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CLINICAL APPLICATION

Continuous Glucose Monitoring-Guided Insulin Dosing in Pump-Treated Patients with Type 1 Diabetes: A Clinical Guide

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Abstract

This article describes our methods for structured continuous glucose monitoring (CGM)-guided insulin dosing in pump-treated type 1 diabetes. Some of the methods have been reported and some are based on clinical experience. It is expected that this guide will help those involved in the care of such patients and who have experience with CGM to achieve better glucose control in their patients. More research needs to be done on insulin dosing and we hope that this article will also encourage others to pursue this field. This is a guide and, as such, is not meant to replace clinical judgment. Also, these dosing approaches apply only to those patients on pump therapy. They do not necessarily carry over to those patients treated with basal analog insulin.

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Introduction

With the first insulin injection that Dr. Fredrick Banting gave to a patient, he must have asked, "How much do I give?"[1] His target was the reduction of ketosis and glucose. This first dosing formula was weight-based: the weight of the patient times the insulin sensitivity he observed in dogs in U/kg. Banting then divided the dose by two in order to avoid hypoglycemia in his first patient but also to conserve the precious small amount of insulin he had.

After 60 years, in the late 1970s and early 1980s, rapid, accurate self-monitoring of blood glucose (SMBG) meters, purified predictable human insulin, reliable insulin pumps, and widespread use of hemoglobin A1c (HbA1c) became available. The Atlanta group of Davidson, Bode, and colleagues[2] pioneered development of the early insulin dosing formulas using these advances. Widely published and used,[3,4] the formulas were based on the pump settings of a group of well-controlled (as defined by HbA1c < 7.0%) patients. We will call them the OLD formulas.

In the late 1990s, continuous glucose monitoring (CGM) was developed. Providing 288 glucose readings per day, it revealed that neither self-monitoring of blood glucose (SMBG) nor HbA1c reflected the postmeal and glucose swings during sleep.[5,6] Using structured CGM studies

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Abbreviations: (CF) correction factor, (CGM) continuous glucose monitoring, (CHO) carbohydrate, (HbA1c) hemoglobin A1c, (HCP) health care provider, (ICR) insulin to carbohydrate ratio, (MDI) multiple daily injections, (SMBG) self-monitoring of blood glucose, (TBD) total basal dose, (TDD) total daily dose, (T1DM) type 1 diabetes mellitus, (T2DM) type 2 diabetes mellitus

Keywords: dosing, continuous glucose monitoring, insulin pump, type 1 diabetes

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and intensely adjusting glucose control, we achieved near-normal glycemia in the outpatient setting. Using research studies in such patients, we reanalyzed the dosing formulas and have reported our findings.[7–9] We will call these the NEW formulas. In turn, these formulas help in the CGM analysis of insulin dosing in pump-treated type 1 diabetes mellitus (T1DM) patients. This process is presented in this article.

Structured Professional Continuous Glucose Monitoring-Guided Insulin Dosing

Structured professional CGM is a method to set insulin dosing in pump-treated T1DM. Guided by daily CGM data over 1 to 2 weeks and mathematical analyses of glucose excursions, dosing parameters are set and may remain stable for long periods in nonpregnant medically stable adults. The results of this method suggest that earlier insulin dosing recommendations for basal insulin were too high and bolus insulin dosing too small. When combined with personal, CGM-guided moment-to-moment changes in glucose management, these methods should move the patient closer to near-normal glucose control.

Continous glucose monitoring can be classified as professional or personal (see **Table 1**). Personal CGM is used by the patient in real time to direct immediate behavior changes to correct the glucose level. Such changes include administering microinsulin boluses, temporarily suspending the basal rate, eating to increase glucose, or increasing activity to lower glucose. Continuous glucose monitoring can also be used by the health care provider (HCP) and is called professional CGM. Professional CGM can be further divided into unstructured and structured. In unstructured professional CGM, the patient is not placed on a set diet/activity program and does not periodically omit meals but continues his or her usual activity in order to answer a specific question during a single CGM tracing of 3 to 5 days. These questions include the following: Why is there a disparity between the HbA1c and SBMG? Is hypoglycemia the cause of periodic symptoms? Structured professional CGM, as presented in this article, is a method to define the basal rate and the bolus dosing factors. All of these CGM approaches—personal CGM, unstructured professional CGM, and structured professional CGM—are mutually supportive.

The structured professional CGM approach utilizes a number of mathematical formulas. These formulas guide not only the initial setting but also ongoing adjustments. Insulin dosing is a balance between hyperglycemia, with its symptoms and complications, and hypoglycemia with its symptoms and effect on quality of life. These simple mathematical equations for determining total basal dose (TBD), insulin to carbohydrate ratio (ICR), and correction factor (CF) (see **Tables 2** and **3**) are estimations and, as such, require clinical experience. They provide not only an estimate of the initial dosing but also help in evaluating established parameters.

Table 1.
Comparison of the Three Applications of CGM

	Personal CGM	Unstructured professional CGM	Structured professional CGM
Purpose	Aid patient with acute behavior changes to affect glucose	Explain glucose paradoxes or symptoms	Establish basal rate and bolus dosing factors
Sensor blackout	No, patient has continuous and current glucose information	Yes, until HCP visit. Then patient and HCP review report	
Costs	Patient pays for CGM system	HCP pays for the CGM system. Patient pays for office visit and for the sensor	

Table 2.
Abbreviations and Definitions

(CF) Correction factor: A number, mg/dl/U, that when divided into the difference between the prevailing glucose and the target glucose, in mg/dl, yields the number of units of insulin[a] to return the glucose to within ±20% of target within 2–4 h.
(CGM) Continuous glucose monitoring
(HCP) Health care provider
(ICR) Insulin to carbohydrate ratio: A number, g/U, that when divided into the grams of carbohydrates to be eaten yields the number of units of insulin[a] to return the glucose to ±20% of premeal glucose within 2–4 h.
(MDI) Multiple daily injections to achieve basal bolus dosing with depot-injected insulin.
(SMBG) Self-monitoring of blood glucose
(TBD) Total basal dose: That dose in U/d that achieves target glucose for fasting (>4 h after a meal), controls early morning hyperglycemia and dawn phenomenon (if any), and does not cause hypoglycemia if a meal is missed. It is further defined by <20% of CGM readings >180 mg/dl and <10% of readings <70 mg/dl.
(TDD) Total daily dose: The sum of the total basal and the total bolus dose for 1 day in U/d.
[a] Rapid acting insulin, i.e., insulin lispro, aspart and glulisine

Dosing Formulas

Briefly, the NEW as compared to OLD formulas suggest lower basal doses and higher bolus doses (lower ICR and CF). In addition, there are interrelationships between NEW dosing factors that further help in initiating and reevaluating pump settings.

