# Misdiagnosis of Type 1 Diabetes Identified at a Primary Care Pharmacist Visit

*Jennifer D. Goldman and Nikhil Sangave*

## Case Presentation

A 68-year-old woman was referred to the primary care pharmacist by her physician in spring of 2021 for the management of uncontrolled type 1 diabetes. She was first diagnosed in 2009 and had since been managed by an endocrinologist with a multiple daily injection (MDI) insulin regimen. She said she checked her fingerstick blood glucose levels intermittently.

Her medical history was significant for hypertension, dyslipidemia, anemia, anxiety, seasonal allergies, and breast cancer. She had stage 2 chronic kidney disease with an estimated glomerular filtration rate of 76 mL/min/1.73 $m^2$ and was negative for albuminuria.

Her relevant diabetes medications included fixed doses of 100 units/mL (U100) insulin glargine 64 units daily and U100 insulin aspart 20 units three times daily with meals (total daily insulin dose 1.6 units/kg). She said she did not count carbohydrates or use any correction insulin doses. She did not have any glucagon at home and reported treating hypoglycemia with orange juice. Her other medications included lisinopril 10 mg daily, spironolactone 50 mg daily, anastrozole 1 mg daily, citalopram 40 mg daily, risperidone 0.25 mg one to three times daily, and zolpidem 10 mg at bedtime as needed.

Her most recent weight was 170 lb (77.27 kg), and her BMI was 31.09 kg/$m^2$.

Table 1 summarizes her medications at the time of each visit, her continuous glucose monitoring (CGM) data for the 14 days before each visit, and her A1C results. Her A1C at the time of referral was 10.4%, and other laboratory test values were all within normal limits.

Her first visit was remote via videoconferencing because of social distancing during the coronavirus disease 2019 pandemic. She had no glucose meter data to report. Given her very large doses of insulin and elevated A1C, type 2 diabetes was suspected. She denied anyone suggesting this to her during her previous visits with her primary care and endocrinology providers since she had been diagnosed in 2009.

She agreed to use an intermittently scanning CGM system. Because of the pandemic, she was taught via videoconference to use CGM and picked up her sensors at the pharmacy. Professional CGM (a CGM system owned by the clinic) was not a considered option because use of a personal CGM system was indicated indefinitely given her use of basal and bolus insulin. Given her use of insulin, glucagon was prescribed in case of hypoglycemic emergency, and she was given education about the signs, symptoms, prevention, and management of hypoglycemia.

Two weeks later, CGM revealed an average blood glucose of 300 mg/dL, with glucose variability (GV) of 14.2%. Her CGM sensor had been active 68% of the time, and glucose management indicator (GMI) data (which roughly correlate to A1C) were unavailable. She scanned her sensor three to six times daily but missed data while sleeping overnight for longer than 8 hours because the sensor for her system had to be scanned at least every 8 hours to capture 100% of her glycemic data (1,2). There was, however, enough data to appropriately evaluate her glycemic management, so professional CGM was deemed unnecessary.

The patient's CGM ambulatory glucose profile (AGP) report revealed that her glucose was very high (>250 mg/dL) 89% of the time and was high (181–250 mg/dL) 11% of time. Her time in range (TIR; 70–180 mg/dL) was 0%, and she spent no time with low blood glucose (<70 mg/dL) or very low blood glucose (<54 mg/dL) (Figure 1). At this visit, her medication adherence was confirmed, and she was asked about the accuracy of her original diagnosis. She

School of Pharmacy Boston, Massachusetts College of Pharmacy and Health Sciences, Boston, MA

