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Case Report

Diabetic Ketoacidosis in a Patient With Type I Diabetes Treated With a Closed-Loop Sensor–Augmented Insulin Infusion System

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ABSTRACT

Background/Objective: Closed-loop insulin infusion systems (CLSs) such as Tandem t:slim with Control-IQ (t:slim CIQ) improve glycemic control and decrease diabetic ketoacidosis (DKA) risk in type 1 diabetes mellitus (T1DM). We report a case of CLS failure, likely from tirzepatide-induced volume depletion, leading to DKA.

Case Report: A 36-year-old woman with T1DM on t:slim CIQ CLS was prescribed tirzepatide for weight loss. Three months later, 4 days after the last tirzepatide injection, she presented with worsening nausea, vomiting, 50-lbs weight loss, minimal oral intake for 3 days, and positive urine ketone result. Her heart rate was 137 beats/min and respiratory rate was 35 breaths/min, and she had Kussmaul breathing, with dry oral mucosa indicating volume depletion. Laboratory examination showed a fingerstick glucose level of 289 mg/dL, serum glucose level of 322 mg/dL, bicarbonate level of 12 mmol/L, and anion gap of 21 mmol/L confirming high-anion-gap metabolic acidosis, suggesting DKA. A concurrent continuous glucose monitor (CGM) reading was 40 mg/dL. The CLS and CGM were removed. DKA resolved within 72 hours (serum glucose level of 143 mg/dL, anion gap of 8 mmol/L, bicarbonate level of 24 mmol/L) on intravenous insulin and fluids. The CLS and CGM were restarted with good glycemic control. Tirzepatide was discontinued to avoid future episodes of volume depletion.

Discussion: Volume depletion affects interstitial fluid glucose levels due to compensatory mechanisms. This may result in CLS failure due to CGM dependence on interstitial glucose measurements, precipitating DKA.

Conclusion: Patients on CLS therapy should be cautioned against CLS failure in volume-depleted states with interstitial glucose–level changes. A back-up plan with multiple daily insulin injections should be discussed.

Introduction

The closed-loop insulin infusion system (CLS) Tandem t:slim with Control-IQ (t:slim CIQ, Tandem Diabetes Care, Inc) is an advanced insulin delivery system launched in January 2020.[1] It comprises a Tandem t:slim X2 insulin pump for insulin infusion and the Dexcom G6 (Dexcom, Inc) continuous glucose monitor (CGM) for interstitial glucose monitoring. The CIQ algorithm utilizes interstitial fluid (ISF) glucose readings from the Dexcom G6 CGM to deliver insulin from a t:slim X2 insulin pump. It allows for automatic adjustments in basal insulin infusion, automatic correction for hyperglycemia, and suspension for hypoglycemia, thereby increasing glycemic time in range (TIR, 70-180 mg/dL).[2]

CGM systems measure ISF glucose concentration, which depends on glucose diffusion from the blood into the ISF and glucose metabolism in the local tissue.[3] Conditions affecting local glucose

Abbreviations: BMI, body mass index; CGM, continous glucose monitor; CIQ, control-IQ; CLS, closed-loop insulin infusion systems; DKA, diabetic ketoacidosis; HbA1c, hemoglobin A1c; ISF, interstitial fluid; MARD, mean absolute relative difference; POC, point of care; T1DM, type 1 diabetes mellitus; TDD, total daily dose; TIR, time in range.

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dynamics, such as exercise or hypoglycemia, affect CGM accuracy. Dehydration is characterized by intravascular fluid depletion, and mobilization of fluid and interstitial glucose, from the interstitium to the intravascular space.[4] CLS systems that depend on such readings may fail in such situations, leading to acute complications such as diabetic ketoacidosis (DKA).

