Insulin Therapy in Type 2 Diabetes Mellitus: A Practical Approach for Primary Care Physicians and Other Health Care Professionals

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The responsibility of diabetes management and insulin therapy has definitively moved to primary care physicians. Within the primary care setting, there is a growing need for clear, evidence-based guidelines related to the management of insulin therapy. Straightforward algorithms regarding insulin initiation, titration, and follow-up management can help physicians effectively treat patients with type 2 diabetes mellitus. Once 2 oral diabetic drugs have failed in a patient whose disease duration is 7 to 10 years, use of insulin therapy with a basal insulin analog should be considered. For patients who receive maximal basal insulin doses without reaching fasting blood glucose and target glycated hemoglobin levels with basal insulin analogs, a mealtime-insulin intensification approach should be considered. The authors discuss how simplified insulin initiation and titration regimens allow primary care physicians and other health care professionals to care for patients with type 2 diabetes mellitus.

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Diabetes affects 25.8 million people in the United States; most (90-95%) adults with a diagnosis of diabetes have type 2 diabetes mellitus (T2DM).[1] Primary care physicians (PCPs) deliver approximately 90% of diabetes care in the United States.[2] Type 2 diabetes mellitus is characterized by progressive β-cell failure and increasing difficulty in maintaining glycemic control.[3,4] Even with multiple oral antidiabetic drugs, many patients need insulin therapy to achieve and maintain glycated hemoglobin (HbA_{1c}) target levels.[4]

The intensification of diabetes treatment—that is, the transition from oral antidiabetic drugs to injectable treatments such as insulin—is often delayed in many patients, which substantially increases the risk of diabetes-related complications.[5-10] In a population-based analysis,[5] 25% of patients with T2DM initiated insulin therapy within 1.8 years and 50% of patients initiated insulin therapy within 5 years of failure to achieve or maintain glycemic control despite multiple oral antidiabetic drugs, even in the presence of diabetes-related complications.

There are several barriers to initiation of insulin therapy. For patients, barriers include fears about injections and the risk of hypoglycemia, difficulties in managing insulin therapy, perceptions that insulin may impose lifestyle restrictions, and beliefs that insulin use indicates greater severity of disease and failure of self-management.[11-13] Physicians' barriers to initiation of insulin therapy include concerns about potential adverse effects (eg, increased hypoglycemia and weight gain) and practical concerns (eg, patient anxiety about insulin, perceived adherence issues, difficulties in training patients to administer insulin).[14,15] In an international survey[16] and a clinical practice review,[17] PCPs and diabetes specialists reported that insulin initiation was prevented by lack of:

- time required to train patients
- clear guidelines and definitions
- support, as represented by Certified Diabetes Educators

- experience in taking a proactive role in insulin initiation
- coordination of care between PCPs and endocrinologists
- motivation

Conversely, improved adherence to insulin therapy can be achieved through better patient-provider communication regarding risks and benefits, shared decision making, and training patients in how to self-manage their disease and their insulin regimen.[18] At the provider level, solutions to overcome barriers to insulin intensification should be appropriately tailored to the setting (ie, specialist or primary care) and could include education, training, and improving collaborative or supportive working practices and communication.[17] Improvements in diabetes care have been reported in pilot studies[19,20] of patient-centered medical homes and health care settings designed to provide comprehensive primary care and to facilitate partnerships between patients, their families, and their physicians.

We offer that insulin therapy should be simplified for PCPs, nurse practitioners, physician assistants, and other health care professionals, as they will have a pivotal role in helping patients manage T2DM. The current guidelines are nonprescriptive and lack practical guiding principles. The present article, however, does not present a set plan that will be applicable to all patients with T2DM, but rather it will address the relative scarcity of simple, scientifically based guiding principles related to the management of insulin therapy in the primary care setting.

