



Bolus Insulin Prescribing Recommendations for Patients With Type 2 Diabetes Mellitus

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Timely initiation and titration of bolus insulin can help improve outcomes for patients with type 2 diabetes mellitus.

Individuals with type 2 diabetes mellitus (T2DM) spend between 5 and 10 years with elevated hemoglobin A_{1c} (HbA_{1c}) before initiation of insulin.¹ Once the basal insulin is initiated, the patient can go years with only adjustment of the basal insulin, resulting in over-basalization. In general, the total daily dose (TDD) of insulin should be composed of about 50% basal “background” insulin and 50% bolus “meal” insulin. When the fasting glucose readings are on target but HbA_{1c} is still above the mutually set goal range, postprandial readings need to be evaluated.

This article focuses on initiating and titrating bolus insulin in nonpregnant patients with T2DM. Before initiation of bolus insulin, it is important for the patient to be actively engaged with a diabetes educator for diabetes self-management education and support (DSME/S), including the understanding of the correct use of insulin, carbohydrate counting, and increasing physical activities. Ensuring the correct technique of insulin administration and self-monitoring of blood glucose (SMBG) is critical. A knowledge deficit of carbohydrate information can lead to uncontrolled blood glucose (BG). The authors have encountered numerous times when patients were drinking sugary beverages or consuming large amounts of “healthy” food without realizing the carbohydrate content. Therefore, treatment in concert with a registered dietitian and certified diabetes educator is highly recommended.

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INITIATION OF BOLUS INSULIN

There are 3 options of postprandial coverage with bolus insulin when a patient is taking basal insulin: basal plus, basal-bolus, or premix insulin. A possible fourth option for postprandial coverage is to add glucagon-like peptide-1 receptor agonist (GLP-1 RA), an injectable noninsulin antihyperglycemic agent, which has shown noninferior efficacy to adding bolus insulin and a favorable effect on weight with less risk of hypoglycemia.²⁻⁵ Although it can be expensive, combining GLP-1 RA to basal insulin results in lowering HbA_{1c} of 0.66 up to 1.74% (or lowering mmol/mol of 7 up to 19) from the baseline.⁶ However, adding bolus insulin may be the only option to avoid glucotoxicity and prevent further diabetes complications when the HbA_{1c} level is well above the goal range. It is usually recommended to discontinue sulfonylurea when bolus insulin is added due to the β -cell exhaustion with advancing natural history of diabetes.^{7,8}

METHOD 1: BASAL PLUS

The health care provider (HCP) needs to consider whether the patient is over-basalized when the HbA_{1c} and postprandial BG readings are still not at goal despite careful titration of basal insulin dose to > 0.5 U/kg/d.⁹ This is the time to discuss with the patient the coverage of meal-time glucose excursions. In the basal plus regimen, the prescribing provider may add 1 bolus insulin injection for the meal with the highest amount of carbohydrates or add 2 bolus injections for the most and second most meals with carbohydrates. Multiple types of bolus insulin are available in the current U.S. market (Table 1).

There are 2 ways to add bolus insulin: fixed and flexible. In the fixed regimen, the patient will take the same amount of bolus insulin regardless of premeal BG readings and carbohydrate content of the food. The authors recommend adding bolus insulin of about 4 to 6 units once or twice a day with meals, depending on the number of meals a day, carbohydrate content of the meal, current and desired degree of diabetes control, and physical activities. Another way to calculate a bolus insulin dose is to start at 0.1 U/kg if adding to the basal insulin.¹⁰ Flexible regimen allows various bolus doses based on premeal BG, carbohydrate intake, and activities. Information on this regimen, will be discussed more later.

Patient Cases

Tables 2 and 3 describe 2 patient cases. For example, patient 1 weighs 80 kg. If the prescribing HCP and patient decide to add only 1 bolus to the largest carbohydrate meal at dinnertime, then the patient may take 8 units ($80 \text{ kg} \times 0.1 \text{ U/kg/meal} = 8 \text{ units for meal}$). The patient's current insulin dose, medical comorbidities, current diabetes control status, living situations, and overall cognition also should be considered.

