

Importance of daily plasma glucose control in type 2 diabetes

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Dr Pollom has disclosed that he is on the advisory boards for Eli Lilly and Company and Novo Nordisk Inc. and is on the speakers bureaus for Eli Lilly and Company, Merck & Co., Inc., and Novo Nordisk Inc.

Normal physiologic pattern of insulin secretion

There are two characteristic features of the normal pattern of insulin secretion in healthy individuals^{1,2}: a low-level basal insulin secretion that occurs continuously to maintain glycemic control between meals and an insulin spike that occurs rapidly in response to a caloric stimulus. After the prandial insulin surge, there is a prolonged insulin secretion that returns to basal levels after 2 to 3 hours (**FIGURE 1**).² Together, basal and prandial insulin secretions maintain control of glucose levels.

Abnormalities in type 2 diabetes

Both insulin resistance and altered insulin secretion contribute to type 2 diabetes. Type 2 diabetes often occurs with obesity and an associated dysregulation of appetite. In the setting of genetic susceptibility, obesity can result in impaired insulin signalling, more commonly known as insulin resistance.³ Patients with insulin resistance often progress to type 2 diabetes. The trigger for this progression is β -cell failure, involving partial loss of β -cell mass and deterioration of β -cell function.³ Abnormalities in insulin secretion resulting from β -cell dysfunction in patients with type 2 diabetes include absence of pulsatility, loss of early-phase insulin secretion after meals, reduced basal and stimulated plasma insulin concentrations, and a progressive reduction in insulin secretory capacity with time and disease progression.⁴ The decline in β -cell function and insulin secretion lead to a progressive loss of control over fasting plasma glucose (FPG) and postprandial glucose (PPG) and eventually to type 2 diabetes.⁴

The abnormalities characteristic of type 2 diabetes, most notably the decline in pancreatic β -cell function, are progressive.⁵ In patients with this disease, along with accelerated β -cell apoptosis, there is a progressive decline in β -cell mass, replication, and regeneration. The loss of β -cell mass and function leads to the increase in glucose that is ultimately expressed as diabetes.⁵ It is important to note that some aspects of β -cell dysfunction (eg, desensitization to stimulation by glucose) are reversible, while others (changes in gene expression with chronic exposure to high glucose concentrations) are not.⁶ Autopsy studies report deficits in β -cell mass ranging from 0 to 65% in patients with type 2 diabetes.⁷ Reduced β -cell function is also characteristic of individuals with prediabetes.⁸

Postprandial glucose: A key determinant of outcomes in patients with type 2 diabetes

Both FPG and PPG are strongly correlated with glycosylated hemoglobin (A1C) levels,^{9,10} and it has been shown that PPG is a stronger determinant of A1C levels than is FPG in patients with relatively well-controlled diabetes (A1C <7.3%).¹¹ In contrast, FPG increasingly contributes to increasing A1C levels in patients whose diabetes is poorly controlled.¹¹ As stated, A1C is strongly linked to risk for long-term microvascular and macrovascular complications of type 1 and type 2 diabetes, and there is cogent evidence to support the effectiveness of antihyperglycemic therapy in avoiding these adverse outcomes.^{12,13}

Contributions of FPG and PPG to long-term diabetes complications

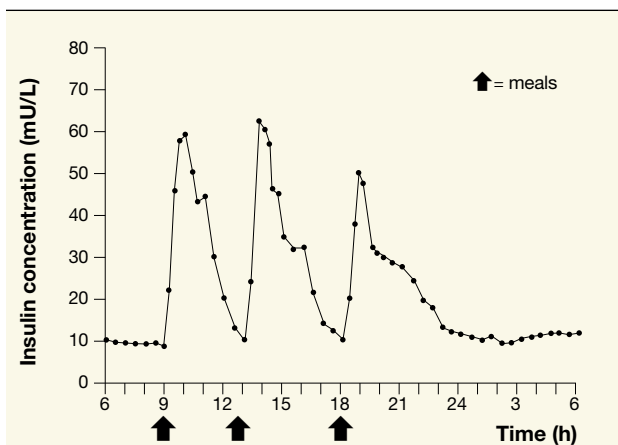
Both FPG and PPG have been demonstrated to be significant independent predictors of long-term complications in patients with type 2 diabetes. Results from multiple large-scale studies have demonstrated significant relationships between FPG and cerebrovascular events, cardiovascular events, heart failure, overt nephropathy, proliferative retinopathy, end-stage renal disease, and death.¹⁴⁻¹⁸