A dual glucagon-like peptide 1/gastric inhibitory peptide analog (GLP-1/GIPa), tirzepatide, was approved by the United States Food and Drug Administration for glycemic control in type 2 diabetes mellitus in May 2022, and is used off-label for weight loss.[5] Because of gastrointestinal adverse effects (nausea, vomiting, diarrhea), tirzepatide may precipitate dehydration.[6] We describe the case of a patient with type 1 diabetes mellitus (T1DM) on CLS (t:slim CIQ) and tirzepatide who developed insulin infusion set failure–induced DKA in the setting of volume depletion.

Case Report

A 36-year-old woman with poorly controlled T1DM on CLS therapy (t:slim CIQ) was prescribed tirzepatide for glycemic control and weight loss (off-label use) when she weighed 192 lbs (body mass index [BMI] 32.2 kg/m^2) with a hemoglobin A1c (HbA1c) level of 9.4% (79 mmol/mol) (normal $\leq$7% [$\leq$53 mmol/mol]). Three months later, the patient had lost 50 lbs (weight 142 lbs, BMI 25.3 kg/m^2) and reported severe nausea and heartburn due to tirzepatide. Despite the advice to stop or decrease the tirzepatide dose, she elected to continue the medication because of ongoing weight loss. At the emergency room presentation 4 days after the last tirzepatide injection, she reported acute worsening of nausea, heartburn, vomiting, and inability to keep anything down for 3 days. Home urine ketone finding was positive. t:slim CIQ reported hypoglycemia leading to suspension. She had not checked capillary glucose to verify CGM reading accuracy and was treating hypoglycemia with glucose tablets.

On examination, the patient was alert and in mild distress, with appropriately attached CLS and CGM. Vital signs showed tachycardia (137 beats/min), tachypnea (35 breaths/min) on room air, elevated blood pressure (155/100 mm Hg), and normal body temperature (98.6 °F). Physical examination showed Kussmaul breathing and dry oral mucosa, indicating volume depletion. The CGM report showed readings between 40 and 180 mg/dL, demonstrating intermittent hypoglycemia. t:slim CIQ report showed intermittent insulin delivery suspension due to hypoglycemia with correction boluses for hyperglycemia (Fig. 1). The total daily dose (TDD) of insulin was 30 units (Supplementary Table). Prior to tirzepatide initiation, the patient's TDD was closer to 70 units.

A point of care (POC) glucose testing measured a glucose level of 289 mg/dL (normal 65-110 mg/dL). Laboratory testing showed a serum glucose level of 322 mg/dL (normal 74-106 mg/dL). Concurrent Dexcom CGM reading showed an interstitial glucose level of 40 mg/dL, markedly different from POC and serum glucose values. Further laboratory testing showed a hemoglobin level of 16.2 g/dL (normal 11.2-15.7 g/dL), hematocrit of 45.3% (normal 34.1%-44.9%), HbA1c of 7.4% [57 mmol/mol], bicarbonate of 12 mmol/L (normal 20-31 mmol/L), sodium of 131 mmol/L (normal 136-145 mmol/L), potassium of 5 mmol/L (normal 3.5-5.1 mmol/L), creatinine of 1.00 mg/dL (normal 0.55-1.02 mg/dL), glomerular filtration rate of 75 mL/min/1.73 m^2 (normal $\geq$ 60 mL/min/1.73 m^2) with an anion gap of 21 mmol/L (normal 6-14 mmol/L) confirming high-anion-gap metabolic acidosis (Table). A betahydroxybutyrate level was ordered but not drawn.

Highlights

- CLS depend on CGM for predictive insulin administration and improved glycemic control.
- CGMs measure ISF glucose, which is comparable to blood glucose in euvolemic and stable glycemic state.
- Volume depletion leads to ISF status and ISF glucose changes; therefore, CGMs may have inaccurate readings.
- CLS may fail in volume-depleted states, causing hyperglycemia and DKA precipitation.
- Patients should be cautioned against CLS failure; a back-up plan with insulin injections should be discussed to avoid DKA.

