Case Study: Leveraging Continuous Glucose Monitoring in the Clinical Management of Adjunctive Pramlintide Therapy

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PRESENTATION

D.B. is a 51-year-old African-American woman referred for an evaluation of type 2 diabetes. She has been on several oral agents and insulin without achieving her blood glucose or hemoglobin A1c (A1C) targets. She was diagnosed with type 2 diabetes by her primary care provider during a routine examination 20 years ago. Her random glucose at that time was ~ 300 mg/dl. Her medical history also includes obesity, degenerative arthritis, hypertension, sleep apnea, hyperlipidemia, and two Cesarian section births. She denies a history of gestational diabetes, alcohol consumption, or cigarette smoking. Her medications include metformin/glyburide, 500 mg/5 mg three times daily; rosiglitazone, 8 mg daily; 60 units of 70/30 premixed insulin before dinner; hydochlorothiazide, 50 mg daily; quinapril, 20 mg daily; fenofibrate, 54 mg daily; and multiple vitamins.

Initial clinical examination reveals a blood pressure of 130/82 mmHg and a BMI of 46.7 kg/m^2. Her cardiac, respiratory, and abdomenal examinations are unremarkable; funduscopic examination reveals no evidence of retinopathy. Her lower extremity examination reveals no evidence of ulcerations. There is adequate peripheral pain sense.

The patient reports self-monitoring of blood glucose (SMBG) before and after breakfast, with readings averaging in the 100-mg/dl range before the meal and 300 mg/dl after the meal. Her A1C is 9.0%. D.B. expresses motivation to intensify her pharmacological therapy regimen and to follow a meal plan and attend diabetes education classes, all of which she hopes will improve her diabetes control.

QUESTIONS

1. What are the shortcomings of intensive insulin therapy and possible consequences uniquely associated with uncontrolled postprandial hyperglycemic excursions?
2. What has the introduction of home continuous glucose monitoring (CGM) revealed about the dynamics and limitations of A1C as a measure of glycemic control?
3. What role does amylin play in regulating glucose homeostasis, and what are the clinical effects of using pramlintide, a synthetic analog of endogenous amylin, as an adjunctive therapy in type 1 and insulin-requiring type 2 diabetic patients?
4. How can CGM help to inform successful management of pramlintide therapy in a community-based diabetes center?

COMMENTARY

The sequelae of symptoms documented at D.B's initial examination represent a veritable clinical Gordian's knot: despite treatment with three oral diabetes medications (metformin, a sulfonylurea, and a thiazolidinedione) all near or at maximally therapeutic doses, her diabetes remained in poor control, as evidenced by an A1C of 9.0%. Marked or complete β-cell failure is likely given the diminished efficacy of the latter therapies and considering that the patient was also administering 60 units of 70/30 premixed insulin before dinner each night.

Mitigating D.B.'s severe hyperglycemia will need to include marked intensification of insulin therapy, which unfortunately substantially increases the likelihood of weight gain. In morbidly obese patients, whether to improve glycemic control at the cost of exacerbating obesity represents a conundrum for health care providers; lowering A1C with an intensive insulin regimen, while reducing the risk for microvascular complications, fails to address and in fact could worsen a patient's risk for obesity-associated macrovascular complications.[1,2]

Heart disease and related complications are the leading cause of death among individuals with diabetes.[3] Recent glucose-sensing studies have shown that the majority of patients receiving intensive insulin therapy, even while achieving favorable A1C levels, experience severe postmeal hyperglycemia, often with dramatic swings into the hypoglycemic range in the postabsorptive and nocturnal periods.[4,5] Furthermore, numerous studies have shown that acute hyperglycemic excursions and perhaps the magnitude of diurnal blood glucose variability increase markers of inflammation and oxidative stress,[6,7] which are known risk factors for cardiovascular disease.[8] Consistent with these reports, long-term longitudinal trials have indicated

that the magnitude of baseline postmeal glucose levels is the aspect of glycemia most strongly associated with future risk for cardiovascular complications.[9–11]

Advances in medical research during the past several decades have led to new insights into the pathophysiology of diabetes. Multiple hormones, including the glucagon from pancreatic α-cells, amylin from pancreatic β-cells, and the incretin gut hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), have been demonstrated to play integral roles in sustaining normal glucose homeostasis.[12] These breakthroughs have provided a better understanding of the shortcomings of conventional diabetes treatments, including the monohormonal insulin-replacement paradigm, and have led to novel pharmacological approaches for treating diabetes.[13–15]