**Corresponding author:** Jennifer D. Goldman, jennifer.goldman@mcphs.edu

N.S. is currently affiliated with AstraZeneca Pharmaceuticals LP, Wilmington, DE

https://doi.org/10.2337/cd22-0049

**TABLE 1** Medications, CGM Data, and A1C at Each Visit

| Visit | Medications at Visit | AGP Report Data for 14 Days Prior to Visit | | | | | | | | A1C, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Sensor Active, % | TIR, % | High Glucose, % | Very High Glucose, % | Low Glucose, % | Very Low Glucose, % | GV, % | Average Glucose, mg/dL | |
| 1 | Insulin glargine U100 64 units daily, insulin aspart U100 20 units three times daily | NA | NA | NA | NA | NA | NA | NA | NA | 10.4 |
| 2 | Insulin glargine U100 64 units daily, insulin aspart U100 20 units three times daily | 68 | 0 | 89 | 11 | 0 | 0 | 14.2 | 300 | NA |
| 3 | Insulin glargine U100 64 units daily, insulin aspart U100 20 units three times daily, metformin XR 2,000 mg daily | 67 | 71 | 26 | 2 | 1 | 0 | 67 | 162 | NA |
| 4 | Insulin degludec U200 56 units once daily, dulaglutide 0.75 mg once weekly, metformin XR 1,000 mg daily | 68 | 27 | 62 | 11 | 0 | 0 | 17.1 | 205 | NA |
| 5 | Insulin degludec U200 82 units once daily, dulaglutide 1.5 mg once weekly, metformin XR 1,000 mg daily | 53 | 37 | 53 | 0 | 0 | 0 | 19.9 | 197 | NA |
| 6 | Insulin degludec U200 82 units once daily, dulaglutide 1.5 mg once weekly, metformin XR 1,000 mg daily, empagliflozin 10 mg daily | 71 | 92 | 8 | 0 | 0 | 0 | 23.7 | 147 | 7.4 |
| 7 | Insulin degludec U200 60 units once daily, dulaglutide 1.5 mg once weekly, metformin XR 1,000 mg daily, empagliflozin 25 mg daily | 63 | 89 | 11 | 0 | 0 | 0 | 21.5 | 140 | NA |

No GMI data were available for any of these visits. NA, not available.

had been undergoing cancer treatment at that time and did not remember any details, and her past medical records were unavailable.

Type 2 diabetes was suspected based on her large insulin doses and her CGM data; she was started on metformin XR 500 mg daily with weekly titration to 2,000 mg daily by week 4. The pharmacist explained that, if she did in fact have type 2 diabetes, metformin would be valuable in her treatment, but if she indeed had type 1 diabetes, it would not be harmful. Diagnostic laboratory tests were ordered.

She missed her next visit and did not return for 3 months, at which time she was taking the full dose of metformin, U100 insulin glargine 64 units daily, and U100 insulin aspart 20 units with meals. Her 14-day AGP report revealed that her TIR was now 71%; she had high glucose 26% of the time and very high glucose 2% of the time; and her glucose was low 1% of the time and never in the very low range. Her sensor had been active 67% of the time, her GV was 32.2%, and her average glucose was 164 mg/dL.

Her C-peptide level came from the laboratory and was 5.4 ng/mL (reference range 1.1–4.4 ng/mL), insulin

MRN: _____
DEVICE: FreeStyle LibreLink

Well Life
PHONE: 9787402300


GENERATED: 11/11/2021

# AGP Report

April 5, 2021 - April 18, 2021 (14 Days)

LibreView

## GLUCOSE STATISTICS AND TARGETS

| | |
|---|---|
| **April 5, 2021 - April 18, 2021** | **14 Days** |
| **% Time CGM is Active** | **68%** |

| Ranges And Targets For | Type 1 or Type 2 Diabetes |
|---|---|
| **Glucose Ranges** | **Targets** % of Readings (Time/Day) |
| Target Range 70-180 mg/dL | Greater than 70% (16h 48min) |
| Below 70 mg/dL | Less than 4% (58min) |
| Below 54 mg/dL | Less than 1% (14min) |
| Above 180 mg/dL | Less than 25% (6h) |
| Above 250 mg/dL | Less than 5% (1h 12min) |
| Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial. | |

| | |
|---|---|
| **Average Glucose** | **300** mg/dL |
| **Glucose Management Indicator (GMI)** | **-** |
| **Glucose Variability** | **14.2%** |