Clinical Relevance

We describe a case of closed-loop insulin infusion set failure due to volume depletion that affected continuous glucose monitor accuracy. Patients with type 1 diabetes mellitus on closed-loop insulin infusion therapy should be made aware of this, and a back-up plan with insulin injections should be discussed.

Examination and laboratory testing did not show a source of infection. Volume depletion was attributed to the gastrointestinal adverse effects of tirzepatide, because of the history of ongoing symptoms.

The patient was diagnosed with DKA based on elevated serum glucose level and high–anion-gap metabolic acidosis and a history of positive ketone on home urine testing. The CLS and CGM devices were removed, and the patient was treated with continuous regular insulin (TDD 33 units) and intravenous normal saline infusion. While an improvement in serum glucose level (143 mg/dL) and closure of the anion gap (8 mmol/L) was seen within 8 hours of treatment, improvement in bicarbonate level (24 mmol/L) took 72 hours (Table). The patient was transitioned to subcutaneous insulin with basal glargine and prandial lispro (TDD 24 units), a significant decrease from the previous TDD 67 units by 64%. This was attributed to tirzepatide-induced weight loss and decreased insulin resistance.

Insulin delivery was transitioned from subcutaneous insulin to the t:slim CIQ system and Dexcom G6 CGM at preadmission settings. Glycemic control remained within the optimal range (TDD 37 units) for the next 24 hours and at outpatient follow-up 10 days later (Fig. 2 and 3). Tirzepatide was discontinued to avoid similar future events.

Discussion

This patient with T1DM, using t:slim CIQ CLS and Dexcom G6 CGM, presented with acute worsening of chronic gastrointestinal symptoms within 24 hours of the last tirzepatide dose with positive urine ketone result. Her CLS was intermittently suspending insulin delivery because of low CGM readings after symptom onset. She had tachycardia, tachypnea, Kussmaul breathing, and dry oral mucosa, indicating volume depletion. Although the POC (289 mg/dL) and serum (322 mg/dL) glucose levels were comparable, the CGM (40 mg/dL) glucose level was markedly different. DKA was suspected because of hyperglycemia, high–anion-gap metabolic acidosis, and positive urine ketone result. We hypothesize that adverse effects from tirzepatide caused volume depletion, leading to serum hyperglycemia and poor CGM accuracy. The CIQ algorithm