Initiating Insulin Therapy

Type 2 diabetes mellitus encompasses β-cell dysfunction and insulin resistance.[21] As β-cell function declines over time, both fasting blood glucose (FBG) and postprandial glucose levels begin to rise and spiral out of control. As a consequence, a disease that was relatively well managed early in the disease lifecycle gradually becomes more difficult to manage. As HbA_{1c} levels begin to rise, multiple drugs may be added to improve glycemic control, causing patients to lose confidence; the extra efforts—which include an increased emotional burden, monetary investment, and need for treatment compliance—do not seem to lead to directly proportional improvement of the disease. The sense of a slowed improvement could leave patients with the perception of personal failure. Patients have been reported to blame themselves when they need to intensify treatment.[22] Likewise, family physicians may experience a sense of frustration.[22] Therefore, for patients who have had T2DM for 7 to 10 years, for whom 2 oral antidiabetic drugs have failed, and for whom HbA_{1c} levels are outside the acceptable range, insulin therapy deserves consideration as a third antihyperglycemic agent instead of a third oral antidiabetic drug or a glucagon-like peptide-1 (GLP-1) receptor agonist.

Transition to Basal Insulin: Basal Insulin Analogs vs Human Insulin

The 2012 American Diabetes Association and the European Association for the Study of Diabetes position statement endorses the addition of a basal insulin to existing oral antidiabetic drugs.[23] There are 2 approved basal insulin analogs in use—insulin glargine and insulin detemir—with additional basal insulin analogs in development.[24] Ideally, basal insulin should have no pronounced peak in activity, a low risk of hypoglycemia, low within-patient variability, and a duration of action of approximately 24 hours to enable once-daily injections.[25] Several studies[26-36] that evaluated the glycemic efficacy of insulin analogs compared with human neutral protamine Hagedorn (NPH) insulin have shown varying results. Regardless, basal insulin analogs have pharmacokinetic and pharmacodynamic advantages over NPH insulin—namely, a less pronounced peak effect, less variable absorption profiles, and a longer duration of

action.[25,37] Insulin analogs are also associated with lower rates of hypoglycemia, particularly nocturnal hypoglycemia, compared with NPH, which may at least partly offset the overall higher treatment costs related to insulin analogs.[38]

Starting Basal Insulin: Fix the Fasting First

Once providers decide to intensify treatment with insulin, they need to determine the optimal regimen for patients. The Treating to Target in Type 2 Diabetes trial[39] investigated the efficacy and safety of 3 different insulin regimens, evaluating which regimen led to optimal glycemic control in patients whose T2DM was poorly controlled with oral antidiabetic drugs. Twice-daily biphasic insulin aspart, 3-times daily prandial insulin aspart, or once-daily (twice if required) basal insulin detemir was added to the treatment regimens of insulin-naïve patients. After 3 years, HbA_{1c} levels were similar in patients receiving biphasic (n=235), prandial (n=239), or basal (n=234) insulin analogs (7.1%, 6.8%, and 6.9%, respectively; $P=.28$), yet fewer patients (75 [31.9%]) receiving biphasic insulin achieved an HbA_{1c} level of 6.5% or lower compared with patients receiving prandial (107 [44.8%], $P=.006$) or basal insulin analogs (101 [43.2%], $P=.03$). Prandial insulin led to more weight gain than the other 2 insulin treatment regimens. The rate of hypoglycemia was lowest with basal insulin (1.7 events per patient per year, $P<.001$) compared with biphasic insulin (3 events per patient per year) and prandial insulin (5.7 events per patient per year). Overall, data from the trial suggest that patients who do not reach optimal glycemic control with oral antidiabetic drugs may benefit most from the addition of basal insulin analog–based regimens.

In general, initiation of a basal insulin analog should occur with a low starting dose; a starting dose of 10 U/d is recommended by various national and international medical societies and is commonly used as a starting point for titration algorithms in clinical trials (*Table 1* and *Table 2*).[31,36,40-48] It is important to consider this dose as a safe starting point only; titration will be required to achieve therapeutic efficacy. Many titration schedules have been developed. The simplest schedule titrates the evening dose of basal insulin on the basis of FBG levels, as in the INSIGHT trial,[46] in which evening insulin doses were adjusted by adding 1 U/d until fasting glucose levels were ≤100 mg/dL (5.5 mmol/L). If the glucose levels

