A Safe and Simple Algorithm for Adding and Adjusting Mealtime Insulin to Basal-Only Therapy

Mary L. Johnson,1 Richard M. Bergenstal,1 Brian L. Levy,2 and Darlene M. Dreon2

Numerous studies have shown that early initiation of intensive treatment significantly improves β-cell function and long-term glycemic control in individuals with type 2 diabetes (1–4). However, despite national and international clinical guidelines that recommend escalation of therapy if individualized glycemic targets are not met within 3–6 months (5), transition to basal-only insulin therapy and then to intensive insulin management is often delayed despite significant and sustained hyperglycemia. As reported by Khunti et al. (6), the time to treatment intensification from noninsulin medications to basal-only insulin therapy is often delayed by up to 7 years in adults with type 2 diabetes with A1C levels $\geq 8.0\%$, and the average time to transition of patients from basal-only insulin to basal-plus-mealtime insulin is 3.2 years.

Failure to intensify therapy when clinically indicated, often referred to as “therapeutic inertia,” can lead to extended periods of hyperglycemia and the potential for poor microvascular and macrovascular outcomes (7). Because initiating and titrating insulin is often complex (8), many clinicians are reluctant to intensify insulin therapy in their patients. The primary obstacles to timely transition to intensive insulin therapy are inadequate knowledge/training, lack of confidence in optimizing insulin regimens, time and resource constraints, and suboptimal treatment adherence (9–15).

In many situations, particularly in primary care settings, clinicians lack ready access to support staff (e.g., diabetes educators) who can deliver the necessary education and training to patients (15). For patients, key factors affecting treatment adherence include the need for multiple injections, understanding of the purpose and importance of their medications, depression, diabetes-related distress, low treatment satisfaction, side effects, poor self-efficacy, cost, and overall burden of daily self-management with insulin therapy (16,17), all of which pose significant barriers to insulin intensification for both patients and clinicians (17,18). Calculating accurate mealtime insulin doses is a common challenge for patients because of inadequate training (19,20). Deficits in numeracy are common among individuals with diabetes, strongly associated with poor glycemic control (21–24), and compounded by low competency in carbohydrate counting (20,25,26).

Given the growing prevalence of diabetes (27) and the increasing proportion of adults with type 2 diabetes who are not meeting their glycemic targets (28–32), new approaches to initiating and intensifying insulin therapy in type 2 diabetes are needed. In this article, we describe a safe and simple insulin titration algorithm that addresses many of the obstacles that clinicians and patients encounter when adding mealtime insulin to a basal-only insulin regimen.

Basal and Mealtime Insulin Titration Algorithm

Concept

The algorithm follows a simple, systematic approach that facilitates simultaneous daily mealtime insulin adjustments with weekly adjustments of both mealtime and basal insulin doses. It should be noted that “mealtime” in this algorithm refers to rapid-acting insulin and “basal” refers to 24-hour long-acting basal insulin.

Patients are asked to check their premeal glucose at each meal and their bedtime glucose with traditional fingerstick blood glucose monitoring (BGM) or, if they are using continuous glucose monitoring (CGM), use the premeal/bedtime glucose value displayed in their CGM reader or smartphone app. This novel approach requires neither carbohydrate counting nor postmeal

1International Diabetes Center, Park Nicollet, Minneapolis, MN; 2Calibra Medical, Johnson & Johnson Diabetes Care Companies, Wayne, PA

Corresponding author: Mary L. Johnson, Mary.L.Johnson@ParkNicollet.com

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glucose testing. Throughout the week, patients use the premeal and bedtime blood glucose values and meal size to adjust doses at each meal. At the end of each week, patients review the data retrospectively to make adjustments in their basal insulin doses and to calculate changes in the “starting” doses for each meal, from which they will make their premeal adjustments. Using this approach, individuals with type 2 diabetes benefit from safe and effective physiologic therapy for achieving optimal glycemic control (33,34).

