The Nuts and Bolts of Achieving End Points With Real-Time Continuous Glucose Monitoring

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Real-time continuous glucose monitoring (RT-CGM) provides detailed information on glucose patterns and trends and promises to be a major advance in diabetes care. To derive full potential benefit from RT-CGM, the patient needs to be skilled in diabetes self-management. In addition, several key concepts and issues need to be addressed in training patients to use RT-CGM. These include *1*) the implications of the physiologic lag between interstitial and capillary blood glucose levels and 2) the increased risk among RT-CGM users for hypoglycemia related to blind postprandial bolusing. Patients need to understand the importance of calibrating during steady-state conditions to improve sensor accuracy. In addition, they need to use fingerstick measurements for treatment decision-making when the glucose level is changing rapidly, i.e., conditions when physiologic lag can lead to a marked discrepancy between blood and interstitial glucose. Consideration of "insulin on board" and the impact of the glycemic index of different foodstuffs on postprandial glucose patterns can help minimize the risk for hypoglycemia from supplemental boluses taken to correct postprandial hyperglycemia. To use continuous glucose data safely and effectively, patients need to be skilled in diabetes self-management, and the widespread adoption of RT-CGM into diabetes care will need to be coupled with comprehensive self-management education.

Diabetes Care 31 (Suppl. 2):S146–S149, 2008

Real-time (RT) continuous glucose monitoring (CGM) provides detailed information on glucose patterns and trends and promises to be a major advance in diabetes care (1,2). To derive full potential benefit from RT-CGM, the patient needs to master the fundamentals of diabetes self-management. Initial experience suggests that individuals who have poor glycemic control because of fear of weight gain may not be good candidates for this technology, and this needs to be considered in patient selection. This article will review several key concepts and issues that need to be addressed in training patients to use RT-CGM safely and effectively in their diabetes self-management.

PHYSIOLOGIC LAG BETWEEN INTERSTITIAL AND CAPILLARY BLOOD GLUCOSE — Currently available CGM devices measure interstitial glucose. The physiologic lag for equilibration of glucose between the blood and interstitial fluid compartment has important implications for sensor calibration and clinical decision-making during times when the glucose level is changing.

Current generations of CGM devices are calibrated by the patient using fingerstick blood glucose measurements. To optimize CGM accuracy, it is important that the patient calibrate the device during steady-state conditions. After meals, the glucose level will often increase by >3 $mg \cdot dl^{-1} \cdot min^{-1}$, and this, in conjunction with the physiologic lag in equilibration of the blood and interstitial glucose that is often in the range of 10–15 min, can lead to differences between glucose levels in the blood and interstitium of as much as 30–45 mg/dl (3). If the CGM is calibrated with blood glucose measurement postprandially, this will lead to upward setting of the sensor and compromise the accuracy of the device in detecting hypoglycemia.

The physiologic lag can have important implications with regard to detection and treatment of hypoglycemia. When the glucose is falling rapidly, the interstitial glucose generally lags behind blood, and in this situation, the actual blood glucose could be quite low, even when the interstitial/sensor glucose is normal (4,5). The practical implication is that in situations when the glucose is falling (such as after exercise), even if the sensor glucose is normal, the patient will need to perform fingerstick glucose measurement to clarify whether to treat; this is especially important before driving. During the recovery from hypoglycemia, the increase in the interstitial/sensor glucose will often lag behind the blood glucose (6). At times when blood glucose has already normalized, the sensor/interstitial glucose will still be low, and some patients who rely on RT-CGM to assess response to treatment will mistakenly assume they need to consume more carbohydrates, resulting in overtreatment of hypoglycemia. The practical implication is that the patient should be instructed of the need to perform fingerstick glucose measurements to assess recovery from hypoglycemia. With the adoption of RT-CGM, the current guidelines for treatment of hypoglycemia (i.e., the rule of 15: take 15 g carbohydrate and recheck 15 min later) need to be modified.

Patients need to be aware that because of physiologic lag when the glucose is either rising or falling rapidly, there will be a marked difference between the sensor reading and fingerstick measurements and that these discrepancies do *not* necessarily indicate that the sensor is inaccurate. Understanding the basis for these

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H.A.W. has received grant support from Medtonic.
This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.
Abbreviations: CGM, continuous glucose monitoring; RT, real-time.
DOI: 10.2337/dc08-s238