Table 1.
Basal Insulin Titration Algorithms From World Medical Societies

Measure	ADA/EASD[40]	AACE/ACE[41]	IDF[43]	CDA[44]
Algorithm				
Initial dosage	10 U/d	10 U/d	Not specified	10 U/d
Titration	2 U every 3 d	1-3 U every 2-3 d	2 U every 3 d	1 U every d
Target FBG, mg/dL	70-130	<110a	<110	72-126
Target HbA_{1c}, %	<7.0	≤6.5	≤6.5	≤7.0

[a] Fasting blood glucose (FBG) target recommendation from the American Association of Clinical Endocrinologists (AACE) 2011 guidelines.[42]

Abbreviations: ACE, American College of Endocrinology; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; EASD, European Association for the Study of Diabetes; HbA_{1c}, glycated hemoglobin; IDF, International Diabetes Federation.

Table 2.
Selected Titration Algorithms for Basal Insulin From Selected Clinical Trials

	INITIATE[45]	Treat to Target[31]	INSIGHT[46]	LANMET[35]	TITRATE[47]	Rosenstock et al[48]
Algorithm						
Initial dose	10 U	10 U	10 U	10-20 U	10 U	12 U
Titration	2-4 U every 3 d	2-8 U/wk	1 U/d	2-4 U every 3 d	No adjustment; if outside target,[a] ±3 U every 3 d	−4 to +12 U/wk
Target FBG Level, mg/dL	72-100	⩽100	<100	72-100	70-90[b] or 80-110[c]	⩽108[d]

[a] For 3.9-5.0 mmol/L target: <3.9, −3 U; >5.0, +3 U. For 4.4-6.1 mmol/L target: <4.4, −3 U; >6.1, +3 U.
[b] 3.9-5.0 mmol/L.
[c] 4.4-6.1 mmol/L.
[d] ⩽6.0 mmol/L.

Abbreviations: FBG, fasting blood glucose; INITIATE, Initiate Insulin by Aggressive Titration and Education; INSIGHT, Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment; LANMET, Lantus plus Metformin; TITRATE, Treat to target with once-daily Insulin Therapy: Reduce A_{1c} by Titrating Effectively.

get much lower than 100 mg/dL, the daily dose can be decreased by 1 U/d until glucose levels are stabilized. Sulphonylurea medication may need reduction as fasting glucose levels approach the target. Such titration algorithms are widely used in real-world clinical practice. For most patients receiving basal insulin analogs, the average insulin dose is less than 50 U/d.[49,50] Generally, targeting FBG levels first will solve most glycemic control problems in patients with T2DM[51]; however, if HbA_{1c} levels are still in excess of 8.5%, reductions in both FBG levels and postprandial glucose levels may be required to achieve the glycemic goal.

"Overbasalization": Too Much Basal Insulin, Too Little Effect

"Overbasalization"[52] describes an issue that arises from increased use of basal insulin in primary care, as well as the complexities of β-cell dysfunction. Early in the management process, adding basal insulin seems to assist β cells and be an efficient step in controlling FBG levels. This premise assumes that the β cell still functions well enough to cover meals with intrinsic insulin synthesis and secretion. However, when basal insulin levels are titrated appropriately on the basis of units per kilogram (while also considering any insulin resistance) and glycemic control remains elusive, adding basal insulin may become detrimental. Overbasalization occurs in clinical practice because upper dose limits for insulin have not been well established. Whereas basal insulin titration has become part of clinical practice, there is no standard ceiling for titration. As currently defined, overbasalization occurs when FBG is not controlled with uptitration of basal insulin and HbA_{1c} targets remain elusive. Providers must understand the concept of overbasalization because it should trigger progression to mealtime insulin intensification in patients.