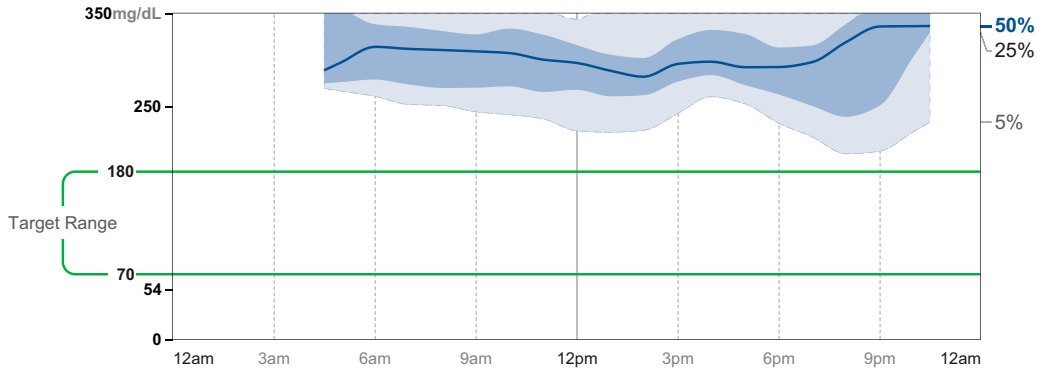
**Defined as percent coefficient of variation (%CV); target ≤36%**

## TIME IN RANGES


| | | | |
|---|---|---|---|
| **Very High** | >250 mg/dL | **89%** | (21h 22min) |
| **High** | 181 - 250 mg/dL | **11%** | (2h 38min) |
| **Target Range** | 70 - 180 mg/dL | **0%** | (0min) |
| **Low** | 54 - 69 mg/dL | **0%** | (0min) |
| **Very Low** | <54 mg/dL | **0%** | (0min) |

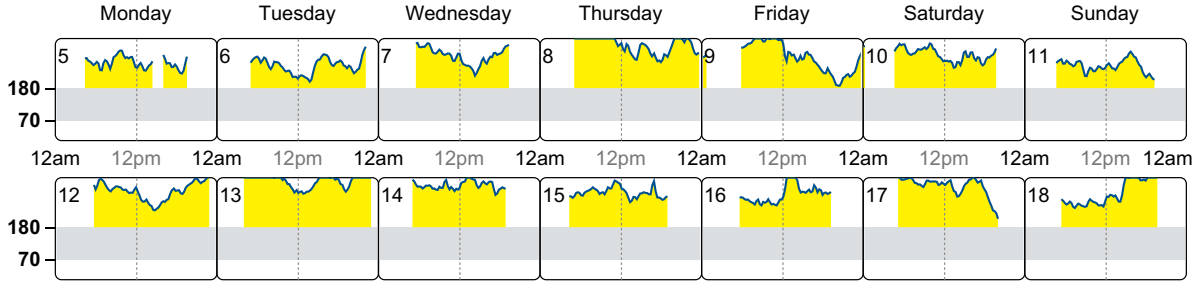
## AMBULATORY GLUCOSE PROFILE (AGP)

*AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.*




## DAILY GLUCOSE PROFILES

*Each daily profile represents a midnight to midnight period with the date displayed in the upper left corner.*




Source: Battelino, Tadej, et al. "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range." Diabetes Care, American Diabetes Association, 7 June 2019, https://doi.org/10.2337/dci19-0028.

FIGURE 1 The patient's AGP report after the first 2 weeks of CGM.

antibodies were negative at <5 uU/mL, ZNT8 antibodies were negative at <15 U/mL, and the GAD65 autoantibody test was not performed because the specimen was grossly lipemic. Thus, type 2 diabetes was confirmed. U100 insulin aspart was discontinued, and dulaglutide 0.75 mg once weekly was initiated. Her basal insulin was changed from U100 insulin glargine 64 units to 200 units/mL (U200) insulin degludec 50 units daily, with up and down self-titration instructions provided based on her fasting blood glucose values, if needed. She complained of gastrointestinal side effects, so her metformin XR dose was decreased to 1,000 mg daily.