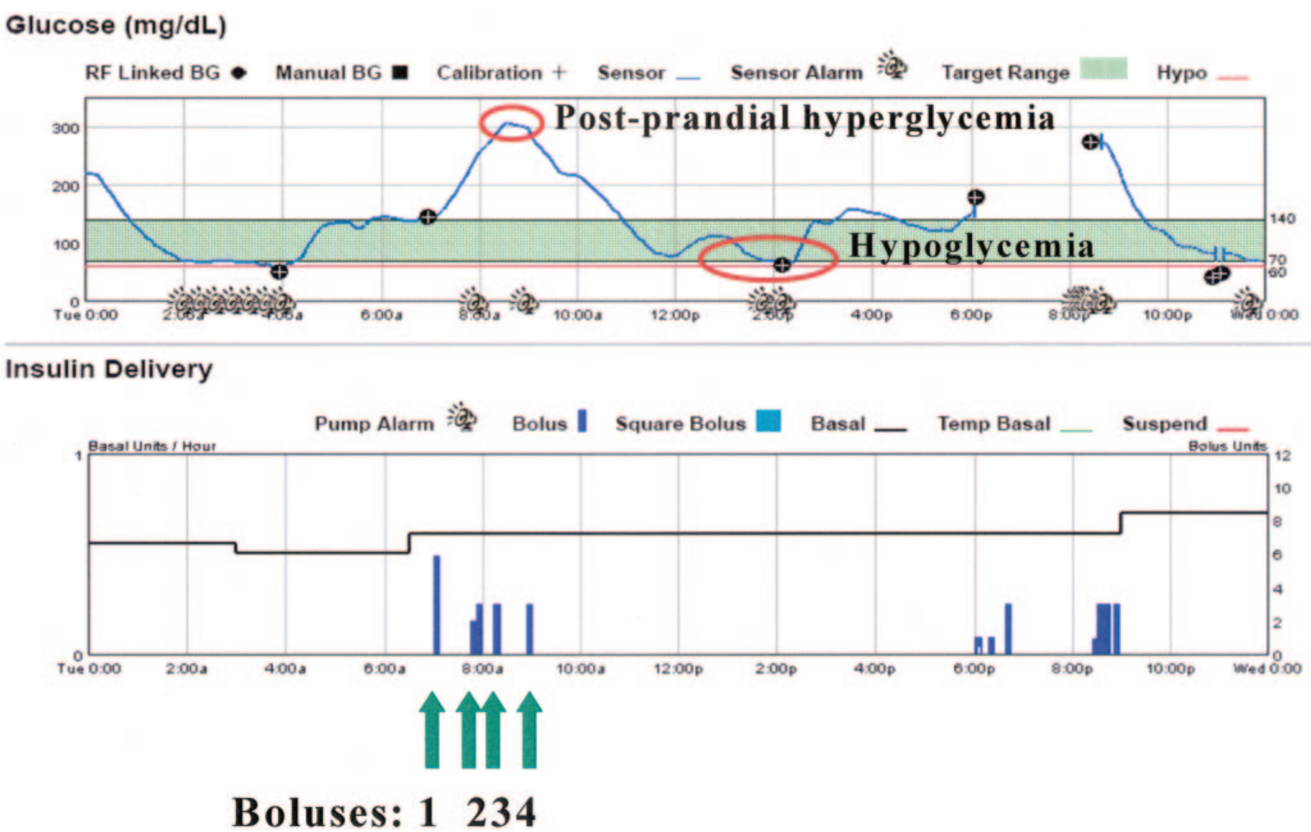

Figure 1—*The top panel shows the download from the glucose sensor. The bottom panel indicates insulin doses taken: each blue bar represents a bolus (units of insulin shown on vertical axis at right). At breakfast, glucose was 140 mg/dl and the individual took bolus 1. In response to postprandial hyperglycemia, the individual took boluses 2, 3, and 4—leading to hypoglycemia. BG, blood glucose; RF, rapid frequency.*

differences can be important in ensuring that patients do not lose confidence in the technology.

INCREASED RISK FOR HYPOGLYCEMIA DUE TO EXCESSIVE POSTPRANDIAL BOLUSING

BOLUSING — While RT-CGM alarms have obvious potential utility in preventing and minimizing hypoglycemia, clinical experience indicates that with some patients, this benefit is counterbalanced by an increased frequency of hypoglycemia due to excessive postprandial bolusing. This tendency for some patients to overreact to postprandial excursions and take excessive insulin is illustrated in Fig. 1 .

This tendency for excessive postprandial bolusing is a common problem with RT-CGM. A major focus of education and follow-up care of the patient using RT-CGM will often need to be addressed at reducing this risk. Factors that patients need to consider before taking extra insulin to treat postprandial hyperglycemia include the following: *1*) Residual insulin "on board" from premeal bolus, *2*) direction of "trend" arrow on glucose sensor, and *3*) type of carbohydrate eaten.