To understand overbasalization, providers should consider the following simple formula and 1 simple rule. In the clinical experience of our lead author (J.R.L.), the total daily insulin requirement for an insulin-resistant patient with T2DM is approximately 1.0 to 1.5 U/kg per

day. According to this formula, if a patient weighed 100 kg, the total daily insulin requirement would be between 100 and 150 U. Further, total daily insulin is divided so that 50% is basal insulin and 50% is postprandial insulin. If this same patient demonstrated a low level of insulin resistance (1 U/kg per day), the total daily insulin requirement would be 100 U (1 U × 100 kg/d=100 U), and the basal insulin requirement would be half the daily requirement (50 U) of NPH, insulin glargine, or insulin detemir. If this patient's basal insulin level had to be titrated beyond 50 U of a basal insulin analog because the FBG level was not less than 100 mg/dL or the HbA_{1c} level was not less than 7%, it is usually time to reassess the overall clinical case rather than add more insulin.

Maximal amounts of basal insulin can be achieved but should not comprise more than 50% of the total daily insulin calculation.[53] Violating the 50/50 rule may lead to overbasalization. At this point, administering additional basal insulin may change the pharmacokinetics of the basal insulin from having a profile without pronounced peaks of activity to a profile with an insulin peak. This addition in turn increases the risk of adverse reactions such as hypoglycemia. If a physician believes the reason for lack of glycemic control is insulin resistance and that more basal insulin is necessary to overcome this resistance, the physician should proceed with the titration schedule for an additional 20 U of insulin. If this degree of basal insulin supplementation has not reduced the FBG level to less than 100 mg/dL or the HbA_{1c} level to less than 7%, then adding further basal insulin may be fruitless. If 2 common oral antidiabetic drugs have failed to improve a patient's condition and if the patient has received basal insulin amounts that account for up to 50% of the calculated total daily dose of insulin, there may be a high degree of insulin resistance and the amount of both basal and mealtime insulin that is needed cannot be synthesized and secreted appropriately. Management strategies at this stage include moving to the next level of insulin intensification or referring the patient to an endocrinologist.

Adding to Basal Insulin: A Stepwise Approach

New therapeutic options, such as GLP-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, are now considered as potential add-on treatments to basal insulin, along with thiazolidinediones and more complex insulin strategies. In the following section, we describe a simpler insulin intensification regimen that parallels the pathophysiologic characteristics of the disease, especially in primary care. Just as there are basal human insulin and long-acting basal insulin analogs, there are also regular human insulin and rapid-acting insulin analogs for mealtime administration. Rapid-acting insulin analogs closely mimic physiologic meal-stimulated insulin release, with faster absorption, higher maximum concentration, shorter duration, and a lower risk of hypoglycemia than regular insulin.[54,55] In addition, rapid-acting premixed insulin analogs—such as biphasic insulin aspart 30 (30% soluble insulin aspart and 70% protamine-crystallized insulin aspart)—have been developed, which can prevent excessive postprandial glucose levels whether injected at the beginning of a meal or 15 to 20 minutes after starting a meal.[56,57]

During mealtime insulin intensification, the patient continues to receive basal insulin therapy but also administers a rapid-acting insulin at the largest meal of the day to manage glucose excursions after meals. Rapid-acting insulin is administered around the time of either the largest perceived meal of the day or the meal with the greatest postprandial glucose increase.[58-60] Several studies[58,61-63] have shown that the addition of only 1 prandial insulin injection can effectively reduce HbA_{1c} levels in patients with T2DM whose disease is poorly controlled with basal insulin and oral antidiabetic drugs. When rapid-acting insulin glulisine was added to insulin glargine and oral antidiabetic drugs at the main mealtime, HbA_{1c} levels showed a statistically significant improvement from 7.3% at baseline to 6.9% at the end of the study ($P<.001$).[61] Furthermore, recent studies[62,63] show that adding 1 prandial insulin injection may be no less effective at improving glycemic control than the stepwise

approach to a full basal bolus regimen of 3 daily prandial injections. Given its inherent simplicity, the addition of only 1 injection appears to be a useful approach to insulin intensification. Also, certain GLP-1 receptor agonists have been shown to improve glycemic control without increased hypoglycemia or weight gain in patients with T2DM who did not achieve glycemic control despite treatment with a basal insulin.[64]

The "How to" of Mealtime Insulin Intensification

A rapid-acting insulin analog is generally administered around the time of the largest meal of the day because maximum glycemic control is likely to be obtained during the highest postprandial glucose excursion.[60] Titration algorithms that are recommended by various national and international medical societies and commonly used in clinical trials are illustrated in *Table 3* and *Table 4*.[40-44,58,61,65-68] The aim of mealtime insulin intensification is to control postprandial glucose excursions during the immediate 2 hours after the meal. Therefore, it is important to check glucose levels just before the first bite of the meal and 2 hours after the meal to assess the effectiveness of the mealtime insulin and to provide guidance for further insulin titration. There is no absolute need for carbohydrate counting with this method.