Table 3 lists the OLD and NEW dosing formulas. Both NEW and OLD formulas are rounded to facilitate calculations. The factors or ratios are derived from the line of best fit comparing the two variables, e.g., weight and TBD. In all cases, this relationship is assumed to be linear and is forced through the *y* axis (the vertical axis of the graph) at a value of zero. Such handling of data is a common statistical method in insulin dosing studies.

Note that TBD can be estimated from both weight and total daily dose (TDD). Also note that both ICR and CF can be derived from both factors, TBD and TDD. Because TBD rather than TDD is used when actively titrating insulin, we used TBD not TDD in estimation formulas, i.e., ICR = 100/TBD and CF = 450/TBD. Both CF and ICR are highly correlated to TBD and to each other. Also, all three are related to each other; 100/TBD = ICR = CF/4.5 (see **Figure 1**). This means that if you know one factor, you will have a fair chance of knowing the other factors. This proportionality between these factors helps to determine the initial dose and the reassessment of the current doses.

Formulas give approximate results (**Table 4**). Sixty-eight percent of the dose settings calculated by the rounded NEW formulas will be distributed in this percentage around the dosing result determined by structured CGM titration. There is a wider spread when determining TBD from weight than from TDD. If one uses the formula 0.2 × weight = TBD, the resulting answer will have a 70% chance of being within 68% lower or 23.4% higher than such a result determined by careful CGM titration. For example, in a patient weighing 70 kg, the TBD would be estimated to be 14 U using the formula TBD = 0.2 × weight. This means there is a 70% chance that the CGM-titrated dose would be between 4.5 U (-0.68 × 14 = -9.5; 14 – 9.5 = 4.5 U) and 17.6 U (+0.234 × 14 = 3.3; 14 + 3.3 = 17.6 U). It is not in the ballpark but is of some use. On the other hand, TBD determined from TDD has an unfair advantage over weight-based formulas because TBD is part of TDD (TDD = TBD + total bolus dose). Also, TBD is a better assessment of insulin sensitivity than just weight. Thus, TBD = 0.4 × TDD will provide an answer closer to that determined by careful CGM titration. For example, let us assume the TDD is 35 U/d and the estimated TBD would be 14 U (**Table 5**). There is a 70% chance that the CGM-titrated TBD would be between 9.1 U (-0.35 × 14 = -4.9; 14 – 4.9 U = 9.1 U) and 16 U (0.142 × 14 = 2.0; 14 + 2 = 16 U). This dosage has less error spread than that calculated from the weight-based formula.

Table 3.
OLD Compared to CGM-Derived NEW Dosing Estimation Formulas[9]

OLD	NEW
0.3 × weight (kg) = TBD	0.2 × weight (kg) = TBD
0.5 × TDD = TBD	0.4 × TDD = TBD
450/TDD = ICR	300/TDD = ICR
1700/TDD = CF	1500/TDD = CF
NR	100/TBD = ICR
NR	CF/4.5 = ICR or CF = 4.5 × ICR

NR, not reported

Table 4.
The Resulting Value of These Formulas Will Be within This % of the CGM-Derived Result About 70% of the Time[9]

Formula	About 70% of results will be within this variance from an analytical CGM-determined value
0.2 × weight = TBD	-68 to +23.4%
0.4 × TDD = TBD	-35 to +14.2%
100/TBD = ICR	-13 to +49%
ICR = CF/4.5	-16.8 to +14.4%

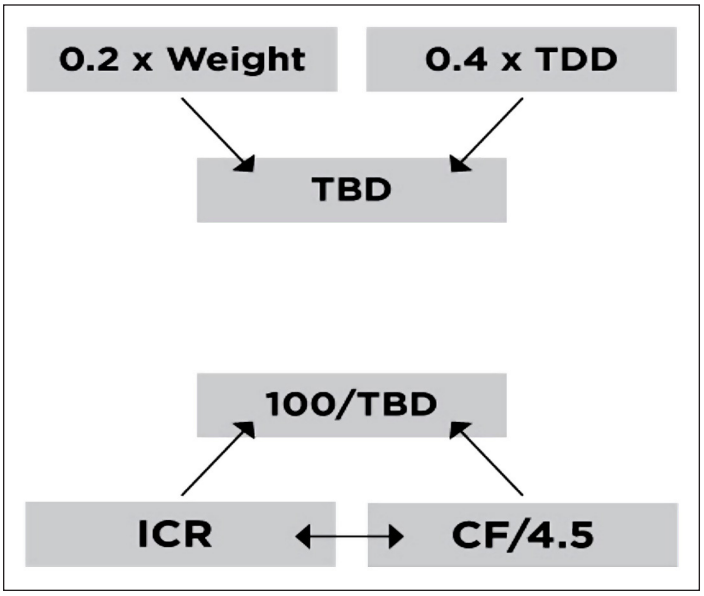

Figure 1. Interrelationships between the dosing factors.[9]

Total daily dose is only as good as the quality of glucose control it reflects. If HbA1c is 10% and all SBMGs are >200 mg/dl, then the TDD may not have the same predictive ability as a TDD in an individual with better control. In addition, the NEW formulas were based on a 50% carbohydrate (CHO) diet. If the diet differs from 50% CHO content, the formulas for calculating TBD from TDD would vary. If the patient is on a high CHO diet, e.g., 70% CHO diet, the ratio of total bolus dose to TBD would change, and the formula may be significantly lower.