One approach stems from the discovery of the endogenous hormone amylin, first identified in 1987. Amylin is a 37-amino acid peptide that is co-stored and co-secreted with insulin from β-cells.[16]Amylin and insulin are both absent in patients with type 1 diabetes and decline in direct proportion to the degree of β-cell deterioration in patients with type 2 diabetes.[17,18] Animal studies have demonstrated that amylin complements insulin's role in controlling postprandial glycemia by regulating the rate of endogenous and exogenous glucose appearance. While insulin stimulates glucose uptake into bodily tissues (i.e., mediates glucose disappearance), amylin regulates glucose appearance by suppressing postmeal hepatic glucose output,[19] slowing the rate of gastric emptying,[20] and reducing meal size by inducing satiety.[21] The amylin receptor has been identified and fully characterized; it is most densely located within various regions of the hindbrain, including areas unprotected by the blood brain barrier;[22] amylin receptors are therefore exposed to nutrients and hormones in peripheral circulation, including glucose, insulin, and amylin.[23] Systematic evaluation using various animal models has shown that the glucoregulatory effects of amylin are mediated via binding to its receptor sites in various nuclei of the hindbrain.[24,25]

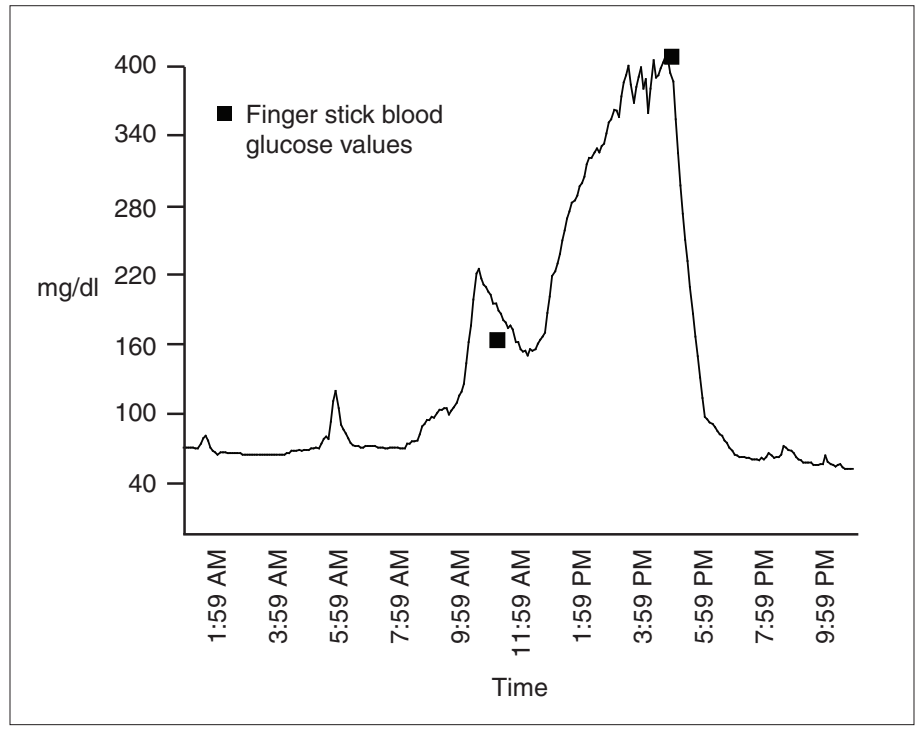

Figure 1a. 24-hour CGM profile: baseline.

The characterization of amylin physiology and associated glucoregulatory actions provided the impetus for developing pramlintide, a synthetic amylin analog that mimics the actions of the endogenous hormone.[26] Mechanistic studies in type 1 and insulin-requiring type 2 diabetic individuals have confirmed that pramlintide, administered via subcutaneous injection adjunctively with mealtime insulin, results in markedly improved postprandial blood glucose levels compared to insulin therapy alone.[17,27] In long-term trials, adjunctive pramlintide therapy reduces A1C levels, daily insulin requirements, and body weight.[28,29] Pramlintide's contribution to suppressing postprandial blood glucose excursions also appears to significantly attenuate markers of oxidative stress, an effect insulin demonstrated in insulin-treated diabetic patients.[30] Pramlintide is contraindicated in patients who have a known hypersensitivity to pramlintide or any of its components, including metacresol; a confirmed diagnosis of gastroparesis; or hypoglycemia unawareness.

Case follow-up. D.B. and the clinician decide to initiate pramlintide in an attempt to improve her overall glycemic control (as measured by A1C), avoid weight gain, mitigate postprandial blood glucose excursions, and decrease her daily insulin requirements. She begins injecting 120 µg pramlintide before meals. During her first week of pramlintide therapy, her premeal insulin dose was reduced by 30%. She experienced transient nausea immediately after dosing; however, the nausea was mild to moderate and dissipated within 2 weeks of starting pramlintide.