Safety is paramount when selecting the starting dose of mealtime insulin. Three to 4 units of a rapid-acting insulin analog is a generally accepted safe starting dose (*Figure*). Titration follows based on the plasma glucose level 2 hours after that meal. For example, 1 U of rapid-acting insulin analog is added at the largest meal the following day if the blood glucose level 2 hours after the meal is greater than 180 mg/dL or if the difference between preprandial and postprandial glucose levels is greater than 50 mg/dL. This titration schedule should continue until the postprandial glucose level is less than 180 mg/dL. As the mealtime insulin target is achieved, the basil insulin dose must be reassessed. If the largest meal is the evening meal and postprandial glucose levels are less than 180 mg/dL, the bedtime dose of the basal

Table 3.
Prandial Insulin Titration Algorithms From World Medical Societies

Measure	ADA/EASD[40]	AACE/ACE[41]	IDF[43]	CDA[44,a]
Algorithm				
Initial dose	4 U	5 U	Not specified	Total daily dose of 0.3-0.5 U/kg; 40% of total = basal; 20% of total = bolus (3 times/d)
Titrate	2 U every 3 d	2-3 U every 2-3 d	2 U every 3 d	NA
Target HbA_{1c} Level, %	<7	≤6.5	≤6.5	≤7
Target FPG Level, mg/dL	<180	≤140[b]	<145	90-180[c]

[a] For initiation of intensive basal/bolus therapy.
[b] Postprandial glucose target recommendation from AACE 2011 guidelines.[42]
[c] Adjust to 90-144 mg/dL if HbA_{1c} targets are not being met.

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; EASD, European Association for the Study of Diabetes; IDF, International Diabetes Federation; NA, not available; PPG, postprandial glucose.

Table 4.
Selected Titration Algorithms for Prandial Insulin From Selected Clinical Trials

Measure	GINGER[65]	OPAL[61]	ELEONOR[58]	Davidson et al[66]	4-T[39]	APOLLO[67]	Liebl et al[68]
Algorithm	*Initial:* 50% of total baseline insulin dose with minimum 6 U each mealtime. *Titrate:* every 2 d based on 2-d highest postprandial glucose level, mg/dL: >135-160: +1 U 160-200: +2 U >200: +3 U	Investigator's discretion to reach target while avoiding hypoglycemia; either breakfast or main mealtime	*Initial:* 0.05 U/kg *Titration:* every 2 d based on 2-d mean postprandial glucose: level, mg/dL: >140: +2 U <100: −2 U 100-140: no change	*Initial:* 10% of basal insulin dose at randomization *Titration:* weekly according to mealtime dose, with increases of 1-3 U if preprandial glucose level was above target and decreases of 1-3 U if preprandial glucose level was below target	*Initial:* 4-6 U *Titration:* Individually titrated based on investigator's discretion to reach target while avoiding hypoglycemia	*Initial:* 4 U *Titration:* weekly *Preprandial glucose level, mg/dL:* >200: + 3U >150-≤200: +2 U >100-≤150: +1 U <100: no change *Postprandial glucose level, mg/dL:* >185: + 2 U >135-≤185: +1 U ≤135: no change	*Initial:* set by investigator according to patient needs; divided 3:1:2 between breakfast, lunch, and dinner *Titration:* weekly during first 6 wk, gradually thereafter if targets not met; titration steps at the investigator's discretion
Target FBG level, mg/dL							
Preprandial	NA	NA	NA	70-109	72-99	<100	NA
Postprandial	≤135	≤135	<140	NA	90-126	<135	≤180
Bedtime	NA	NA	NA	70-129	NA	NA	NA