The very close relationship between ICR and CF is logical because both reflect the insulin sensitivity of the same tissue, mainly muscle. Thus, if the ICR deviates significantly from CF/4.5 should be reevaluated. The CF calculated from an ICR of, let us say, 10 g/U, would be about 37.4 mg/dl/U (-0.168 × 45 = -7.6; 45 – 7.6 = 37.4) to 51.5 mg/dl/U (+0.144 × 45 = 6.5; 45 + 6.5 = 51.5 mg/dl/U) 70% of the time.

To facilitate the dosing estimations, we have developed a dosing chart (**Table 5**). The range of values for the weight, TDD, and TBD represents those actual subject ranges within our assessment of dosing reported earlier.[9] They are not extrapolated. Either the weight or the TDD could be used to find the estimate of TBD with the considerations mentioned earlier.

Table 5.
A Guide to Insulin Dosing with Calculations Made According to NEW Formulas

0.2 × weight = TBD		0.4 × TDD = TBD		100/TBD = ICR 4.5 × ICR = CF		
Weight kg	TBD U/d	TDD U/d	TBD U/d	TBD U/d	ICR g/U	CF mg/dl/U
50	10	15	6	5	20	90
55	11	20	8	8	13	59
60	12	25	10	10	10	45
65	13	30	12	12	8	36
70	14	35	14	15	7	32
75	15	40	16	18	6	27
80	16	50	20	20	5	23
85	17	60	24	25	4	18
90	18	70	28	30	3	14
95	19	80	32	40	2	9
100	20	90	36	50	2	9

Table 6.
Overview of Structured Professional CGM Process

1. Patient selection: Not everybody will benefit from this study.
2. Patient preparation: Reviewing SMBG, diet, diary, glucose targets, and basal testing.
3. Reset insulin dosing parameters: Reduce duration of the study by changing the pump dose setting closer to the NEW formulas.
4. The study:
a. Usually 1–2 weeks on diet and CGM monitoring with daily CGM downloads and parameter adjustments;
b. Basal rate testing by serial daily meal omissions in the sequence of dinner, lunch, then breakfast.

Structured Professional Continuous Glucose Monitoring Process

Although there may be small and transient changes in insulin sensitivity (and therefore ICR, CF, and basal rate), in most stable nonpregnant adults, dosing factors remain stable. We and others[10–12] have demonstrated that insulin sensitivity remains stable for more than 2 weeks and even up to years. In order to determine these dosing factors accurately, one eliminates variation caused by variable food intake and insufficient number of glucose measurements.

General Concepts

1. ***Law of proportionality.*** (See **Table 6**.) TBD, ICR, and CF are reflective of insulin sensitivity; so, it is not surprising that they are all mathematically related. This was presented earlier (**Figure 1**). When adjusting or setting dosing parameters, consider these mathematical relationships. They provide an anchor to guide change. The TBD relationship to ICR or CF is not perfect, and variance from this relationship is expected. The ICR and CF relationship is tight and would be unlikely to deviate greatly from ICR = CF/4.5 or ICR × 4.5 = CF.

2. ***Reduction of error.*** Every step in determining dose parameters has an error, and total error is equal to the sum of all errors. Self-monitoring of blood glucose has an error of ±10–20%, insulin effect of ±10%, counting CHOs of ±20%, etc. If any error can be minimized, do it. Thus, the diet for structured professional CGM is fixed, and patients are encouraged to weigh and measure food.

3. ***Conservative approximation.*** Although we have attempted to reduce errors, it is still inherent in our calculations. In order not to overestimate the insulin dose, we use a conservative approach to the

analytics in CGM adjustments. The formulas to be presented will tend to underestimate the dosing parameter change.

4. ***Delayed insulin action.*** The glucose-lowering effect of a bolus of insulin or an increase in basal rate is not immediate. When it is felt depends on the amount of insulin bolus or basal rate increase. **Figure 2** demonstrates the pharmacodynamics of various bolus sizes of the rapid-acting insulin analog, glulisine (same for the other rapid-acting analogs, i.e., lispro and aspart). Note that the peak action occurs nearly 2 h after the bolus. Also note that the more insulin is injected, the later the peak and the longer the duration of action. The same holds for the onset of peak action after raising the basal rate.

5. ***Morning hyperglycemia (the dawn phenomenon).***[14] Especially in those patients with complete loss of beta-cell function (undetectable C-peptide levels), the glucose level rises around 0400–0600 hours, peaks at 0900–1000 hours and falls to baseline by 1200–1400 hours. Although the cause may still be unresolved in some minds, it appears that increases in growth hormone during the early morning hours give rise to a later morning increase in hepatic glucose production. Part of this dawn phenomenon coincides with the first meal of the day's postprandial hyperglycemia. This potential confusion can be clarified by omitting the breakfast meal to evaluate the basal glucose during this period. Once revealed, only by raising the basal rate hour(s) before the morning rise in glucose can one abort the phenomenon, and larger meal boluses at breakfast may not be needed.

Overview of Structured Professional CGM Process

Step 1: Patient Selection

Although there are advantages in knowing the basal rates and bolus dosing factors, there are situations in which the study should be delayed or not done. These would be the following:

1. Patient could not adhere to performing the monitoring, wearing the sensor, returning daily to the clinic, eating within the dietary restrictions, following instructions, etc.

2. Temporary fluctuations in insulin sensitivity such as infection, short-course treatment with glucocorticoids, failing renal function, and others.