Imagine patient 1 is taking 14 units daily of a long-acting insulin (LAI). If the patient is taking a fairly low dose of LAI, has multiple comorbidities, recent BG log/HgA_{1c}, and lives alone but demonstrates good cognition to follow instructions, the prescriber may consider adding the bolus insulin of 4 units for dinner; thus, the bolus dose is about one-third of total basal insulin dose. However, if the patient is on 40 units of LAI and has symptoms of hyperglycemia, 6 to 8 units for the dinner is reasonable. An important point to convey to this patient is to make sure there is carbohydrate consistency. The patient's premeal BG was 137 mg/dL (7.6 mmol/L) on Monday, but it rose significantly to 313 mg/dL (17.4 mmol/L) after dinner. On Wednesday, the patient's premeal BG prior to dinner was 150 mg/dL (8.3 mmol/L); it rose to 202 mg/dL (11.2 mmol/L) after dinner, which is high but not as high as on Monday.

Multiple factors may affect this variability; for example, on Monday the patient may have consumed more than the usual amount of carbohydrates for dinner, forgot to take oral medication for dinner, or missed his/her usual after-dinner walk. Or simply, the patient may have eaten a lot less than the usual amount of carbohydrates, walked the neighborhood, or vacuumed the entire house after dinner on Wednesday. Thus, it is im-

Table 1. Pharmacokinetics of Fast/Rapid-Acting Injectable Insulins¹⁰

Insulins	Onset of Action	Peak Effect	Duration of Action	Clinical Considerations
Fasting acting				
Regular (Novolin, Humulin)	30 min	2-4 h	6-8 h	Taken 30 min prior to eating Useful in patients with gastroparesis or chronically poorly controlled diabetes
Rapid acting				
Aspart (Novolog)	≤ 15 min	1-3 h	3-5 h	Taken 0-10 min before meal
Lispro (Humalog)	≤ 15 min	1 h	2-4 h	Taken within 15 min before or immediately after a meal
Glulisine (Apidra)	≤ 15 min	1 h	3.5-4.5 h	Taken within 15 min before or within 20 min after starting a meal

perative to carefully assess the patient's lifestyle and recommend carbohydrate consistency at each meal.

A 50-year-old patient weighs 110 kg and has significantly high postprandial BG and hyperglycemic symptoms (Table 3). For this patient, the prescriber may consider 11 units ($110 \text{ kg} \times 0.1 \text{ U/kg/meal} = 11 \text{ U}$) of mealtime insulin. Basal plus is an easy way to eventually introduce the patient to a basal-bolus regimen by adding only 1 or 2 bolus injections to basal insulin. This allows the patient time to adjust to a more intensified insulin regimen.

METHOD 2: BASAL-BOLUS

When basal plus is insufficient to get the HbA_{1c} and BG readings to goal, taking bolus insulin for all main meals containing carbohydrates must be considered. This is often called basal-bolus, multiple daily injections, or intensive insulin therapy.

In order to understand the concept of basal-bolus, HCPs should consider normal physiology. The pancreas releases a constant amount of insulin, aka background insulin, to cover glucose produced by the liver to the cells between meals. In addition, a burst of insulin, aka

Table 2. Patient 1, 70-Year-Old, 80 kg

Day	Morning Fasting mg/dL (mmol/L)	Prelunch mg/dL (mmol/L)	Predinner mg/dL (mmol/L)	Bedtime mg/dL (mmol/L)
Monday	130 (7.2)		137 (7.6)	313 (17.4)
Tuesday	111 (6.2)	92 (5.1)		
Wednesday			150 (8.3)	202 (11.2)
Thursday	250 (13.9)	161 (8.9)		

Table 3. Patient 2, 50-Year-Old, 110 kg

Day	Morning Fasting mg/dL (mmol/L)	Prelunch mg/dL (mmol/L)	Predinner mg/dL (mmol/L)	Bedtime mg/dL (mmol/L)
Monday	135 (7.5)		322 (17.9)	392 (21.8)
Tuesday	120 (6.7)	342 (19.0)		
Wednesday				499 (27.7)
Thursday	142 (7.9)	302 (16.8)		

bolus insulin, to meet the blood glucose elevation from food to maintain homeostasis. In patients with T2DM, the relative amount produced by the pancreas is insufficient to meet the demand due to pancreatic exhaustion or insulin resistance. This necessitates the need to replace background and bolus insulin.⁷