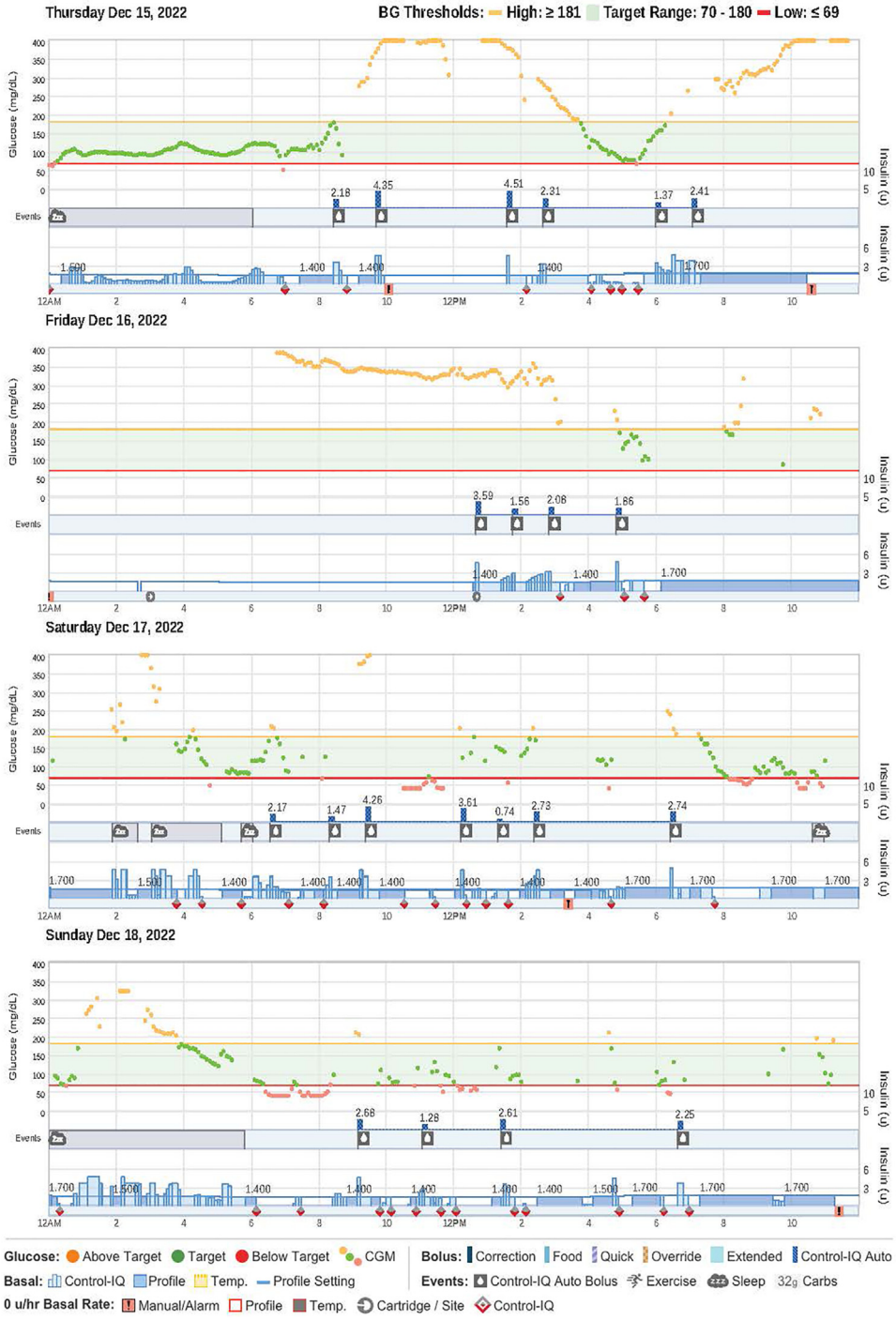

Fig. 1. t:slim CIQ report from 3 days prior to admission showing the intermittent and inaccurate Dexcom G6 CGM sensor readings. *CGM* = continuous glucose monitor; *t:slim CIQ* = Tandem t:slim with Control-IQ.

intermittently suspended insulin delivery for CGM-sensed hypoglycemia, compounded serum hyperglycemia, and precipitated DKA due to infusion set failure.

Insulin infusion systems available in the United States are from insulin device companies such as Medtronic MiniMed, Inc, Insulet Corp, and Tandem Diabetes, Inc. The CGM products available in the United States include Dexcom G6 CGM (Dexcom, Inc), Freestyle Libre CGM systems (Libre 14 day, Libre 2, Libre 3, Abbott Diabetes Care), and Medtronic Guardian CGM (Medtronic MiniMed, Inc). CGM accuracy is measured by the mean absolute relative difference (MARD), which compares glucose data from CGM with capillary blood glucose measurement.[7]

CLS products that work with CGMs include Medtronic MiniMed 670G and 770G pumps (loops with Medtronic Guardian CGM), Omnipod 5 (loops with Dexcom G6 CGM), and t:slim CIQ (loops with Dexcom G6 CGM). The t:slim CIQ has become popular because of the predictive algorithm that protects against hyperglycemia and hypoglycemia. Brown et al demonstrated that this system increased glycemic time in range (TIR, 70-180 mg/dL) with DKA/hyperglycemia occurring due to infusion set failure rather than chronic