To complement A1C assessments, the clinic obtained 24-hour CGM profiles before and 6 months after

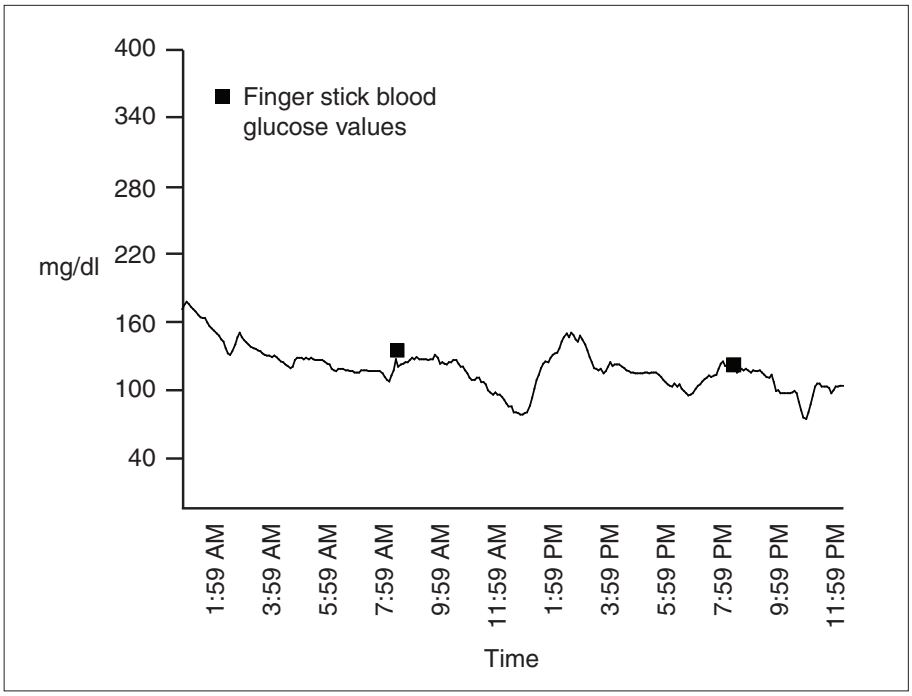

Figure 1b. 24-hour CGM profile: 6 months on adjunctive prmlintide 120 mcg TID.

D.B. started pramlintide therapy. This afforded evaluation of pramlintide's effect on diurnal glucose fluctuations in the patient's normal environment.

After 6 months on adjunctive pramlintide therapy, D.B.'s A1C level was reduced by 1.0% but was still not at goal. The patient's baseline CGM profile revealed that nearly 70% of glucose readings were > 180 mg/dl between 9:00 a.m. and 6:00 p.m. with no readings above 180 mg/dl from 6:00 p.m. to 9:00 a.m. (Figure 1A). CGM re-assessment after 6 months on pramlintide revealed no readings > 180 mg/dl between 9:00 a.m. and 6:00 p.m. For the full 24-hour profile (288 glucose readings), nearly 85% of D.B.'s values were between 80 and 140 mg/dl, with no value < 72 mg/dl or > 178 mg/dl (Figure 1B). These improvements in glycemic control were achieved without weight gain. Finally, although a second dose of 10 units of 70/30 insulin was added before breakfast during the 6-month period, D.B.'s overall daily insulin requirements decreased by ~ 18%.

Until recently, therapeutic approaches for improving glycemic control in patients such as D.B., (i.e., morbidly obese, insulin-requiring type 2 diabetic patients) have been limited. In this case, for example, improving glycemic control in the past would have involved intensifying the insulin regimen, which would likely have had unfavorable consequences, most notably for D.B., weight gain. Today's multihormonal strategy of using pramlintide adjunctively with insulin is an effective new approach to unraveling the Gordian's knot of clinical challenges associated with diabetes and co-existing obesity. New CGM technology offers a valuable complement to routine A1C testing, which can be insensitive to diurnal glucose fluctuations. The use of CGM can be leveraged to determine the quality of day-to-day glycemic control regardless of A1C result. Future research is needed to investigate the long-term effects of improved diurnal blood glucose control on complications of diabetes.

CLINICAL PEARLS

- CGM technology provides a useful tool for quantifying the magnitude and frequency of acute diurnal blood glucose fluctuations and can be effectively leveraged to assess the effects of a pharmacological anti-hyperglycemic therapy on aspects of glycemic control that are not well characterized by A1C measurement alone.
- In obese, severely insulin-resistant patients with type 2 diabetes inadequately controlled with high doses of exogenous insulin, adjunctive pramlintide therapy can be an effective treatment strategy, affording improved overall glycemic control while:
  - attenuating 24-hour glucose fluctuations,
  - decreasing exogenous insulin requirements, and
  - mitigating weight gain.

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