weariness, and lightheadedness. This level of awareness enables patients to continue receiving GLP-1 RA medication, which is frequently extremely effective, without jeopardizing their hemodynamic control[9].

Learning Points

- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may amplify the hypotensive effects of thiazide diuretics through additive natriuretic and volume-depleting actions.
- Symptomatic hypotension can occur even in patients with previously stable blood pressure when GLP-1 RAs are introduced alongside diuretic therapy.
- Careful blood-pressure monitoring and timely adjustment of diuretic doses allow safe continuation of semaglutide and other GLP-1 RA treatments.

CONCLUSION

Oral semaglutide and hydrochlorothiazide are shown to have a possible pharmacodynamic interaction, which results in repeatable clinical hypotension, as this research demonstrates. Particularly in patients who are elderly or who have limited fluid reserves, the instance highlights the importance of customized antihypertensive therapy when beginning treatment with GLP-1 receptor agonists. Assuring that patients continue to reap the metabolic and cardiovascular benefits of GLP-1 therapy can be accomplished through careful monitoring and early dose adjustments of concurrent diuretics. This can help prevent the needless termination of GLP-1 therapy.

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Author 2 (Co-Author): Contributed to the analysis and interpretation of data, critically revised the manuscript for important intellectual content, and approved the final version.

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