Table
Laboratory Results During Hospital Admission

Laboratory test	Normal	Day 1	Day 1 (8 h later)	Day 2	Day 3
Hemoglobin A1c	<7% (<53 mmol/mol)	7.4%			
Hemoglobin	11.2-15.7 g/dL	16.2		10.6	11.0
Hematocrit	34.1-44.9%	45.3		34.8	34.5
Serum glucose	74-106 mg/dL	322	143	99	86
Sodium	136-145 mmol/L	131	138	138	141
Potassium	3.5-5.1 mmol/L	5.0	4.2	3.9	3.4
Bicarbonate	20-31 mmol/L	12	14	16	24
Anion gap	6-14 mmol/L	21	8	7	9
Serum creatinine	0.55-1.02 mg/dL	1.00	0.72	0.66	0.58
GFR	≥60 mL/min/1.73 m^2	75	111	117	120
Urine hCG	Negative	Negative			

Abbreviations: GFR = glomerular filtration rate; hCG =human chorionic gonadotropin.

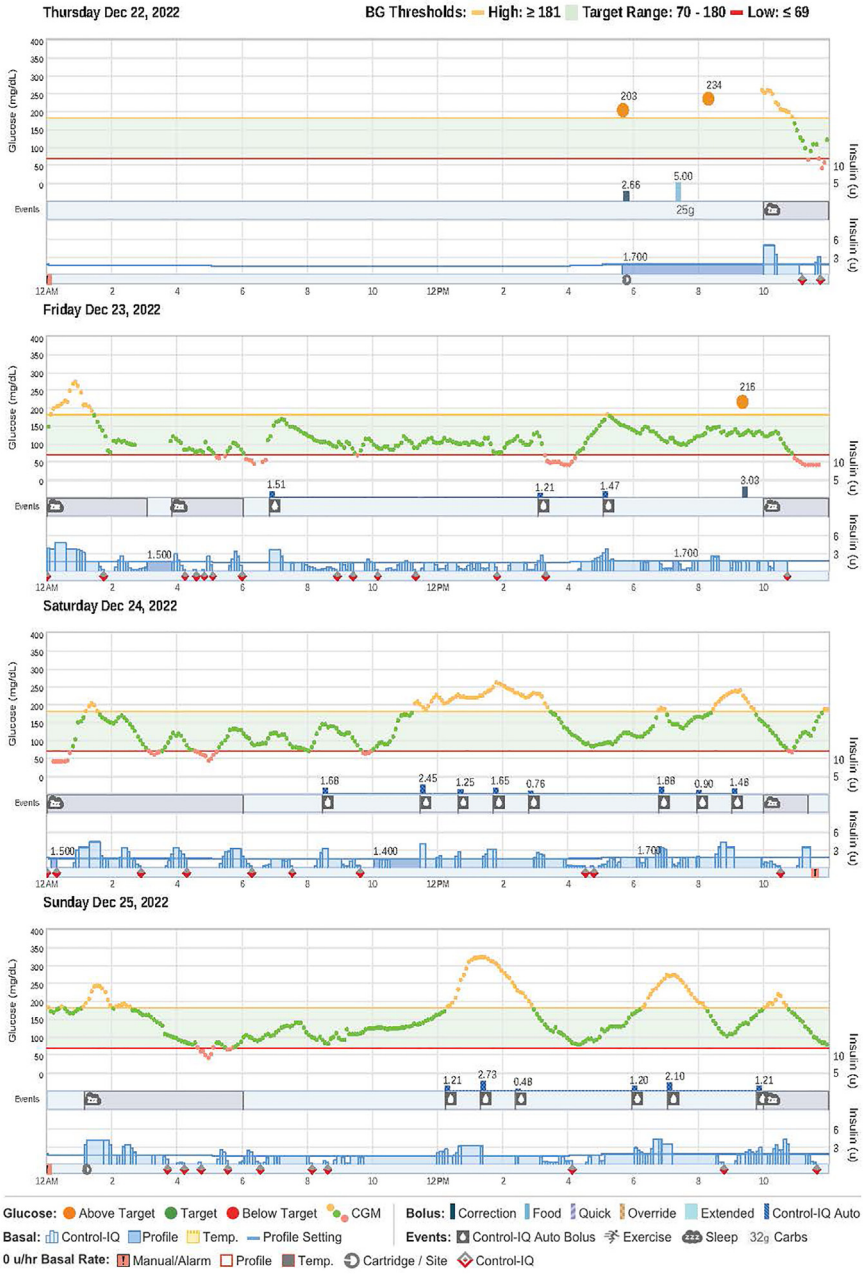

Fig. 2. t:slim CIQ report after the resolution of DKA and insertion of new Dexcom G6 CGM sensor (days 1 and 2). *CGM* = continuous glucose monitor; *DKA* = diabetic ketoacidosis; *t:slim CIQ* = Tandem t:slim with Control-IQ.