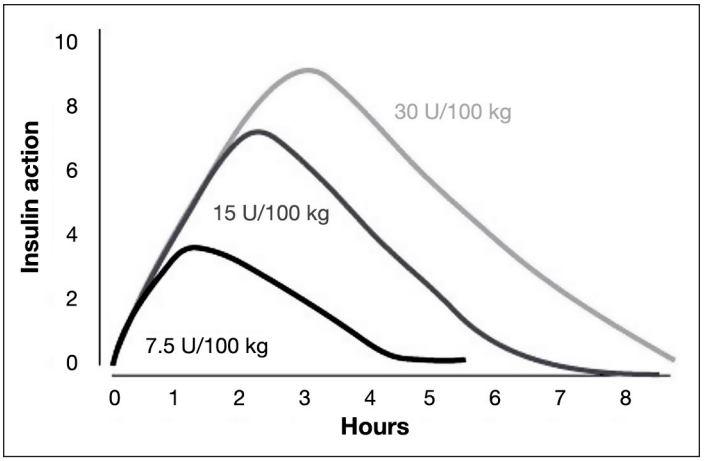

Figure 2. Comparison of pharmacodynamic effects of bolus insulin glulisine in increasing doses.[13] A similar response is true of all three of the rapid-acting analog insulins: insulin lispro, aspart, and glulisine.

Table 7.
Setting Insulin Action Time

Insulin action time sets the insulin-on-board formula in bolus estimators. As a rule-of-thumb,

Average size of bolus	Insulin action time
2 units	3 h
10 units	5 h
20 units	7 h

Remember, these are approximate and may vary from patient to patient. (Estimated from Becker and colleagues.)[13]

Before starting a study, review with patients what the procedure is and what is expected.

Step 2: Patient Preparation

- ***Diet***

  During the time of the titration, the diet is constant. This means the following:

  1. Isocaloric to avoid weight change with its effect on insulin sensitivity;

  2. Constant with regard to the composition of CHOs, fats, and protein;

  3. Constant with regard to the meal size for time of day;

  4. Constant with the same meal for that time of day;

  5. Food carefully measured for volume and weight;

  6. Meal omissions for assessments of the basal glucose control for that time of day;

7. All hypoglycemia is treated with 4 g glucose tablets because they are more quantifiable for this analytic method. They replace exactly what is missing, which is the glucose. Also, they do not taste that good so they will not be abused!

We have divided caloric-size preplanned meals for 1200, 1500, 1800, 2100, and 2400 calories.

- *SMBG*

It is important for SMBG to be accurate because CGM is calibrated by the SMBG. At times, one must rely on the SMBG because of failure of CGM, and it may be used for confirmation of CGM with a 7- or 8-point SMBG. In pharmaceutical trials, the Food and Drug Administration accepts SMBG data over CGM.

The following are utilized to ensure accurate SMBG:

1. Patient demonstrates proper technique;
2. Replace patient's meter with a new meter to guarantee battery and proper time and date;
3. The meter is properly coded, if needed;
4. Patient is not using outdated strips.

- *Glucose Targets*

Because of insulin action fluctuations and the error in glucose measurements, targets are given in a range. These ranges are in the following table (**Table 8**).

Of course, in certain situations, the targets should be raised to avoid hypoglycemia if there is no need for tighter control (see **Table 9**) These conditions would be the following:[15]

1. Very young and old (inability of patients to contribute to their own care and the danger of hypoglycemia);
2. Severe hypoglycemia (hypoglycemia unawareness, requiring that the targets should be set higher until the unawareness is resolved);
3. Shortened life expectancy (long-term complications that are related to hyperglycemia are not relevant);

Table 8.
Glucose Targets[15]

Area	Target	Target range
Fasting or premeal	100 mg/dl	70–130 mg/dl
Postmeal, 2–4 h	140 mg/dl	100–180 mg/dl

Table 9.
Setting Target Glucose for Bolus Estimator

Setting the glucose target on the bolus estimator allows the bolus estimator to calculate the bolus dose for a correction of glucose. The following is a guide derived from our clinical experience:

Clinical situation	Target
No extenuating circumstances	100 mg/dl
Hypoglycemic unawareness	120–150 mg/dl
Significant morbidity with hypoglycemia	150–180 mg/dl

4. Advanced micro/macrovascular complications (acutely lowering the glucose level into the target range may aggravate the complication);
5. Extensive comorbidities so that a goal of <7.0% would be difficult to achieve (the patient's social, cultural, financial, or psychological situation would not allow the extra effort to control glucose).

- *Insulin Injection/Infusion*

It is also important to have the patient demonstrate a proper insulin injection and, if using an infusion set, set insertion.

1. Is the insulin expired? If unsure, give the patient a new insulin vial.
2. Inspect the insertion/injection sites. Look for lipohypertrophy or palpate for nodular induration from chronic site overuse. Such will lead to decreased and/or variable insulin absorption.
3. Have the patient demonstrate the proper injection or insertion technique.
4. Set the bolus on standard and not extended or combination until the dosing parameters are set. Individual bolus forms may help determine how fast the glucose level returns to target.
5. Review with the patient the symptoms, significance, and treatment of hypoglycemia.

- ***Diary***

  Of the tools used in assessing glucose control, one of the most important is the patient's diary. In this diary, the patient records the SMBG, meals eaten (with weight/volume), insulin boluses, and hypoglycemic treatments, which are always treated with glucose tablets. Instructions from the HCP to the patient are also included in the diary such as which meals to skip.

  The diary form used is the same as offered by iPro (Medtronic, Northridge, California) and can be obtained from them.

- ***Basal Testing***

  Our first priority is to establish basal glucose control. This is not to say that one cannot contemporaneously assess the ICR and CF individually. To check a true basal glucose, one must wait ≥4 h after the meal. In order to evaluate the basal glucose, meals must be omitted. A low carb meal has been compared with a meal omission.[16] The results are depicted in **Figure 3**.

  As one can see, meal omission does not appear to affect basal glucose but a low CHO meal is associated with an average increase of 50 mg/dl. This increase could be from the small amount of CHOs in the meal (<10% content of the meal) or meal protein stimulation of hepatic glucose output assisted by the meal fat content delaying cellular glucose uptake.