Postprandial hyperglycemia may play a particularly important role in diabetes-related cardiovascular risk. It has been shown to be a predictor of macrovascular complications (eg, myocardial infarction) and mortality in patients with type 2 diabetes.¹⁹⁻²¹ In both the Honolulu Heart Study,²⁰ and the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study,¹⁹ elevated PPG levels were associated with increased risk for fatal and total cardiovascular mortality.

Results from DECODE showed that elevated 2-hour postload glucose concentrations were correlated with an increased mortality risk that was independent of FPG.¹⁹ Results from the Diabetes Intervention Study²¹ showed that PPG was an independent risk factor for myocardial infarction and cardiovascular disease mortality in patients with type 2 diabetes. Results from the San Luigi Gonzaga study²² demonstrated that PPG, but not FPG, was an independent risk factor for cardiovascular events in patients with type 2 diabetes, with a stronger predictive power in women than in men.

FIGURE 1

Normal 24-hour physiologic insulin secretion



Phillips P. Insulins in 2002. *Australian Prescriber*. 2002;25:29-31. Reprinted with permission from Australian Prescriber. Copyright © 2002. National Prescribing Service.

Plasma glucose variability

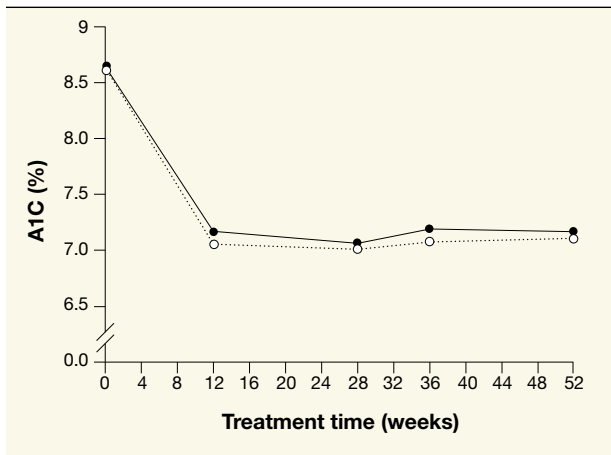
Recent analysis of glucose variability has determined that marked glycemic fluctuations are associated with an increased cardiovascular risk.²³ This may be associated with an increase in oxidative stress.²⁴ An increase in glucose variability is also correlated with higher central blood pressure.²⁵ All of these results underscore the importance of controlling FPG as well as the excessive PPG excursion so commonly seen in patients with diabetes.

Mimicking physiologic insulin secretion for achievement of glycemic control

The American Diabetes Association treatment goal for patients with diabetes is A1C <7%.²⁶ Although this result may be achieved initially with dietary and lifestyle changes and oral antihyperglycemic medications, most patients will ultimately require insulin.²⁷ As discussed above, effective use of insulin must control both FPG and PPG to provide optimal risk reduction for long-term diabetes complications. Patient characteristics and habits, as well as the degree of disease progression, should guide the transition to insulin therapy in type 2 diabetes.²⁷

Making the transition

Several approaches can be used in making the transition from oral agents to insulin therapy in patients

FIGURE 2**Change in A1C with addition of insulin detemir or insulin glargine to oral drug treatment**

A1C, glycosylated hemoglobin.

Black circles, insulin detemir; white circles, insulin glargine.

Reprinted with permission from Rosenstock J, et al. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetologia*. 2008;51:408-416. Copyright © 2008 Springer Berlin/Heidelberg.

with type 2 diabetes. Two commonly used approaches are the addition of basal insulin to ongoing oral therapy and the initiation of treatment with a pre-mixed insulin.