Evidence of Safety and Efficacy

The safety and efficacy of the basal and mealtime insulin titration algorithm was demonstrated in a 48-week, randomized, multicenter, multinational open-label, parallel, two-arm interventional trial involving 278 adults with type 2 diabetes, A1C 7.5–11%, who were currently treated with basal-only insulin therapy (35). Inclusion required that participants be taking ≥0.3 units/kg/day of insulin, an indication that addition of mealtime insulin was needed. Participants were randomized (1:1) to one of two treatment arms that used different insulin delivery methods to add mealtime insulin before all meals to existing evening administration of insulin glargine: 139 participants used the CeQur Simplicity patch insulin delivery device (CeQur, Marlborough, MA, formerly of Calibra Medical, Wayne, PA) with insulin aspart, and 139 used the NovoRapid Flex Pen with insulin aspart (Novo Nordisk Pharmaceuticals, Plainsboro, NJ).

Unlike traditional insulin pumps, the CeQur Simplicity is designed for manual administration of mealtime insulin only. The small wearable device (65 × 35 × 8 mm) can be worn on the abdomen for up to 3 days (36). The patch holds up to 200 units of mealtime insulin and delivers a 2-unit dose via a subcutaneous cannula with each simultaneous click of two buttons on either side of the device. For example, to deliver 10 units of mealtime insulin before a meal, a patient would click the buttons five times.

Participants were instructed on the details of using the algorithm by going through a sample participant’s weekly diary and were given their own diary, which contained all the elements of the algorithm, to complete. After the first week of their new insulin regimen, they had a phone visit with a member of the study team who reviewed their diary and provided any additional training needed before they changed their baseline doses for the next week. The weekly brief touchpoints continued through the first month and then occurred biweekly during the second month, with the expectation that patients would continue to implement weekly titrations. At each subsequent protocol visit, the diaries were reviewed with patients.

Mean A1C at baseline was 8.7% for the patch group and 8.6% for the pen group. As early as week 12, participants in both groups achieved a significant reduction in A1C from baseline (−1.4%, \(P < 0.0001\)), with an even greater reduction by week 24 (−1.7 and −1.6% from baseline, respectively; \(P < 0.0001\)), which was sustained through week 44. Importantly, the incidence of severe hypoglycemia was extremely low, with only three incidents reported in each study group. In a subgroup analysis of 97 participants who wore a CGM device in blinded mode (37), investigators assessed glycemic control using the recommended CGM metrics for percentage of time in range (TIR; >70% at 70–180 mg/dL), time above range (TAR; <25% at >180 mg/dL), and time below range (TBR; <4% at <70 mg/dL) (38). At week 24, both groups had increased their TIR (to 74.1 and 75.2%, respectively) and had marked reductions in TAR (21.1 and 19.7%, respectively) but with a slight increase in TBR (4.7 and 5.1%, respectively) (all \(P < 0.0001\)). As expected, the addition of mealtime insulin resulted in weight gain in both groups by 24 weeks (3.9 and 4.0 kg, respectively) and by 44 weeks (5.1 and 5.3 kg, respectively).

Calculating Starting Doses for Basal and Mealtime Insulin

The first step in the process of transitioning from a basal-only to a basal and mealtime insulin regimen is determining a patient’s starting insulin doses. To do this, first divide the patient’s current total daily dose (TDD) of basal insulin in half. Half of the TDD is given as the starting basal insulin dose, administered in the evening. The other half is given as the starting mealtime insulin dose, split evenly among meals. Figure 1 presents an example of how the starting doses are calculated with a patient currently treated with 48 units of long-acting glargine insulin. In patients with A1C <9.0%, reduce the TDD by 10% before splitting it into basal and mealtime insulin doses to decrease the potential for hypoglycemia.

Daily Mealtime Insulin Dose Adjustments

Mealtime insulin dose adjustments may be made for every meal and any snack. These adjustments can be to either reduce insulin (subtract), increase insulin (add), or make no adjustment (no change) to the current prescribed dose based on the patient’s premeal glucose value and estimated meal size: smaller than usual (small), usual size (usual), or larger than usual (large).
(Table 1). Note that we specifically chose not to use the term “medium” because patients’ definitions of small, medium, and large can vary dramatically, whereas comparing a meal size to smaller than usual or larger than usual is customized to the individual. The meal size was also not based on the carbohydrate content of the meal because participants were not instructed in carbohydrate counting; rather, they were simply instructed in what foods contained carbohydrates to be able to treat any possible hypoglycemia.