At the next visit, her TIR was only 27%. She had high glucose 62% of the time and very high glucose 11% of the time, with no low or very low glucose readings. Her GV was 17.1%, and her average glucose was 205 mg/dL. There was no GMI because her sensor was active only 68% of the time, with long periods of inactivity overnight, when she slept for longer than 8 hours. She had not titrated her basal insulin past 56 units, and there was a significant worsening of her glucose without the mealtime insulin and with only half her previous dose of metformin.

At this visit, dulaglutide was increased to 1.5 mg once weekly, insulin degludec was increased to 60 units with a titration schedule to increase by 2 units every 4 days, and metformin XR 1,000 mg daily was continued.

At the next visit, her CGM sensor had been active 53% of the time, so a GMI could not be calculated. Her TIR was 37%, and her glucose was high 53% of the time, with no time in the very high range or in the low or very low glucose ranges. Her GV was 19.9% (GV target ≤36%), and her average glucose was 197 mg/dL. She had self-titrated to 82 units of insulin degludec and continued her other medications. Empagliflozin 10 mg daily was initiated to help with postprandial blood glucose. Her basal insulin dose was ∼1 unit/kg, and she was counseled on appropriately decreasing the dose as necessary based on her fasting blood glucose readings.

Three months later, her TIR was 92% and her glucose was high 8% of the time, with no time in the very high, low, or very low ranges. Her CGM was active 71% of the time, but no GMI was reported. Her glucose variability was 23.7%, and her average glucose was 147 mg/dL. Her A1C, measured 1 week before the appointment, was 7.4%. At this visit, her insulin degludec was decreased from 70 to 60 units, and empagliflozin was increased from 10 to 25 mg daily.

The patient missed her next appointment and rescheduled for 3 months later. No medications had been changed, but her CGM was evaluated remotely.

Five months after the last assessment, her CGM revealed a TIR of 89%, with glucose in the high range 11% of the time. She spent no time with very high, low, or very low glucose levels. Her CGM was active only 63% of the time, primarily because it was not active overnight. Her glucose variability was 21.5%, and her average glucose was 140 mg/dL.

## Questions

1. What are the recommendations for a diagnosis of type 1 diabetes?
2. Who is a suitable candidate for CGM?
3. What data support the regular use of CGM?
4. Are there data to support pharmacists' involvement with CGM management for patients with diabetes?

## Commentary

A consensus statement by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes sheds light on differentiating between type 1 and type 2 diabetes. Adults suspected of having type 1 diabetes should be tested for islet cell antibodies. Positive results confirm a diagnosis of type 1 diabetes. However, patients with negative results who are >35 years of age can start a trial of noninsulin therapy. After 3 years, a C-peptide level can be ordered, and elevated levels are indicative of type 2 diabetes. If C-peptide levels are low, the patient has type 1 diabetes (3).

Significant improvement in glycemia with the use of metformin, although not confirmatory, certainly supports a diagnosis of type 2 diabetes. In this case, past medical records were not available, but the diagnosis was most likely complicated by the patient's simultaneous cancer diagnosis and poor attendance at appointments. Risperidone is also known to raise blood glucose and weight, but its impact in this patient's case is unknown.

The ADA recommends CGM for adults and youth with type 1 or type 2 diabetes on MDI or insulin pump based on patient circumstances, desires and needs. CGM can also be recommended for pregnant patients, those with nocturnal hypoglycemia, and those with hypoglycemia unawareness (4). This patient was clearly a suitable candidate for CGM. The use of the CGM data coupled with her clinical presentation helped to identify the correct diagnosis and make positive treatment changes.

Randomized control trials have shown that regular use of CGM has an overall positive effect on A1C and hypoglycemia. Patients with type 1 or type 2 diabetes who used an MDI regimen or insulin pump therapy were the original test subjects, and it was found that virtually all age-groups received benefit from real-time CGM. Newer data have also shown that intermittently scanned CGM reduces A1C and hypoglycemia in patients with type 2 diabetes who have an MDI insulin regimen, use mixed therapies, or use basal insulin (4–6).

