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Chapter 2

Semaglutide as a Single-Agent Strategy for Diabetes, Obesity, and Hypertension: An 18-Month Case Experience

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Abstract

GLP-1 receptor agonists have revolutionized the treatment of type 2 diabetes mellitus (T2DM) and obesity, demonstrating strong efficacy in glycaemic control, weight loss, and cardiovascular protection. Landmark drugs like tirzepatide and semaglutide improve renal outcomes and are being investigated for conditions such as liver disease, arthritis, and neurodegeneration. Increasing evidence highlights their antihypertensive potential. We report an 18-month case study of an obese type 2 diabetic patient with uncontrolled hypertension who achieved significant weight loss, normalized blood pressure, and a sustained reduction in HbA1c (from 9.2% to 6.0%) without antihypertensive or lipid-lowering drugs. Mechanistically, GLP-1 receptor agonists may enhance vascular function through nitric oxide pathways, endothelial modulation, weight reduction, and suppression of the renin-angiotensin-aldosterone system (RAAS). Clinical studies and empirical data underscore GLP-1 receptor agonists as versatile medications that mitigate metabolic, cardiovascular, and renal risks, facilitating their integration into comprehensive treatment plans for high-risk metabolic diseases.

Keywords: GLP-1 receptor agonists, Semaglutide, Type 2 diabetes, Obesity, Hypertension, Weight loss, Glycaemic control, Cardiovascular protection, Renal outcomes, RAAS suppression

1. Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists have become cornerstone treatments for obesity and type 2 diabetes mellitus (T2DM). These agents provide glycaemic control, weight loss, cardiovascular protection, and renal benefits [1]. Semaglutide and tirzepatide, administered once weekly, have demonstrated superior efficacy in reducing HbA1c, promoting weight loss, and preventing cardiovascular events compared to earlier therapies [2].

Hypertension frequently coexists with T2DM and is a major driver of cardiovascular morbidity. Although not primarily prescribed as antihypertensives, evidence suggests GLP-1 receptor agonists may reduce blood pressure (BP) through nitric oxide-mediated vasodilation, endothelial modulation, weight loss, and RAAS suppression [3]. The coexistence of diabetes, hypertension, and obesity creates a high-risk metabolic profile, often requiring multiple medications, which can lead to adverse effects and poor adherence. GLP-1 receptor agonists have the potential to simplify management by addressing hyperglycemia, weight, and BP simultaneously. Clinical trials, such as SUSTAIN-6, have shown modest but significant BP reductions with semaglutide [2]. However, longitudinal real-world case data remain limited.

2. Aim

To evaluate the long-term effects of semaglutide on weight, glycaemic control, and blood pressure in a patient with type 2 diabetes and obesity over 18 months.

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2.1. Objective

- Evaluate the long-term effects of semaglutide on weight, blood pressure, and HbA1c.
- Determine if semaglutide enables discontinuation of oral hypoglycemic and antihypertensive drugs.
- Examine mechanisms underlying blood pressure reduction beyond weight loss.

3. Methods

This longitudinal case study involved a 48-year-old obese male with type 2 diabetes and uncontrolled hypertension. Baseline measurements included blood pressure of 156/96 mmHg, HbA1c of 9.2%, and BMI of $38 kg/m^2$. Lipid levels were within normal ranges. The patient had discontinued antihypertensives due to intolerance. Semaglutide was initiated at 0.25 mg weekly and titrated to 1 mg over six months. Clinical parameters, including body weight, blood pressure, lipid profile, and HbA1c, were measured at 3, 6, 9, 12, 15, and 18 months. Primary outcome measures were long-term changes in blood pressure, weight, lipid profile, and glycaemic control.

Investigation Report: Mechanisms and Outcomes of GLP-1 RA Therapy in Hypertension and Metabolic Disease

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed the therapeutic landscape for type 2 diabetes (T2D) and obesity. While their efficacy in glycaemic control and weight reduction is well-established, their pleiotropic effects on cardiovascular and metabolic parameters are under active investigation. This report integrates evidence from an 18-month longitudinal case study [1] with a review of GLP-1-based therapies [4] to explore the mechanisms, clinical implications, and future directions of GLP-1 RAs in managing hypertension and cardiometabolic disease.

4. Case Summary

The case involved a 48-year-old obese male (BMI $38 kg/m^2$) with T2D and uncontrolled hypertension (BP 156/96 mmHg) despite prior triple antihypertensive therapy, which was discontinued due to side effects [1].
Key outcomes include:

- **Glycemic Control:** HbA1c reduced from 9.2% to 6.0%.
- **Weight Loss:** Sustained reduction from 106 kg to 87 kg (17.9% loss).
- **Blood Pressure:** BP normalized to ˜118/76 mmHg without antihypertensive medications.
- **Lipid Profile:** Maintained within normal limits without lipid-lowering therapy.
- **Medication Simplification:** All oral antidiabetic agents (glimepiride, pioglitazone, metformin) were discontinued.