The ideal final total bolus insulin amount (the sum of all meal bolus doses) should be about half the basal dosing. Calculation of starting bolus dosing can be done as in the basal plus regimen, either 4 to 6 units per meal or 0.1 U/kg/d.¹⁰ Alternatively, if the patient is on 60 units of long-acting analog and BGs are well above goal range, the prescriber could consider about 20 units of bolus dose (60 U divided by 3 meals) if the patient eats 3 routine meals a day with at least 30 g of carbohydrates, and physical activity levels are fairly consistent. If the patient eats the most carbohydrates at lunchtime, consider more bolus at lunch (ie, 18 U of bolus for breakfast and dinner and 24 U of bolus for lunch coverage). Patients need to separate the time between the bolus doses, usually a minimum of 4 hours apart, to avoid insulin stacking, which is a common reason for hypoglycemia. Insulin stacking occurs when additional quick or rapid insulin is injected when the previous insulin is still in the body or when there is insulin on board.^{8,11}

Table 4. Insulin Premixture Formulations¹²⁻¹⁶

Brand Names	Composition
Humulin 70/30	70% human insulin isophane suspension, 30% regular human insulin
Humalog Mix 75/25	25% insulin lispro, 75% insulin lispro protamine suspension
Humalog Mix 50/50	50% insulin lispro, 50% insulin lispro protamine suspension
Novolin 70/30	70% human insulin isophane suspension, 30% regular human insulin
NovoLog Mix 70/30	70% protamine-crystallized insulin aspart, 30% insulin aspart

Typically, bolus analogs stay in the body for about 4 to 6 hours, thus necessitating separation of the doses at least 4 hours apart. Patients sometimes inject more bolus insulin after high postprandial readings, which can result in insulin stacking. In some cases, the patient may misunderstand and take mealtime insulin at a scheduled time instead of at the time of the meal.

Injecting bolus insulin for every snack must be avoided to prevent a vicious cycle: Postprandial hyperglycemia → extra bolus insulin, resulting in insulin stacking → hypoglycemia → overtreatment with food → hyperglycemia → extra bolus insulin, resulting in insulin stacking → and so on. Whenever there are readings in the hypoglycemic and hyperglycemic range, address hypoglycemia first because hyperglycemia often is due to overtreatment of hypoglycemia.

METHOD 3: PREMIX OR SPLIT-MIX (PATIENT-MIX) INSULIN

Postprandial BG excursions can be minimized by changing basal insulin to premix or split-mix (patient-mix) insulin that has a mixture of mealtime and intermediate action insulin (Table 4).¹²⁻¹⁶ The use of premixed insulin is a viable option due to its ease of use and for those who have restrictions based on the complexity of the basal-bolus regimen.⁷ If a patient has routine meals and prefers not to carry around insulin for lunch, the schedule of premix insulin taken at breakfast and dinner is ideal.

Some caveats for safe prescribing should be understood. A recent summary of premixed insulin regimens noted that they seem to have a similar efficacy and safety profile compared with regimens that include basal insulin with or without mealtime insulin; however, cost

and patient adherence are improved.¹⁷ It is important to monitor insulin-naïve patients for hypoglycemia and reduced efficacy when used twice daily compared with basal plus 3-times daily prandial insulin in patients needing insulin intensification.¹⁷

A randomized trial noted that hypoglycemia rates were twice as high with premixed insulin compared with basal-bolus insulin.¹⁸ This study also noted that the premixed insulin group experienced the highest dropout rate, partly due to hypoglycemia. A regimen of basal insulin with the option to add a single prandial insulin injection at the main meal was as effective in reducing HbA_{1c} with less hypoglycemia. The premixed insulin is convenient but does not allow a separate correction of either mealtime or intermediate-acting insulin doses. If the premixed dose needs to be adjusted due to fasting hyperglycemia > 180 mg/dL (10.0 mmol/L), the TDD can be increased by 10%.²

