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Improved Glycemic Control using Oral Semaglutide in a Patient with Type 2 Diabetes with Insulin Allergy

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Abstract

We present a unique clinical scenario of a patient with type 2 diabetes mellitus (T2DM) who exhibited an allergic reaction to all forms of insulin. The patient had previously maintained good glycemic control with maximum-dose metformin. However, her glycemic control deteriorated once she became pregnant. Trials with various types of insulin resulted in allergic reactions, but this was managed successfully using insulin pump therapy, which was discontinued postpartum. Upon reassessment, her HbA1c had deteriorated to 80 mmol/mol. After re-attempting various insulin formulations without success, she was trialed again using the closed-loop Omnipod system. Initial management with the closed-loop system failed to achieve optimal glycemic control. Therefore, oral semaglutide was added. The introduction of oral semaglutide to her treatment regimen led to a significant improvement in her glycemic status. This report compares the patient's glycemic control while on the closed-loop Omnipod system alone versus in combination with oral semaglutide. The findings suggest that oral semaglutide, in conjunction with a closed-loop system, may offer a viable alternative for patients with insulin-dependent type 2 diabetes who cannot tolerate insulin.

Keywords
- insulin allergy
- semaglutide
- GLP-1
- insulin pump

Introduction

Insulin allergy is a rare but challenging condition for individuals with diabetes. The prevalence of insulin allergy has decreased since the introduction of human recombinant insulin preparations and is estimated to affect up to 3% of diabetics.[1] Hypersensitivity reactions range from injection site erythema and swelling to anaphylaxis.[2] While some reported reactions are to excipients (zinc, protamine, metacresol), many are to the recombinant insulin itself, with type I, type III, and type IV hypersensitivity reactions all having been reported.[2]

For some patients, managing their diabetes through diet or oral antidiabetic medications makes it possible to switch insulin preparation or avoid insulin use. However, in some complex insulin-dependent patients, this approach is not effective, and they require desensitization with continuous subcutaneous insulin infusions (CSII) using an insulin pump.[3]

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Closed-loop insulin pump systems (also known as artificial pancreas) use a programmable pump to continuously deliver rapid-acting insulin subcutaneously. The Omnipod system used in this case consists of a small insulin pump worn on the body and the personal diabetes manager (PDM), a wireless handheld device used to monitor and control the insulin pump. CSII is most commonly used as treatment for people with type 1 diabetes mellitus in whom multiple daily injection (MDI) therapy has failed to achieve glycemic control. These closed-loop systems work by delivering insulin either continuously at a basal rate or as a bolus. The basal rate is the amount of insulin infused per hour, and this can be adjusted hour by hour according to the patient's needs. This allows for much greater flexibility in optimizing glucose control. Multiple different basal rate profiles may be stored, used, and adjusted over time, resulting in more optimal glucose control. Bolus doses are adjusted depending on carbohydrate consumption, physical activity, and premeal blood glucose concentrations. There is strong evidence to show that CSII can effectively reduce HbA1c levels and the frequency of hypoglycemia episodes in these patients.[4]

In some cases, despite the use of continuous insulin infusions, achieving good glycemic control can still be very difficult, and given how restricted treatment options are, these patients can be quite challenging to treat.

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), works by mimicking the GLP-1 hormone's functions. The Peptide Innovation for Early Diabetes Treatment (PIONEER) clinical trials demonstrated that oral semaglutide lowered blood glucose levels and improved weight and cardiovascular outcomes.[5] A meta-analysis found it led to greater HbA1c and weight reductions compared to most other GLP-1 RAs in type 2 diabetes mellitus (T2DM) patients, and it also lowered major cardiovascular events and was more cost-effective.[6]

We report here a unique clinical scenario of a patient with T2DM who exhibited an allergic reaction to all forms of insulin and benefited from an unusual approach.

Case Description

This case report presents a unique clinical scenario of a patient with T2DM who exhibited an allergic reaction to all forms of insulin. The patient had previously maintained good glycemic control with maximum-dose metformin. However, her glycemic control deteriorated once she became pregnant. Trials with various types of insulin resulted in allergic reactions, but this was managed successfully using insulin pump therapy, which was discontinued postpartum. Upon reassessment, her HbA1c had deteriorated to 80 mmol/mol. After re-attempting various insulin formulations without success, she was trialed again using the closed-loop Omnipod system. Initial management with the closed-loop system failed to achieve optimal glycemic control. Therefore, oral semaglutide was added. The introduction of oral semaglutide to her treatment regimen led to a significant improvement in her glycemic status. This report compares the patient's glycemic control while on the closed-loop Omnipod system alone versus in combination with oral semaglutide. The findings suggest that oral semaglutide, in conjunction with a closed-loop system, may offer a viable alternative for patients with insulin-dependent T2DM who cannot tolerate insulin.