Abbreviations: 4-T, Treating to Target in Type 2 Diabetes; APOLLO, A Parallel design comparing an Oral antidiabetic drug combination therapy with either Lantus once daily or Lispro at mealtime in type 2 diabetic patients failing Oral treatment; ELEONOR, Evaluation of Lantus Effect ON Optimization of use of single dose Rapid insulin; FBG, fasting blood glucose; GINGER, Glulisine in Combination with Insulin Glargine in an Intensified Insulin Regimen; NA, not available; OPAL, Orals Plus Apidra and LANTUS.

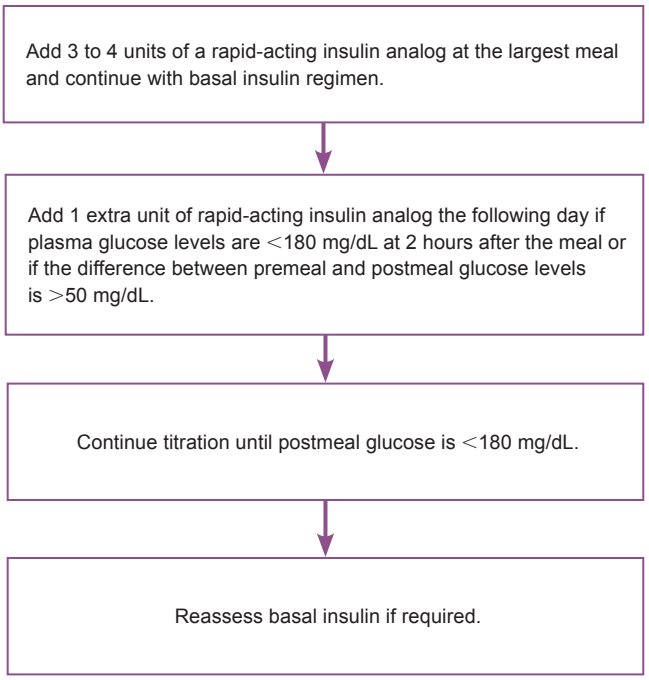

Figure.
Proposed insulin intensification scheme in patients who are receiving maximal basal insulin without achieving target fasting blood glucose and glycated hemoglobin levels.

insulin may have to be titrated downward by 1 or more units, particularly if the FBG level is consistently less than 100 mg/dL. This measure may be necessary in order to avoid the potential for nocturnal hypoglycemia in a patient whose T2DM is more controlled than at initiation of insulin intensification.

Further insulin intensification beyond 1 prandial injection is the same process: a rapid-acting insulin analog is administered at a meal in addition to the largest meal of the day. Stepwise titrating of rapid-acting insulin alongside a full basal bolus regimen is emerging as a favored approach to insulin intensification.[58-60,62,63] Sequentially adding up to 3 insulin injections in a stepwise manner if HbA_{1c} levels do not remain (or decrease) below 7% may mirror a full basal bolus approach.[59] In a study by Raccah et al,[59] stepwise addition of up to 3 daily injections of insulin glulisine to basal insulin glargine resulted in a statistically significant level of reduced weight gain than the basal bolus approach ($P=.04$). Statistical noninferiority for the adjusted difference in HbA_{1c} levels at the study completion, however, was observed in a subgroup analysis of patients with a HbA_{1c} level of 8% or less at randomization (95% confidence interval, −0.175 to 0.349; $P=.087$).[59] Finally, reports of other studies[62,63] have suggested that the stepwise approach to insulin intensification may lead to less hypoglycemia than premixed insulin, with similar proportions of patients achieving the glycemic control goal of HbA_{1c} levels below 7%, as well as lower blood glucose levels.[62,63]

Conclusion

For PCPs and other nonspecialists who care for patients with T2DM, simple algorithms are now available to effectively manage insulin initiation, titration, and follow-up. Physicians should continually monitor for overbasalization and consider using a mealtime insulin intensification approach for patients who receive basal insulin analogs but who have not reached target levels of FBG and HbA_{1c}.

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