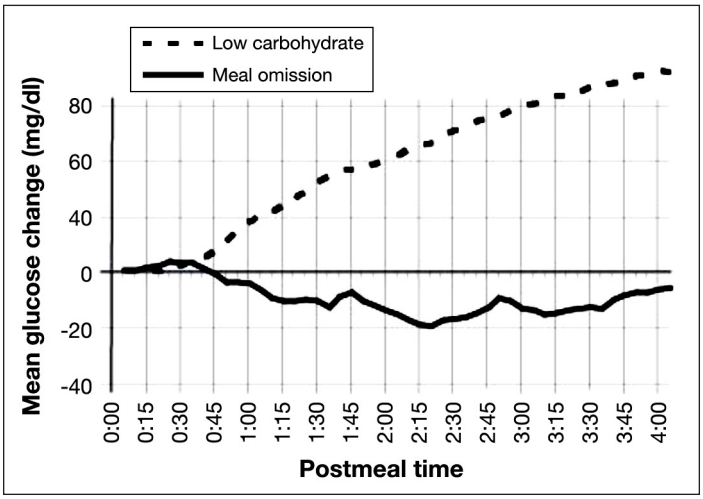

Figure 3. A randomized crossover study of four pump-treated T1DM patients on one omitted meal or one low CHO meal/day each. The means for the three postmeal periods of the day are shown.[16]

With basal testing, only one meal a day is omitted. We recommend that the order of meal omissions be supper, lunch, and then breakfast. If the basal glucose target is not reached or confirmed, this schedule is repeated.

Step 3: Reset Current Dosing Parameters

A sensor's life is limited. To get the most from a sensor, start the assessment with dosing that is close to where you will end. If the basal rate or bolus dosing factors are far off, needless time will be wasted. Therefore, before starting, we reevaluate the current dosing using the NEW formulas and adjust accordingly. Using the patient's current dosing or our changed dosing, we begin CGM titration immediately.

- ***Basal Rate***

  When a patient is placed on the study's 50% carbohydrate diet, the TBD should be 40% of TDD. If the TBD/TDD is <0.30 or >0.50, consider changing the ratio to 0.4. The reasons why a ratio could be higher than 0.4 are the following:

  1. Deliberate underbolus dosing to avoid hypoglycemia, therefore resulting in a reduced total bolus dose;

  2. Using nonfasting BG to titrate, therefore increasing the basal rate;

  3. Increasing basal rate is easier than dealing with the complexities of meal boluses.

  When basal rate is carefully titrated, rarely should a patient have more than five basal rates changes a day.[7] The average is 2.6 changes a day. If there are more than five changes, reduce to less than six. For example, a patient is on the following basal rates: At 2400 hours, 0.3 U/h; 0200 hours, 0.4 U/h; 0400 hours, 0.6 U/h; 0600 hours, 0.8 U/h; 0800 hours, 0.6 U/h; 1000 hours, 0.4 U/h, etc. Change to the following or something similar: 2400 hours, 0.35 U/h, 0400 hours, 0.7 U/h, and 1000 hours, 0.5 U/h.

  If a patient is changing from multiple daily injections (MDI) to a pump, there are two ways of setting the initial basal rate:

  1. Set one single basal rate for the entire 24 h. Target glucose should be achieved at least during part of the day (usually in the afternoon).

The advantage of this method is that it is easier to spot and correct for the dawn phenomenon. This is how the rate is set:

a. Calculate the TBD using clinical judgment, weight [0.2 × weight (kg) = TBD] and/or TDD (0.4 × TDD = TBD).

b. Then, compute the average hourly rate (TBD/24 h = average hourly rate).

c. Then, use 80% of this rate (0.8 × average hourly rate).

d. If the patient has T1DM and minimal insulin secretion, e.g., C-peptide < 0.5 mg/ml, expect the dawn phenomenon to occur. Usually, the glucose begins to rise at 0400–0600 hours, peaks at 0900–1000 hours at 200–300 mg/dl, and returns to normal at 1200–1400 hours.

2. Start with two rates. The advantage of this method is that the basal rate will be closer to the eventual rate required. This is how the rates are set:

a. Calculate the average hourly rate as described earlier.

b. Start one rate at 1.4 × the average, 1 h after the usual sleep time, and run for 8 h.

c. Start the second rate at 0.8 × the average hourly basal rate and run for the rest of the 24 h.

- ***ICR/CF***

There is a linear relationship between the total meal CHO content (range from 20 to 188 g) and the amount of bolus insulin to maintain target glucose postmeal.[17–19] The meal fiber content[19] and glycemic index[19,20] do not appear to alter the bolus dosing and therefore are not included in the bolus calculation. Although meal fat content may not have a role, meal protein does have a small one, about a 20–30% increase in bolus dose requirement.[21,22]

Unfortunately, there is both underestimation and error in patients' estimation of meal content of CHOs. In children with T1DM, Bishop and colleagues[23] found that only 23% of patients estimated the CHO content within 10 g/meal. In adults, Rabasa-Lhoret and colleagues[19] found that only 85.2% of their nine T1DM patients calculated meal CHO content within 15% of a computer-generated calculation. One of our studies[24] indicated that well-trained, experienced pump-treated T1DM patients vary about 10% in their estimate, and their estimate is usually 10% lower than the actual CHO content. The lessons from these studies are that we need to continually educate the patient on the importance of CHO counting, emphasize weighing and measuring food, and rely on the pump bolus calculator.

As stated earlier, there is a relationship between dosing factors: 100/TBD = ICR = CF/4.5. If the patient's ICR exceeds 30% of that calculated by 100/TBD = ICR, one could assume that it is probable that one of the values is wrong 70% of the time. If it is, we would change the ICR. If the ratio of the existing bolus dosing factors exceeds 15% difference in ICR = CF/4.5, then there is a 70% chance that one of these factors is in error. Choose the factor that is closest to the relationship to TBD, e.g., 100/TBD = ICR or 450/TBD = CF, and change the other to reflect the ratio of ICR = CF/4.5.

Step 4: Begin the CGM-Directed Titration

- ***CGM***

Continuous glucose monitoring provides 288 glucose readings each day and thus provides insight into nocturnal and postmeal glucose excursions not possible with the usual frequency of SMBG. In addition, the mere fact of rousing to check a BG by finger prick will be enough to elevate glucose and thus provide a falsely elevated reading. However, there are some shortcomings of CGM (see **Table 10**).