The example presented in Figure 2 illustrates how a morning mealtime insulin dose would be calculated based on a usual mealtime dose (8 units).

**Weekly Basal Insulin Dose Adjustments**

Basal insulin dose adjustments are made at the end of each week and used for the nightly bedtime basal insulin dose throughout the next week. The dose adjustments are made after a retrospective review of morning glucose results recorded during the prior week. As shown in Table 2, these adjustments are made based on glucose values that indicate an increased risk for hypoglycemia or hyperglycemia. The example presented in Figure 3 illustrates how the basal insulin dose is calculated for the following week.

**Weekly Mealtime Insulin Dose Adjustments**

Mealtime insulin dose adjustments are also made at the end of each week and used for each subsequent week. These are calculated based on the prior week’s midday mealtime (for morning meal), evening mealtime (for midday meal), and bedtime glucose (for evening meal) patterns from the previous week as shown in Table 3. These newly calculated doses are then adjusted for each meal during the week based on meal size and glucose level at the time of the meal (see daily mealtime insulin dose adjustments above).

The example presented in Figure 4 illustrates how mealtime starting doses are calculated for the following week. In this case, we have calculated the new dose for the morning meal using the glucose values from the current week’s midday meal. The same process is used for all meals.

**Considerations for Implementing the Algorithm**

When introducing the algorithm to patients, it is important to explain that achieving glycemic targets is a gradual process and that they should not expect to see immediate results. For the algorithm to work, patients must adhere to the dose recommendations provided.

| Adjustment for Premeal Glucose | Adjustment for Meal/Snack Size |
|-------------------------------|--------------------------------|
| **Glucose, mg/dL**            | **Meal/ Snack Size**           |
| <70                           | Subtract 2 units               |
| 70–180                        | No change                      |
| >180                          | Add 2 units                    |
| Not applicable                |                               |
| Not applicable                |                               |

These cut points vary slightly from those used in the study to align with new consensus guidelines (35).
patients experience sustained hypoglycemia or hyperglycemia despite following the dose adjustment schedule, they should contact their health care team. Because some patients may find that making their daily mealtime adjustments becomes second nature and may stop tracking their blood glucose results and doses, it is important that clinicians emphasize that these data are needed for appropriate weekly adjustments to both their premeal starting mealtime dose adjustments and basal insulin dose adjustments. The protocol specifies that a weekly change can be made only if there are a minimum of three blood glucose measurements obtained that would affect that specific time point (e.g., three blood glucose measurements before evening meals would allow a change in the next week’s midday mealtime insulin starting dose). A blank diary for tracking adjustments is provided in Supplementary Materials.

Discussion
Insulin regimens that use long-acting basal insulin in combination with rapid-acting insulin analogs at mealtimes provide an effective, physiological approach to achieving optimal glycemic control in people with type 2 diabetes who require insulin

### TABLE 2 Basal Insulin Dose Adjustment Based on Morning Blood Glucose Pattern From Previous Week

| Glucose Results Before Morning Meal or Upon Waking | Bedtime Basal Insulin Dose Adjustment |
|-----------------------------------------------|--------------------------------------|
| Two or more morning glucose values <70 mg/dL | Subtract 4 units                     |
| One morning glucose value <70 mg/dL           | No change                            |
| No morning glucose values <70 mg/dL AND      | Add 2 units                          |
| Three or more morning glucose values >130 mg/dL OR | OR Add 4 units                      |
| No morning glucose values <70 mg/dL AND      | No change                            |
| Three or more morning glucose values >180 mg/dL |                                       |
| If none of the above apply                    |                                      |
therapy (33,34). However, current approaches to these regimens are often too complex for both patients and clinicians.