The patient was diagnosed with T2DM in June 2020, having previously been diagnosed with polycystic ovarian syndrome and inflammatory arthritis. She was initially managed with lifestyle modifications. However, as her condition progressed, she required metformin therapy to maintain blood glucose levels. Over time, her metformin dosage was gradually increased to the maximum dose of 1,000 mg twice daily, resulting in effective blood glucose control, as indicated by her HbA1c reading of 48 mmol/mol.

During her pregnancy in 2020, her blood glucose control deteriorated, necessitating insulin therapy. Initially, she was prescribed human insulin, both short and long acting, but experienced adverse local reactions shortly after administration. Despite switching to insulin analogs such as Levemir, Lantus, NovoRapid, and Apidra, these adverse reactions persisted. To address this, continuous insulin pump therapy with the Omnipod DASH system and Fiasp insulin was initiated. This resulted in excellent blood glucose control with an HbA1c of 45 mmol/mol throughout the remainder of her pregnancy without increased risk of hypoglycemia. No allergic reaction was noted following the use of the CSII. Following delivery, insulin pump therapy was discontinued, and she resumed treatment with metformin 1,000 mg twice daily alone.

One month after discontinuing the use of the Omnipod system, the patient's blood glucose control was found to have worsened, prompting a trial of Toujeo 20 units and Humalog U-200 8 units thrice a day. However, she developed red, hot, painful lumps postadministration and was subsequently switched to Fiasp insulin. Unfortunately, the patient continued to experience these adverse reactions, so we decided to offer her the closed-loop Omnipod system. Although this system was well tolerated without local reactions, blood glucose control remained inadequate, with continuous glucose monitoring (CGM) data showing time in the range between 10 and 20% (►**Fig. 1**).

The adverse local reactions described following the administration of various types of insulin prompted a clinical diagnosis of insulin allergy. No serological or skin prick tests were used to investigate this allergic status further, and the reactions resolved without further intervention.

Part of the difficulty involved in achieving good blood glucose control in this case was that the patient was highly insulin resistant as a result of a high body mass index (BMI) and polycystic ovarian syndrome. The patient, therefore, initially required over 200 units of insulin per day.

Due to persistently suboptimal control and insulin resistance attributed to high BMI and polycystic ovarian syndrome, we decided to introduce oral semaglutide 3 mg, a GLP-1 receptor agonist, to her treatment regimen on February 7, 2024. Significant improvement was observed within days,