1. ***Immediately after initiating CGM.*** After the sensor needle is inserted into the subcutaneous tissue, a tissue reaction occurs around the sensor. This may interfere with the initial reading while the sensor is "settling down." This period

Table 10.
Important Factors for the Calibration Blood Glucose

1. Calibration SMBG: Consider using three simultaneous blood glucose measurements and poll the results, i.e., average the two that are closest together.
2. Select SMBG calibration times in which the glucose is most stable, i.e., usually preceding a meal.
3. Spread the times of calibration SMBG throughout the day including, when possible, at night.

may last hours but, in our experience, occasionally lasts a couple of days. During this period, there will be poor correlation between the sensor reading and a simultaneous BG.

2. ***Near the end of the sensor's life*** (5–7 days with the iPro). The sensor may stop functioning due to the exhaustion of the sensor-core glucose oxidase or due to the progressive accumulation of tissue reaction at the sensor, called biofouling. This can be recognized as a lack of signal output from the sensor.

3. ***During the sensing.***

   a. Poor SMBG calibration. Continuous glucose monitoring data cannot be better than the accuracy of the calibrating BG. Therefore, patients should wash their hands before testing, use proper technique, and be sure that the BG test is done during a stable period of BG change (before meals). It has been shown that more than 50% of CGM errors are due to poor BG calibration.

   b. Tissue-blood glucose interface/delay. CGM measures interstitial glucose, and SMBG measures arterialized capillary (fingertip) blood. Glucose changes in arterial blood occur more rapidly than in interstitial blood. During rising or falling glucose, the interstitial values will lag by about 10 min.

   c. Sensor movement. Despite proper taping, we have seen unphysiological swings in the CGM glucose tracing. These changes are >50% of the mean glucose level and make interpretation difficult. These changes could be caused by debris on the connectors of the sensor or by physical motion of the sensor during patient movement. If this is the case, the sensors must be replaced. We find that about 10% of sensors fail before the fifth sensor day.

Basal Rate Changes

The increase in BG from 2300 hours to peak at about 0400 hours occurs for 2 consecutive days (see **Figures 4** and **5**). It is best to have 3 consecutive days of similar change to confirm this increase but many times we do not. Assume that the target BG is 100 mg/dl. The peak glucose is about 100 mg/dl over target.

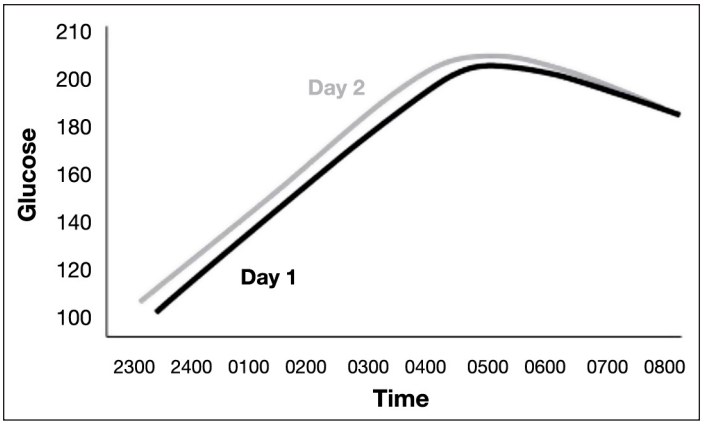

Figure 4. An example of elevated basal glucose.

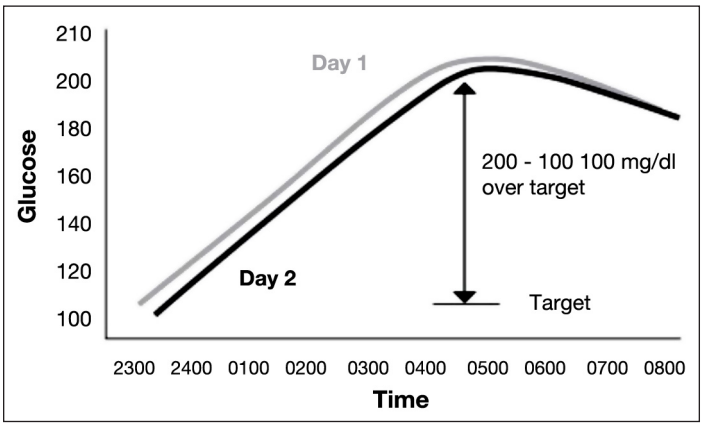

Figure 5. The increase in glucose.

To estimate the increase in basal rate to compensate for this increase, divide the glucose increase by the CF and then divide by 5: [(Δ Glucose/CF)/5 = change in rate], where 5 reflects the insulin action time or the average duration of action of the rapid-acting insulin. In this case, let us assume the CF is 50. The change in basal rate would then be estimated to be [(200 – 100 mg/dl)/50 mg/U] /5 h = 0.4 U/h.

Next, we calculate when to begin and end the change in the rate. The timing depends on the degree of rate increase. In a study of the pharmacodynamics of basal insulin infusion by pump, Heinemann and colleagues[25] reported that the duration of the delay increases with the degree of rate increase. **Table 11** gives a rough guide.

Using this information, one would alter the rate according to the degree of change. As noted in **Figure 6**, the glucose change began at 2300 hours and peaked at 0400 hours. Since the change is <0.5 U/h, you would change the rate 1 h before it began, at 2200 hours, and return to the prior basal rate 1h before the peak, at 0300 hours.

Now, let us look at correcting for a low basal glucose.

In this case (see **Figure 7**), not only did the glucose fall below target (assume target is 100 mg/dl) but the patient was required to take five 4 g glucose tablets (5 × 4 = 20 g). Also note that this was over 2 consecutive days. Again, the more consistent results, the more reliable the dosing conclusions.

To calculate basal rate changes, add the basal rate change calculated from the lower glucose and the amount of CHOs ingested. The glucose fell to about 50 mg/dl, and the target is 100 mg/dl. So, using the same formula as with a high glucose and using the same CF of 50 mg/dl/U, the calculation would be the following: basal rate change = [(100 – 50 mg/dl)/50 mg/dl/U]/5 h = 0.2 U/h.