In contrast, a split-mix (patient-mix) insulin regimen allows for the ability to vary the amount/ratio of combinations and adjustment of bolus and intermediate insulin doses. The disadvantages of split-mix insulin include the inconvenience of manually mixing of insulin and the potential for dosing errors. The patient needs to be taught additional steps on how to mix both insulins. Ensure the correct mixing order to maintain insulin potency; regular first, then neutral protamine Hagedorn (NPH). An HCP should remember the RN acronym if the patient is combining regular insulin and NPH. If there is doubt about the patient's insulin injection technique, HCPs should ask the patient to demonstrate how to correctly pull up a dose of normal saline and inject it during a clinic visit. The only basal insulin that can be physically mixed with quick or rapid insulin is NPH. It should never be mixed with long-acting analogs. The patient should not even use the same syringe to draw up bolus analog insulin and inject it and then use the same syringe to draw up long-acting analog insulin.

One caveat to a fixed regimen (same amount of insulin dose) is that providers often expect that the patient will eat a consistent amount of carbohydrates at each meal and premeal glucose readings are fairly

stable. Oftentimes, this is not true. If a patient took a bolus dose of 8 units of rapid-acting insulin and ate a 6 oz steak, 3 oz baked potato, steamed broccoli at a dinner; and no bread, the after dinner BG might register 145 mg/dL (8.1 mmol/L). Then, the next day for dinner, if he or she took the same amount of 8 units of rapid-acting insulin and ate 1 cup of spaghetti, ½ cup of spaghetti meat sauce, and 2 slices of garlic bread, the after dinner reading might be

Table 5. Titration of Insulin Doses

Reaction	Situation	Options to Take
Hyperglycemia	Fasting hyperglycemia	Assess bedtime BG and see if bedtime readings are high. If so, may consider increasing dinner bolus insulin Increase basal insulin dose Rule out hypoglycemia around 2-3 AM if patient is on NPH
	Bedtime or nighttime hyperglycemia	Increase dinner bolus insulin Increase basal insulin
	Postprandial hyperglycemia	Increase previous bolus insulin
	Steroid-associated acute hyperglycemia	Increase morning NPH or basal insulin temporarily for 3-4 days or consider adding mealtime insulin, depending on types of steroid used
	Hyperglycemia all the time	Consider increasing basal insulin; if the basal insulin is ≥ 50% of TDD insulin, may consider increasing bolus insulin doses
Hypoglycemia	Fasting hypoglycemia	Assess bedtime BG and see if bedtime readings are low. If so, may consider decreasing dinner bolus insulin Decrease basal insulin dose
	Bedtime or nighttime hypoglycemia	Decrease dinner bolus insulin Decrease basal insulin
	Postprandial hypoglycemia	Decrease previous bolus insulin
	Postexercise/activity hypoglycemia	Decrease previous bolus insulin If unplanned activity and the patient took full-dose bolus insulin already, check BG before exercise or activities, and consider eating or carrying a snack
	Hypoglycemia all the time	Consider decreasing basal insulin if the basal insulin is < 50% of TDD insulin, may consider decreasing all bolus insulin doses

Abbreviations: BG, blood glucose; NPH, neutral protamine Hagedorn; TDD, total daily dose.

Table 6. Bolus Insulin Initiation/Titration Guidance

Actions	Guidance	Monitoring
Starting bolus insulin	Around 4 to 6 units 1, 2, or 3 times a day with meals Or 0.1 U/kg if adding to basal insulin	This is an ideal time for patient to learn carb counting with focus on carb consistency, consider the patient's current insulin dose, medical comorbidities, diabetes control status, living situations & overall cognition
Titration of bolus	Increase the mealtime insulin by 1 U if the mealtime insulin is < 10 U, by 2 U if < 20 U Or by 10% of the mealtime insulin dose	Titrate if Δ value of premeal & 2 h postmeal is > 50 mg/dL (2.8 mmol/L)

322 mg/dL (17.9 mmol/L). The patient's BG was higher on the second day because of the higher carbohydrate content of the meal. If the rapid-acting insulin was increased to 12 units of bolus based on the high carbohydrate meal and the patient ate a lower carbohydrate meal, hypoglycemia could ensue. Thus, it is important to work with the patient regarding the consumption of a consistent amount of carbohydrates and refer to a registered dietitian for carbohydrate consistency.