In the STAR 1 trial involving sensor-augmented insulin pumps, subjects followed guidelines to modify food and correction boluses based on the rate of change of the glucose levels detected by the real-time sensor (7). It was recommended that if the glucose level is rising at 1–2 mg $\cdot$ dl^{-1} $\cdot$ min^{-1}, the calculated food/correction bolus should be increased by 10%, and if the level is rising >2 mg $\cdot$ dl^{-1} $\cdot$ min^{-1}, the calculated bolus should be increased by 20%. Conversely, if the glucose level is declining at 1–2 mg $\cdot$ dl^{-1} $\cdot$ min^{-1}, the calculated food/correction bo-

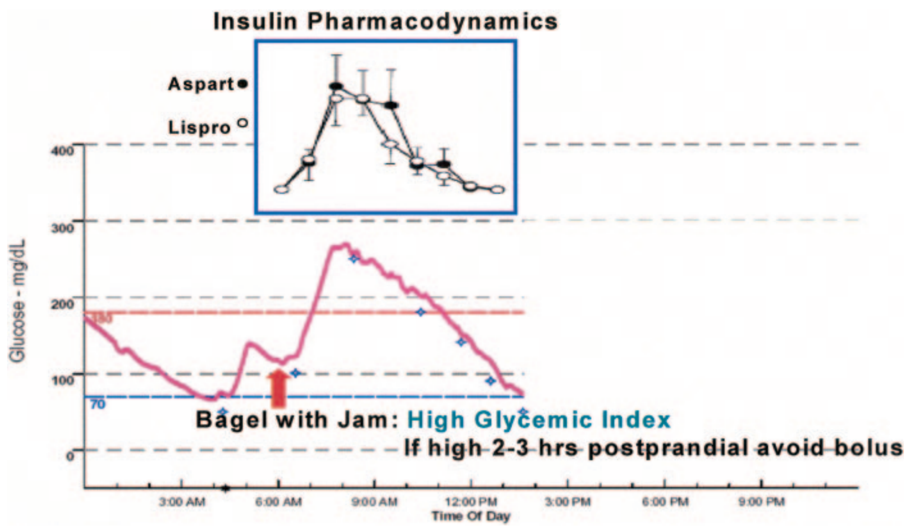

Figure 2—*At breakfast, glucose was 140 mg/dl and the individual took insulin bolus number 1. Early rise in glucose due to mismatch between insulin action and carbohydrate absorption.*

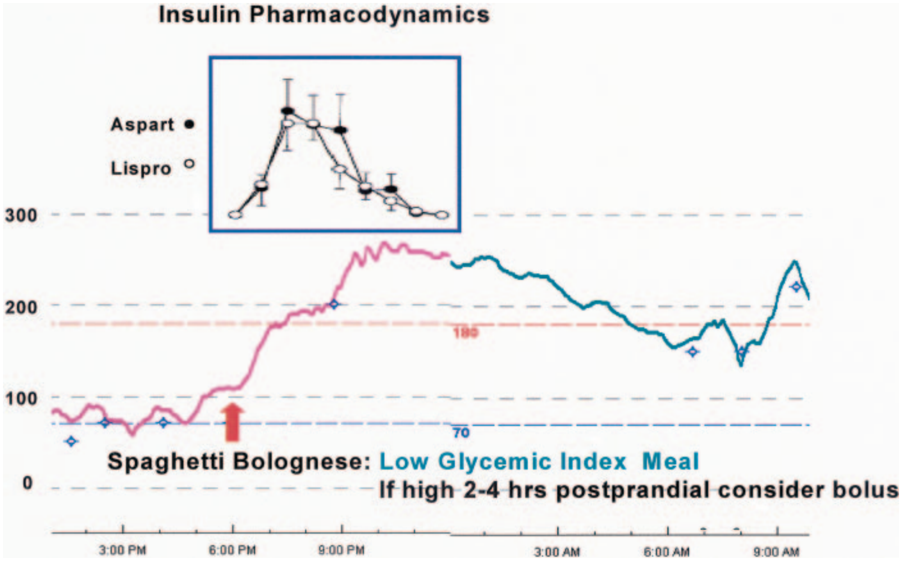

Figure 3—*Delayed rise in glucose due to low–glycemic index meal.*

lus should be decreased by 10%, and if the level is declining by >2 mg · dl^{-1} · min^{-1}, the calculated bolus should be decreased by 20%.

As illustrated in Fig. 2, after eating high–glycemic index carbohydrate foods, there is a rapid spike in glucose level (8). The insulin pharmacodynamic curve (9) indicates that at the time when glucose is peaking (~1–2 h after the meal), there is a substantial amount of residual insulin "on board" from the premeal bolus, and if the patient were to take an extra bolus, there would be a considerable risk for hypoglycemia from dose stacking.

In contrast, as illustrated in Fig. 3, after a low–glycemic index meal, glucose absorption tends to be prolonged, and if the glucose is elevated ≥2 h after the meal, an additional bolus may be needed to bring the level down to target.