Next, add the correction based on the grams of CHOs eaten (20 g total) and let us assume the ICR is 10 g/U. The additional basal rate adjustment would be the following: basal rate change = [20 g/10 g/U]/5 h = 0.4 U/h.

The total adjustment in basal rate would be 0.2 + 0.4 U/h = 0.6 U/h. If the initial basal rate was 1.0 U/h, the new basal rate would be 1.0 – 0.6 U/h = 0.4 U/h.

The drop in glucose started at 2400 hours and stopped at 0400 hours. Using the suggested delay in **Table 11** for rate changes of 0.5 – 1.0 U/h, one would start the new rate of 0.4 U/h at 2200 hours and end this rate at 0200 hours.

ICR and CF

The bolus dosing factors are closely related. If you establish one, the other one can be calculated by the formula ICR = CF/4.5 or CF = 4.5 × ICR. If the glucose is at target before a meal and the insulin bolus for the CHOs, the grams of CHOs consumed, and the glucose level following the meal are known, then the ICR can be identified. In the example in **Figure 8**, the patient eats 80 g of CHOs after a bolus of 10 U. The glucose prior to the meal is at target, 100 mg/dl, but the glucose postmeal is not less than 200 during the 4 h postmeal period. The initial ICR is 8 g/U.

First, calculate the additional insulin that was needed for this meal. Assume that the CF is 50 mg/dl/U. The difference between the height of the postmeal glucose

Table 11.
Approximate Time of Onset or Offset with Basal Rate Changes. Based on Heinemann and Colleagues[25]

Rate change in basal insulin	Hour(s) delay
<0.5 U/h	1 h
0.5 to 1.0 U/h	2 h
>1.0 U/h	≥ 3 h

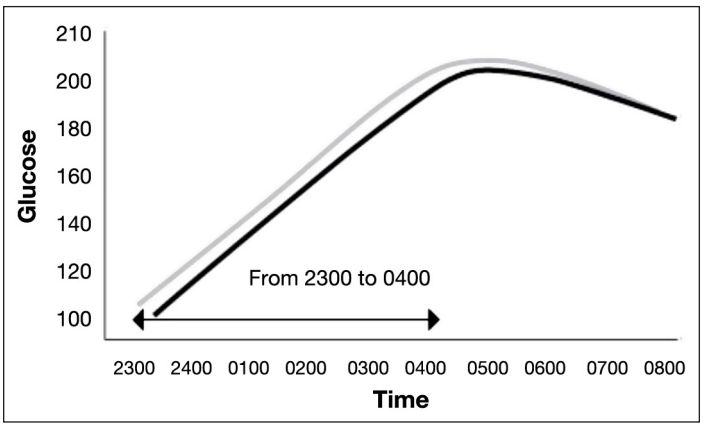

Figure 6. Timing of basal rate change. Because the glucose increase started at 2300 hours and peaked at 0400 hours, the rate increase would be timed from 2200 to 0300 hours.

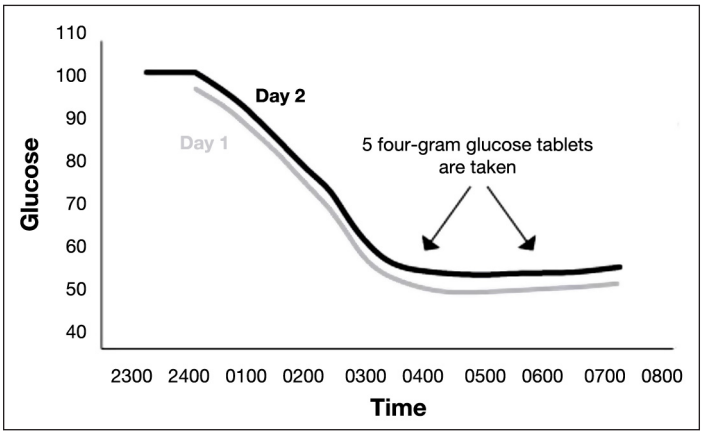

Figure 7. Example of a below-target basal glucose. Note the fall in glucose to about 50 mg/dl and the taking of five 4 g glucose tablets.

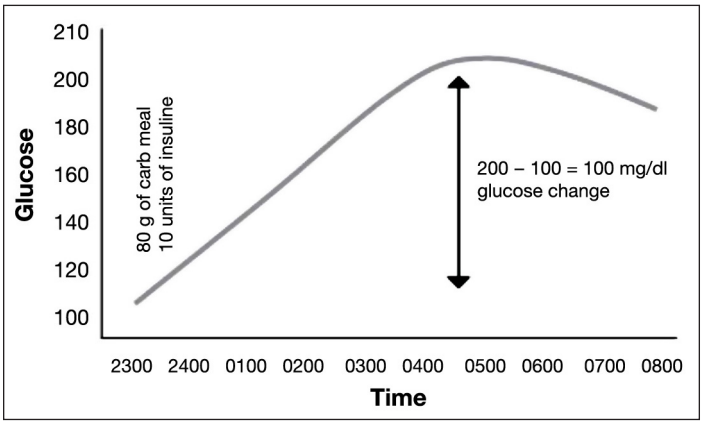

Figure 8. An example of a calculation of ICR.

and target is 100 mg/dl (200 – 100 mg/dl = 100 mg/dl). Then, divide the CF into the difference. The additional insulin required was 2 U (100 mg/dl/50 mg/dl/U). Now, add the insulin that was given to the additional needed (10 U + 2 U = 12 U). To calculate, the new ICR = 80 g CHO/12 U = 6.7 g/U. Because of the close relationship, one would change the CF by the formula CF = 4.5 × ICR. In this case, 6.7 × 4.5 = about 30 mg/dl/U.

If one has the situation of episodic hyperglycemia unrelated to a meal, one can assess the CF. Let us use the following example in **Figure 9**.