This case exemplifies the multifactorial benefits of GLP-1 RAs, particularly semaglutide, extending beyond glucose control to sustained antihypertensive effects.

4.1. Investigation of Antihypertensive Mechanisms

Weight-Dependent Effects

Significant weight loss (17.9% of body weight) likely contributed to improved hemodynamics and reduced cardiac workload. Weight loss enhances insulin sensitivity and reduces sympathetic nervous system overactivity, a key factor in obesity-related hypertension [2].

Weight-Independent (Direct) Vascular Effects

Sustained BP control after weight loss plateaued suggests additional mechanisms:

- **Vasodilation via NO/cGMP Pathways:** GLP-1 receptor activation on vascular endothelial and smooth muscle cells stimulates cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) production, leading to nitric oxide (NO)-mediated vasodilation and reduced peripheral vascular resistance [3].
- **Natriuresis and Diuresis:** GLP-1 RAs promote sodium excretion by inhibiting the sodium-hydrogen exchanger in the renal proximal tubule, reducing plasma volume and BP [4].
- **Modulation of the RAAS:** GLP-1 RAs may inhibit the renin-angiotensin-aldosterone system, reducing vasoconstriction and aldosterone-mediated sodium retention [5, 6].
- **Reduction in Sympathetic Tone:** GLP-1 RAs may attenuate obesity-related sympathetic nervous system activity, lowering heart rate and BP (case patient pulse: 70/min) [7].

5. Result

Over 18 months, semaglutide therapy yielded significant metabolic improvements.
The following table summarizes the key outcomes:

Parameter	Baseline	18 Months	Change
HbA1c	9.2%	6.0%	-3.2%
Body Weight	106 kg	87 kg	-19 kg (17.9% reduction)
Blood Pressure	156/96 mmHg	118/76 mmHg	-38/-20 mmHg
HDL Cholesterol	44 mg/dL	52 mg/dL	+8 mg/dL
LDL Cholesterol	98 mg/dL	73 mg/dL	-25 mg/dL

Additional outcomes:

- **Safety:** No episodes of hypoglycemia, vertigo, or other adverse effects were reported.
- **Medication Discontinuation:** All oral antidiabetic drugs (glimepiride, pioglitazone, metformin) were discontinued by the 15-month mark.

6. Clinical Implications and Future Directions

The case study and review article highlight several clinical implications:

1. **Therapeutic Simplification and Adherence:** Semaglutide enabled control of T2D, obesity, and hypertension with a single agent, reducing the need for multiple medications and improving adherence.
2. **Addressing Therapeutic Inertia:** GLP-1 RAs offer a potent alternative for patients with obesity, T2D, and hypertension struggling with polypharmacy.
3. **Expanding Indications:** GLP-1 RAs are being explored for heart failure, chronic kidney disease (CKD), metabolic-associated steatotic liver disease (MASLD), and neurodegenerative disorders. The FLOW trial demonstrated a 24% reduction in renal events with semaglutide in T2D patients with CKD, suggesting renal protective effects relevant to BP management [2, 8].
4. **Next-Generation Therapies:** Emerging options include oral GLP-1 RAs (e.g., orforglipron), triple agonists (e.g., retatrutide), and combinations with amylin analogues (e.g., CagriSema), promising enhanced metabolic and cardiovascular benefits [2].

7. Discussion

This case highlights the multidimensional effects of GLP-1 RA therapy. Sustained BP improvements, even after weight loss plateaued, suggest direct vascular effects, including endothelial nitric oxide-mediated vasodilation, cGMP upregulation, natriuresis, and RAAS inhibition [9]. These findings align with SUSTAIN-6 and meta-analyses showing modest BP reductions with GLP-1 RAs [2]. Reviews further indicate expanding indications for GLP-1 RAs in cardiovascular, renal, and neurodegenerative conditions [1].

8. Conclusion

This 18-month case study of semaglutide use, supported by mechanistic and clinical evidence, demonstrates sustained BP control through weight-dependent and direct vascular, renal, and neurohormonal mechanisms. GLP-1 RAs, like semaglutide, have shifted the treatment paradigm from glucose control to holistic cardiometabolic risk reduction. As next-generation therapies emerge, their role in personalized medicine for cardiometabolic disease will continue to expand, offering improved outcomes and simplified treatment strategies.

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