For the flexible regimen, the prescriber may consider using an insulin to carbohydrate (IC) ratio and sensitivity factor (SF), also called sliding scale or correction factor. The IC ratio represents how much insulin is needed to cover consumed carbohydrates. For instance, if the patient uses IC ratio of 1:15, 1 unit of bolus insulin will cover 15 g of carbohydrates. If the patient eats a meal with 60 g of carbohydrates and is using IC ratio of 1:15, the patient will inject 4 units of bolus insulin. Sensitivity factor represents how much BG will be lowered in mg/dL by taking 1 unit of bolus insulin. For example, if the patient uses SF of 1:50, 1 unit of bolus insulin will lower BG by 50 mg/dL (2.8 mmol/L). When the desired (target) BG reading is 100 mg/dL (5.6 mmol/L) and the patient's current BG is 200 mg/dL (11.1 mmol/L), the patient will divide 100 mg/dL (5.6 mmol/L) by 50 (derived from SF of 1:50). The net result is 2 units of bolus insulin are needed to lower BG by 100 mg/dL (5.6 mmol/L). If the premeal BG is 200 mg/dL (11.1 mmol/L) and 60 g of carbohydrates are eaten, then the patient will need a total of 6 units (4 U for carbohydrate and 2 U for high BG) bolus before the meal. For additional information,

readers are encouraged to read the articles by Petznick and by Joslin Diabetes Center for IC and SF.^{19,20}

BOLUS INSULIN TITRATION

When the difference in BG readings before and 2 hours after a meal, called the Δ value, is > 50 mg/dL (2.8 mmol/L), the bolus insulin may need to be adjusted after ensuring the patient is ingesting consistent carbohydrates and performs the usual amount of activities around mealtime. For example, if the premeal reading was 130 mg/dL (7.2 mmol/L) but the 2-hour postprandial reading is > 180 mg/dL (10.0 mmol/L), the prescriber can increase the mealtime insulin by 1 unit if the mealtime insulin is < 10 units, by 2 units if < 20 units, or by 10% of the mealtime insulin dose. If the premeal BG is < 80 mg/dL (4.4 mmol/L) and the drop in BG is > Δ value of 50 mg/dL (2.8 mmol/L), the prescriber can decrease the mealtime insulin using the same calculation. Monitoring BG and titration recommendations are shown in Table 5. When adjusting the bolus insulin dose, it is best to make adjustments gradually rather than making several changes at once.

The 15/15 rule needs to be followed in cases involving hypoglycemia.²¹ When the BG is \leq 70 mg/dL (3.9 mmol/L) and the patient is conscious and able to eat or drink, it is recommended they eat 15 g (30 g if BG is below 50) of carbohydrates then repeat BG check every 15 minutes until the BG is in the target range.^{22,23} If the patient is unconscious, providers should administer glucagon (if available), place the patient in a lateral position to avoid aspiration, and call 911. If hyperkalemia is an issue in chronic kidney disease, patients should consume apple juice rather than orange juice due to its lower potassium content. If the patient is taking α glucosidase inhibitors (AGI) like acarbose or miglitol, only pure glucose like glucose tablets needs to be given to treat hypoglycemia instead of regular soda or candy, as the AGI will slow absorption of other types of carbohydrates.^{24,25} After the severe hypoglycemic episode, it is imperative to assess for the cause and explore ways to prevent subsequent hypoglycemia. Providers also should advise the patient to wear medical emergency identification.

CONCLUSION

To avoid clinical inertia and promote better patient outcomes, bolus insulin needs to be initiated and titrated in a timely fashion (Table 6). In addition, it is recommended to refer patients to a diabetes educator and/or registered dietitian for DSME/S at the time of DM diagnosis, annually or as indicated.²⁶ By utilizing multiprofessional

approaches to DM management, control may be maximized. The fundamental aspect of DM management is to establish good rapport with the patient and initiate and titrate insulin safely. ●

Author disclosures

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