By using individualized meal sizes (i.e., small, usual, and large) in conjunction with immediate and retrospective glucose data, the insulin titration algorithm outlined above provides a simple, holistic approach that facilitates simultaneous adjustments of mealtime and basal insulin doses. This approach not only shortens the amount of time needed to safely achieve optimal glycemic control, but also encourages persistent, simultaneous dose adjustments to maintain desired glucose levels. This strategy keeps mealtime and basal insulin in balance, thus avoiding over-insulinization with either mealtime or basal insulin, either of which can lead to hypoglycemia. For example, if patients are physically active, too much basal insulin onboard can lead to hypoglycemia during the day (39), whereas too much mealtime insulin, particularly at the evening meal, increases the risk for overnight hypoglycemia (40).

As reported, participants in both the patch and pen study groups achieved clinically and statistically significant reductions by as early as 12 weeks (~1.4%) and continued to experience improved glycemic control throughout the study through persistent use of the algorithm (35).

Moreover, this algorithm means that patients do not have to wait for their clinician to make needed dose adjustments, thereby addressing the issue of therapeutic inertia and facilitating more timely achievement of optimal glycemic control. However, it is important that clinicians and patients review the diary together to make sure patients understand what to do. Instructing patients in the use of the algorithm also creates opportunities for clinicians to learn more about initiating and adjusting mealtime insulin.

Importantly, whereas insulin therapy is generally associated with lower patient satisfaction and reduced quality of life (41), findings from our study showed high treatment adherence in both the patch and pen groups (79 and 78%, respectively) and significant improvements in several patient-reported outcome measures (35), suggesting that use of this simplified insulin titration algorithm will likely improve medication adherence in real-world settings (42).

It should be noted that participants in our study based their insulin adjustments on glucose values

![FIGURE 3 Example showing how to adjust basal insulin doses. BG, blood glucose; U, units.](image-url)
obtained from traditional fingerstick BGM. However, the algorithm can be easily applied to individuals who use CGM. In addition to eliminating the need for multiple daily fingersticks, CGM provides an additional level of safety by providing information about glucose trends, direction and velocity of changing glucose, and alerts that warn patients of current and impending adverse glycemic events. Although BGM is the most common glucose testing method currently in use by people with type 2 diabetes, with growing positive clinical trial and real-world study results of CGM in individuals with insulin-treated type 2 diabetes, use of CGM within this population continues to expand. Although the algorithm can be used regardless of glucose monitoring method (BGM or CGM), an important consideration relevant to persistent treatment adherence and quality of life is the method used for insulin delivery. Although participants in both of our study groups achieved equally significant A1C reductions, patient-reported outcomes revealed that overall satisfaction with the insulin delivery system and satisfaction with ease of use were notably higher with the patch than with the insulin pen. Differences in quality-of-life measures such as ability to dose without attracting attention, painless mealtime insulin delivery, ease of administration, and lifestyle flexibility also favored patch use. There was a significantly higher preference for using the patch device than the pen among study participants who used the patch for the full 44 weeks. A higher preference was also reported by pen users who crossed over to patch use for only 4 weeks at week 44 (35). Moreover, study clinicians also reported favorable ratings for the patch for all measures of preference. Specifically, 91.1% of health care providers preferred the patch to the pen to advance their patients with type 2 diabetes to a basal-and-mealtime-insulin regimen, and 89% reported that it took <30 minutes to train participants to use the patch (35).
Given the large and growing proportion of patients with type 2 diabetes who are not meeting their glycemic targets (28–32), innovative approaches to initiating and titrating basal-plus-mealtime insulin therapy are needed. When used in conjunction with a simplified insulin delivery technology such as a mealtime insulin patch device, this insulin algorithm may facilitate more frequent intensification of therapy and result in significant improvements in medication adherence, treatment satisfaction, patient quality of life, and clinical outcomes.

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AUTHOR CONTRIBUTIONS

All of the authors conceived the presented idea, contributed to the writing of the manuscript, and made extensive comments, criticism, and revisions to the manuscript. All reviewed and approved the final version. M.L.J. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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