A pilot study was launched for patients with type 2 diabetes to examine efficacy of CGM-enhanced online consultations (7). The study compared A1C, patient acceptability, and time to visit when patients were seen by a clinical pharmacist versus an endocrinologist. A1C and patient acceptability were comparable in both groups, but time to initial visit was about twice as long with the endocrinologist versus the clinical pharmacist (45 vs. 22 days). This retrospective study also found that patients with CGM were more than twice as likely to reach their A1C target at 3 and 6 months. Pharmacists were able to make individualized and targeted recommendations such as for modifying diet, adding or increasing bolus insulin, and discontinuing or decreasing basal insulin (7). The use of CGM was essential to these improvements, as these patients were in a pharmacist-managed diabetes service for at least 3 months before CGM was incorporated and yet were still not meeting glycemic goals.

The use of intermittently scanned CGM enabled the pharmacist to help identify the misdiagnosis of type 1 diabetes in the patient described in this case. There were also other clinical clues such as the higher doses of insulin that supported a diagnosis of type 2 diabetes.

There is a shortage of endocrinologists in the United States, and 90% of patients with diabetes are managed by primary care professionals (8). The ADA strongly supports the use of CGM to manage diabetes in specific populations and the role of pharmacists as part of the care team. Adding a pharmacist to primary care or endocrinology to manage both medication regimens and glucose monitoring can be an excellent addition that benefits patients and health care professionals (HCPs) alike. Pharmacists can collaborate with other HCPs to help manage complex cases to improve glycemic control, promote weight loss, and help prevent major adverse cardiovascular events. This primary care pharmacy service will continue to work with the patient's primary care clinician to manage drug therapy.

## Clinical Pearls

- If type 1 diabetes is suspected in an adult, order islet cell antibodies and, if negative, consider initiating noninsulin treatment and checking the C-peptide level in 3 years.
- Initiate CGM in all people with type 1 diabetes, if possible, and consider its use in people with type 2 diabetes who take insulin.
- Consider collaborating with a primary care pharmacist or specialist pharmacist for management of medication therapy and glucose monitoring for patients with complex therapeutic needs.

### DUALITY OF INTEREST

J.D.G. is on speakers bureaus for Abbott Diabetes, Amarin, Boehringer Ingelheim, CeQur Lilly, Novo Nordisk, and Xeris. N.S. has served on an advisory panel for Sanofi and, since article submission, has become an employee of AstraZeneca Pharmaceuticals.

### AUTHOR CONTRIBUTIONS

Both authors researched data and wrote and edited the manuscript. Both are guarantors of this work and, as such, take responsibility for the integrity of the case presentation and commentary.

### REFERENCES

1. Abbott. Get started: your guide to the Freestyle Libre 2 system. Available from https://www.freestyle.abbott/content/dam/adc/freestyle/countries/us-en/documents/get-started-guide.pdf. Accessed 26 August 2022

2. Krakauer M, Botero JF, Lavalle-González FJ, Proietti A, Barbieri DE. A review of flash glucose monitoring in type 2 diabetes. Diabetol Metab Syndr 2021;13:42

3. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2021;64:2609–2652

4. Draznin B, Aroda VR, Bakris G, et al.; American Diabetes Association Professional Practice Committee. 7. Diabetes technology: *Standards of Medical Care in Diabetes—2022*. Diabetes Care 2022;45(Suppl. 1):S97–S112

5. Martens T, Beck RW, Bailey R, et al.; MOBILE Study Group. Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes treated with basal insulin: a randomized clinical trial. JAMA 2021;325:2262–2272

6. Wright EE Jr, Kerr MSD, Reyes IJ, Nabutovsky Y, Miller E. Use of flash continuous glucose monitoring is associated with A1C reduction in people with type 2 diabetes treated with basal insulin or noninsulin therapy. Diabetes Spectr 2021;34:184–189

7. Ulrich H, Bowen M. The clinical utility of professional continuous glucose monitoring by pharmacists for patients with type 2 diabetes. J Am Pharm Assoc (2003) 2021;61:e76–e82

8. Davidson JA. The increasing role of primary care physicians in caring for patients with type 2 diabetes mellitus. Mayo Clin Proc 2010;85(Suppl. ):S3–S4