EXCESSIVE REDUCTION IN BASAL RATES WITH RT-CGM, LEADING TO EXAGGERATED REBOUND — Figure 4 illustrates the tendency of some patients to respond to declining glucose levels (shown in the upper panel) by suspending basal delivery of insulin by their pump (shown in the lower panel). The end result is an increase in glycemic variability.

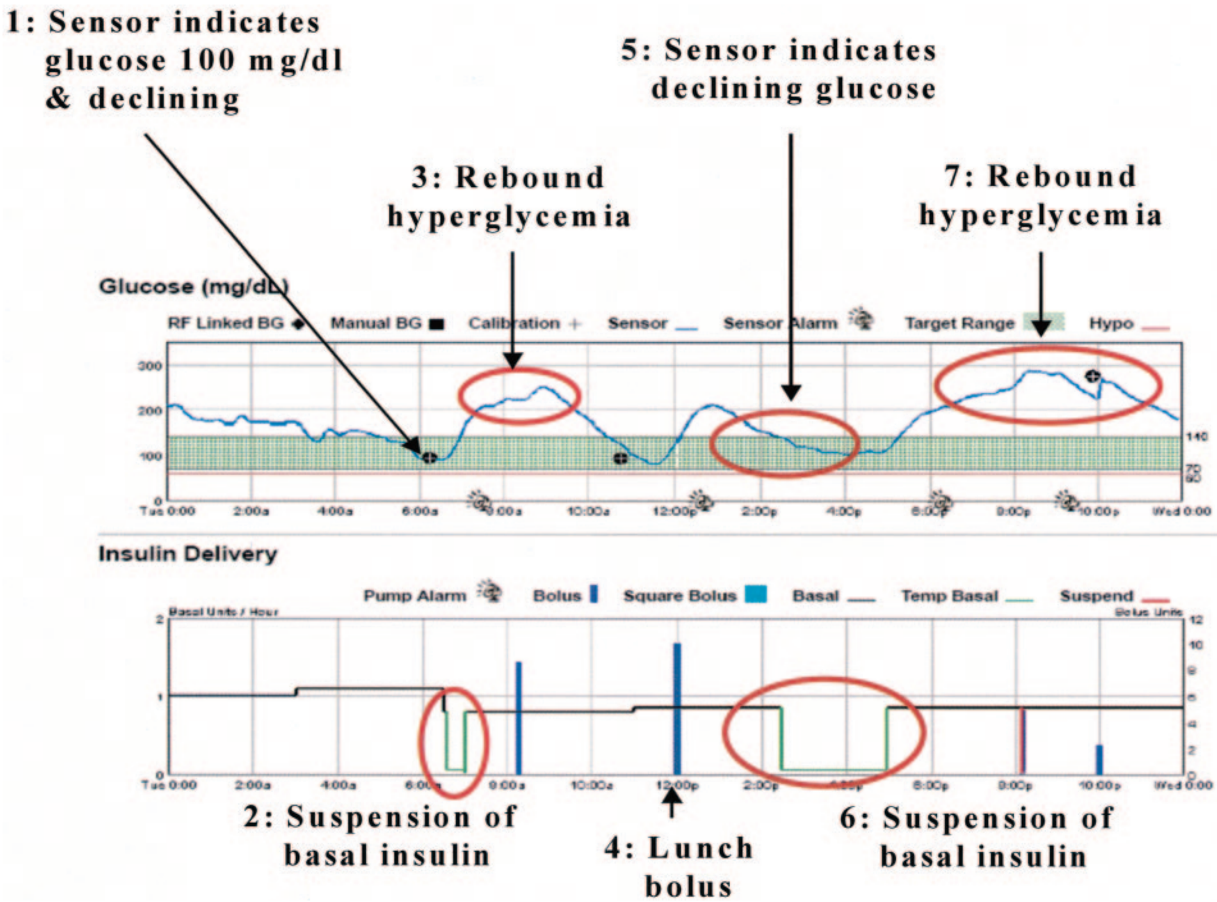

Figure 4—*Inappropriate reduction in basal rates in response to hypoglycemia leads to rebound hyperglycemia. BG, blood glucose; RF, rapid frequency.*

This practice (which is in part an attempt to minimize carbohydrate/calorie intake for treatment of hypoglycemia) has been noted in ~30% of pump patients using RT-CGM. Patients need to be aware that suspending basal insulin is often not an effective way to treat hypoglycemia and should receive careful guidance to prevent and minimize this cause for glycemic instability.

CGM can be of potential benefit to patients with type 1 diabetes using intensive insulin therapy. To use continuous glucose data safely and effectively, patients need to be skilled in diabetes self-management, and the widespread adoption of RT-CGM into diabetes care will need to be coupled with comprehensive self-management education.

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