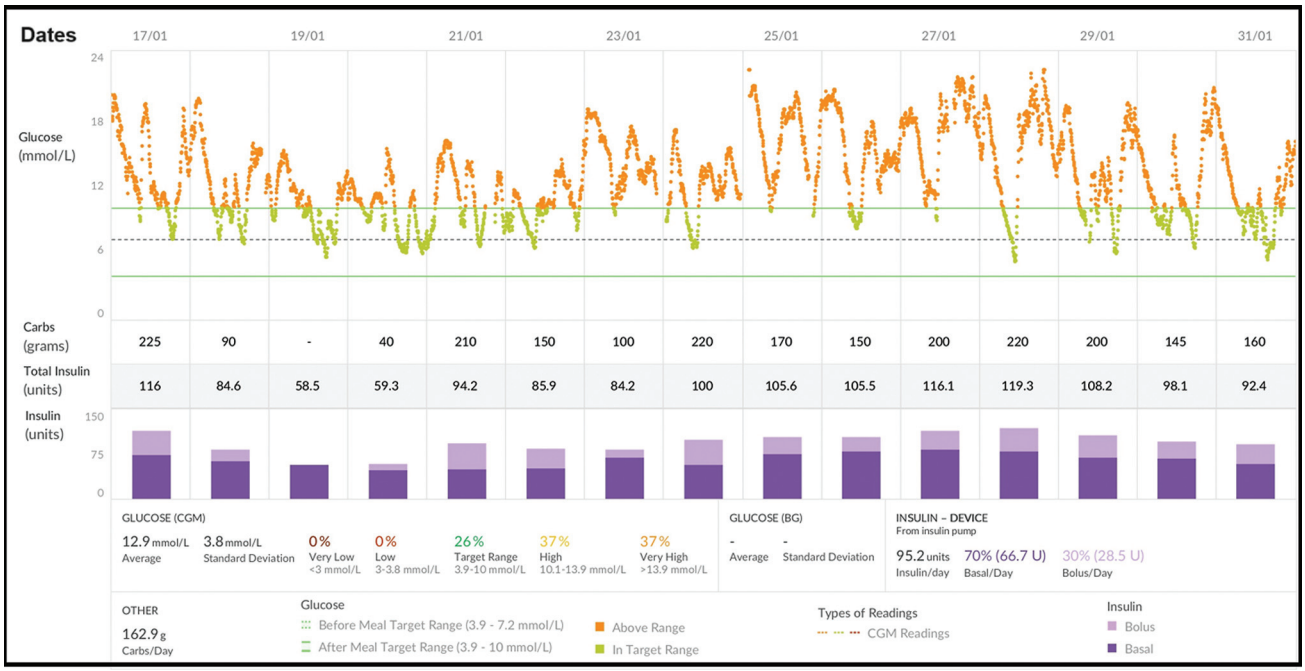

Fig. 1 Illustration of the suboptimal control initially achieved using CSII from January 17 to 31.

with time in range increasing to 75% and a reduction in insulin requirements without any increased risk of hypoglycemia (►**Fig. 2**). The semaglutide dose was increased to 7 mg after 4 weeks, resulting in continued improvement in CGM data and a time in range during April of 97%. Daily insulin requirement fell from an average of 113 units per day in February to 40 units per day in April (►**Fig. 3**).

The additional weight loss helped improve blood glucose control. Before initiation of treatment, the patient weighed 102.5 kg with a BMI of 40.04 kg/m^2 (class obesity 3), and after 3 months, the weight reduced to 99.1 kg for a BMI of 38.71 kg/m^2 (class 2 obesity).

Conclusion

This case report highlights the intricate management of a patient with T2DM who presented a complex challenge due to her insulin allergy. Despite tolerating a CSII with the Omnipod system, glycemic control remained poor, and large amounts of insulin were required daily. The addition of oral

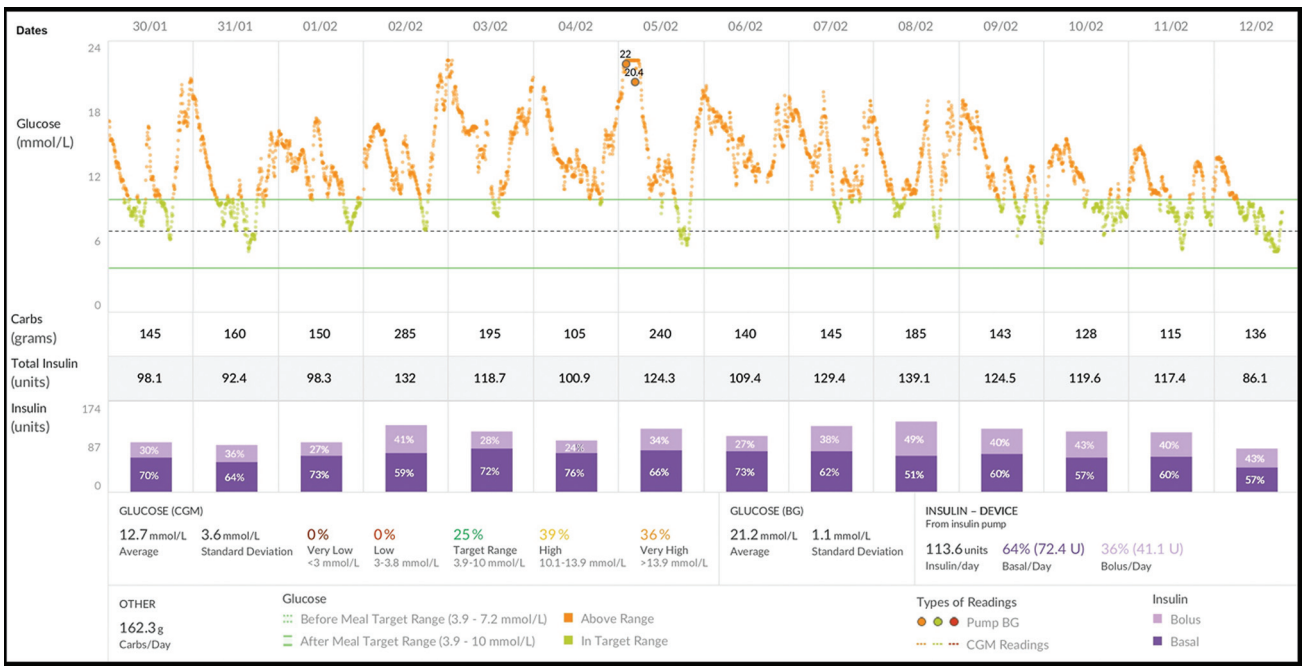

Fig. 2 Illustration of the continuous glucose monitoring (CGM) data from February; oral semaglutide 3 mg was introduced on February 7.