In this case, let us assume that a 4 U bolus was given and the CF was 50 mg/dl/U. The bolus was calculated to be 300 – 100 (target) mg/dl/50 mg/dl/U (CF) = 4 U. However, the glucose level dropped to only 200 mg/dl. The additional insulin needed could be double the dose since only half the goal glucose was reached. The glucose response to insulin is linear. However, we chose to calculate the change in a conservative manner. The additional insulin = 200 mg/dl – 100 mg/dl (target)/50 mg/dl/U (current CF) = 2 U. Therefore, 2 U + 4 U = 6 U would be needed. To recalculate, the CF = 300 mg/dl (initial glucose) – 100 mg/dl (target)/6 U = 33 mg/dl/U.

Bolus Sculpting

Perhaps the most important factor in bolus dosing is that the patient actually gives his or her bolus, especially before the meal. However, if we can assume that the patient will do so, then we can utilize the bolus form: standard bolus (or all at once), extended over time, or a combination (some of each of the former two bolus forms). We define the proper bolus dose as that which returns the glucose within ±20% of the premeal or target glucose within 2–4 h. The optimum form may help to achieve control for the entire 4 h postmeal period.

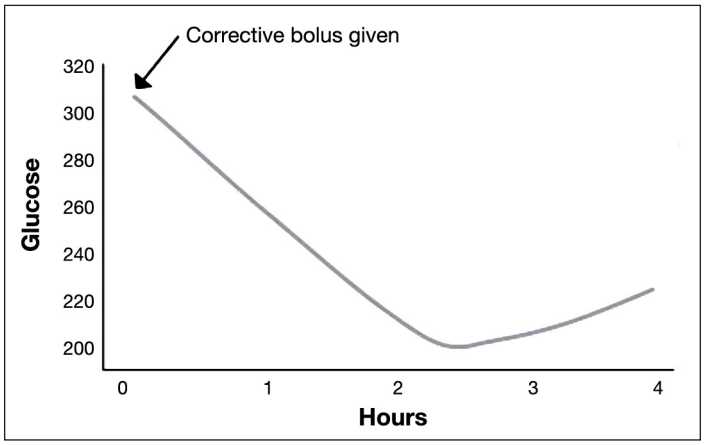

Figure 9. Example of a CF calculation.

In our clinic, we recommend the combination bolus for most average meals with a mixture of CHOs, fats, and protein. Further, we set the split between the standard and the extended component at 50:50 or 70:30 and use the 3 h extended bolus. For meals purely of CHO with a high glycemic index, we would use a standard or all-at-once bolus. Meals that are protracted with a low CHO intake per hour—grazing—would be a case for an extended bolus. Heinemann[26] has appropriately pointed out that none of the various bolus forms have been vigorously proven to be better than a standard bolus.

The major task in achieving postmeal control is dampening hepatic glucose production. Glucagon, the polypeptide hormone from the alpha cells of the pancreas, is not suppressed and actually is elevated in both T1DM and type 2 diabetes mellitus (T2DM). Glucagon, in turn, is a major stimulus to hepatic glucose production, which is undesirable in the postmeal period. Insulin will suppress hepatic glucose but it must be given early, before the meal and in good amount. Very rapidly acting insulins are being developed. In addition, new classes of medications that suppress glucagon and thus liver glucose production, e.g., glucagon-like peptide-1 agonists and amylinomimetics (pramlintide), are available. Pramlintide is indicated for T1DM for premeal treatment. It suppresses hepatic glucose release, delays gastric emptying, and reduces hunger. Because of possible hypoglycemia due to the concurrent insulin bolus, a 50% reduction in bolus amount is recommended. Upon initiating pramlintide at the starting dose of 15 μg before meals, we[27] have found that a reduction is not needed if the patient is CGM-titrated and the bolus is given in an extended form. When comparing various bolus forms[28] (see **Figure 10**), the extended form appears to provide the best postmeal control without the early meal hypoglycemia threat of other bolus forms.

Conclusions

In stable adult patients, dosing parameters are constant and can be identified by using structured professional CGM. Setting these dosing parameters in the patient's pump does not mean that the patient will have perfect glucose control. Patients will continue to be patients, and their glucose will wander with the variations of the day. Personal CGM, if used most of the time, will moderate these glucose excursions.

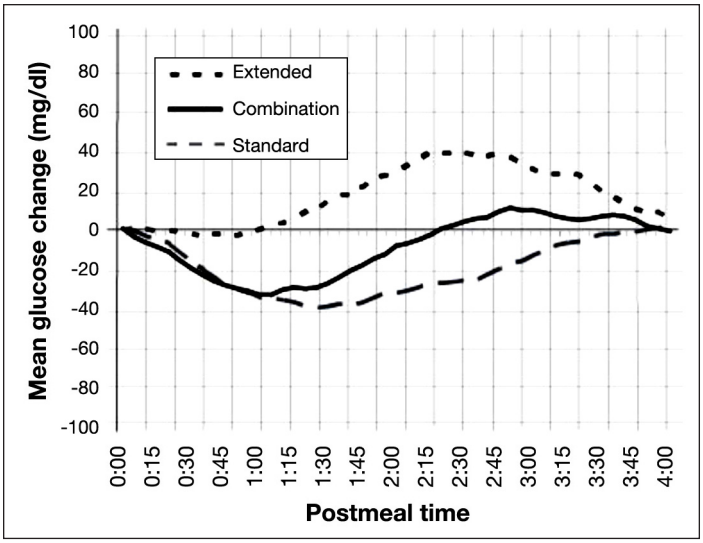

Figure 10. Comparison of three bolus forms the postmeal CGM glucose on pump-treated, pramlintide-treated (60 μg, before meals, TIDM) T1DM patients.[28]

So, if a patient tells you, "I don't have the slightest idea where my pump setting should be," apply what you have learned from this paper to help the patient be more secure in knowing approximately where his or her settings should be.

In this article, we did not discuss applications of these formulas and methods to dosing in MDI-treated T1DM nor T2DM. We are assessing these new applications. Also, remember that many of these recommendations and formulas are based on clinical experience or small studies. There is still a great need for evaluating the art of insulin dosing scientifically,[26] even 90 years after Banting first used insulin.

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