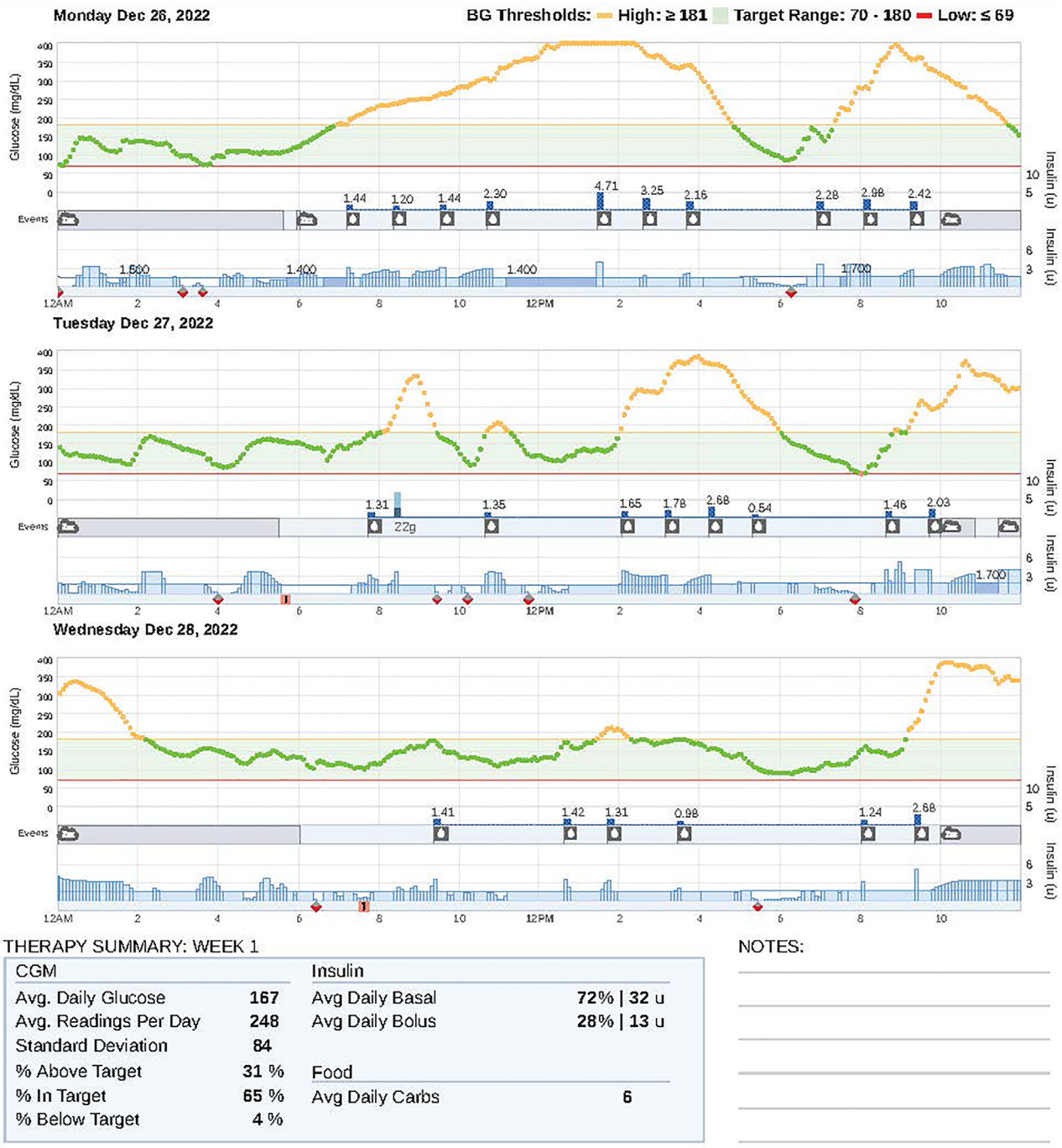

Fig. 3. t:slim CIQ report after the resolution of DKA and insertion of new Dexcom G6 CGM sensor (days 3 and 4). *CGM* = continuous glucose monitor; *DKA* = diabetic ketoacidosis; *t:slim CIQ* = Tandem t:slim with Control-IQ.

glycemic control.[2] Infusion set failure was defined as connectivity problems, component failure requiring replacement or reset, error messages, unresponsive interface, or inappropriate calibration-related behavior.[2] Because the t:slim CIQ algorithm depends on Dexcom G6 CGM accuracy, Dexcom G6 CGM errors may lead to an infusion set failure as in our patient.

All CGM systems, including the Dexcom G6 CGM, read ISF glucose level. It is well-known that there is a delay between serum and ISF glucose readings.[8] However, in a euvolemic and stable glycemic state, ISF glucose level is comparable to serum glucose level, which contributes to CGM's accuracy.[3] Conditions such as physical exercise, with quick glucose utilization, transiently cause a bigger difference in the glucose concentration between serum and ISF readings, because of local tissue glucose diffusion and metabolism changes.[3] Conversely, in fluid loss–induced volume depletion, decreased intravascular water content leads to serum hyperglycemia.[9] The compensatory mobilization of fluid and electrolytes from the interstitial compartment to the intravascular space leads to ISF glucose concentration changes.[3] In this situation, CGM systems may show an inaccurate ISF glucose reading. Our patient, who had chronic gastrointestinal adverse effects from tirzepatide, suffered from acute worsening of nausea and vomiting

with the most recent tirzepatide injection. Because she could not keep up her oral intake, she went into a volume-depleted state. We believe that the compensatory ISF depletion most likely led to false hypoglycemia on Dexcom G6 CGM. Volume-depletion–induced intravascular hyperglycemia and intermittent insulin delivery suspension from t:slim CIQ resulted in DKA. After DKA resolution and correction of volume depletion, the CLS and CGM were restarted without issues, suggesting that volume depletion possibly triggered insulin infusion set failure (Fig. 2 and 3).

This case highlights the relationship between total body volume status and ISF glucose- dependent CLS systems. Closed-loop insulin infusion systems such as t:slim CIQ improve glycemic control; however, it is important to ensure monitoring of CGM accuracy and concurrent medications. Patients should be counseled to check the capillary glucose level to verify CGM accuracy in situations of fluid loss to avoid insulin infusion set failures and life-threatening complications such as DKA. A back-up emergency plan for insulin administration with multiple daily injections should be discussed, especially in T1DM.

Further studies are needed to determine the relationship between CLS products, body volume status, and overall effect of glycemic control.

Disclosure

The authors have no multiplicity of interest to disclose.

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Author Contributions

All authors made individual contributions to the authorship. All authors have reviewed and approved the final draft.

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