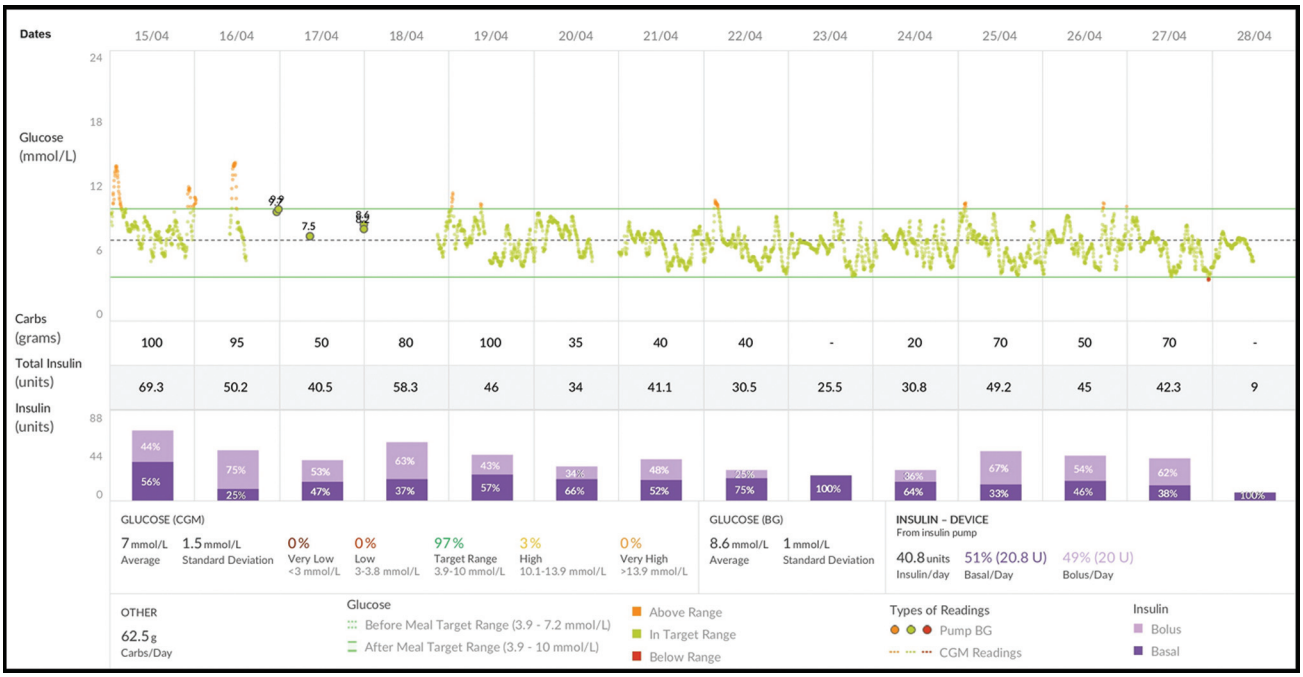

Fig. 3 Illustration of the continued improvement in blood glucose control following an increase in the dose of semaglutide from 3 to 7 mg 4 weeks after initially starting.

semaglutide into her treatment regimen proved to be a pivotal intervention. Blood glucose control was significantly improved, marked by a notable increase in time spent within the target range and a reduction in insulin requirements without any increased risk of hypoglycemia. It also had the additional benefit of weight loss.

This case underscores the importance of considering alternative therapeutic approaches in insulin dependent T2DM patients who face challenges with insulin allergy or have poorly controlled blood glucose levels. The successful outcome observed here suggests that oral semaglutide, in conjunction with existing therapies, may offer a promising alternative for managing glycemia in such complex cases. Further research is warranted to validate and refine this approach, potentially offering solutions to individuals facing similar therapeutic problems.

Statement of Patient Consent

The authors confirm that they have obtained an informed consent from the patients for the anonymous reporting of their data.

Authors' Contribution

All the authors drafted and/or critically revised the manuscript. K.A. treated the patient in the clinic and gathered the data, while M.G. performed the literature review. All the authors read and approved the final manuscript.

Compliance with Ethical Principles and Statement

At our institution, no prior ethical approval is required for single-case reports or small case series, provided the patients provide informed consent. The tenets of the Helsinki declaration were followed throughout.

Conflict of Interest

None declared.

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