Oral therapy plus basal insulin

The effectiveness of adding a long-acting insulin analog to oral therapy has been demonstrated in a 9-month, open-label, multicenter, observational study²⁸ in which add-on insulin glargine (dosed according to the judgment of the treating physician) was initiated in 12,216 patients with type 2 diabetes inadequately controlled with oral drugs. Study results showed that the addition of insulin glargine reduced A1C levels by 1.5% and fasting blood glucose (FBG) levels by 69 mg/dL without an increase in body mass index. A recent comparison²⁹ of glargine and detemir as add-on therapy to oral drug treatment in 582 patients with type 2 diabetes indicated that both agents were effective in lowering A1C and self-monitored FPG (FIGURE 2), with no difference in the relative risk for overall or nocturnal hypoglycemia. Among patients who completed the study, weight gain was slightly less with insulin detemir than with insulin glargine

(3.0 vs 3.9 kg, respectively).

For patients with type 2 diabetes who do not respond adequately to oral agents and lifestyle modification, insulin therapy may begin with the addition of a single evening dose of approximately 10 U of a long-acting insulin preparation, with weekly upward titration based on an FPG target of <100 mg/dL. In patients who experience hypoglycemia (FPG <72 mg/dL), titration should be discontinued for 1 week or the insulin dose reduced before being resumed. Once the target FPG level is obtained, titration can be maintained.³⁰ A simple insulin adjustment scale is vitally important for helping patients reach their target glucose levels once started on an insulin regimen. The algorithm will define both pre- and postmeal glucose targets and the method for achieving target control.

Premixed insulins

Switching patients to a premixed insulin is also effective when glycemic control can no longer be maintained with oral therapy. Premixed analogs are available as 75% neutral protamine lispro suspension/25% insulin lispro mix (75/25), 50% neutral protamine lispro suspension/50% insulin lispro mix (50/50), and 70% insulin protamine aspart suspension/30% insulin aspart mix (70/30). Results from a study³¹ in which a mixture of 75% neutral protamine lispro and 25% insulin lispro was substituted for glyburide showed that twice-daily administration of this preparation (morning and evening) for 4 months reduced A1C levels by 1.4% vs 0.7% in the glyburide group ($P = .004$), FPG by 2.8 mmol/L (50.4 mg/dL) vs 1.1 mmol/L (19.8 mg/dL) ($P < .01$), and evening 2-hour PPG by 4.4 mmol/L (79.2 mg/dL) vs 1.5 mmol/L (27.0 mg/dL) ($P < .001$). Similar benefits have been demonstrated for insulin biphasic insulin aspart in a trial in which it was added to optimized treatment with metformin in a 34-week study that enrolled 191 patients with type 2 diabetes.³²

Next steps

Continued treatment with premixed insulin

Mixed formulations are a good choice for patients who eat meals on a regular schedule and whose lifestyles are more consistent day to day. These patients are not your “diet du jour” individuals, and they have little interest

in or aptitude for carbohydrate counting. Premixed insulins can be administered up to 3 times daily. A dose of premixed insulin may also be used at noon for those patients not achieving their A1C goal on a twice-daily regimen. With the appropriate guidance and education, patients will adjust their mealtime doses to fit the amount of calories consumed at the meal in question. Premixes containing regular human insulin should be administered 30 to 60 minutes prior to meals. This is a recommendation that is rarely followed for a variety of reasons. Analog mixtures can be taken within 15 minutes of a meal due to their rapid onset of action.¹

A recent comparison³³⁻³⁵ of premixed insulin analogs vs premixed human insulin formulations suggests similar effectiveness in lowering A1C and FPG levels, but superior effectiveness for premixed analogs in lowering PPG levels (**TABLE 1**).

Garber and colleagues have provided a simple and easy-to-follow approach for dosing premixed insulin analogs (**FIGURE 3**).³⁶ With this regimen, a biphasic preparation of insulin aspart (BIAsp30) is dosed initially once daily before dinner (12 U) along with oral therapy. If A1C remains >6.5%, oral secretagogues are discontinued and a second insulin dose is added at breakfast (3 U, if FBG is ≤110 mg/dL; 6 U, if FBG is >110 mg/dL). If A1C still remains >6.5%, a third insulin dose (3 U) is added at lunch. Clinical study results showed that 70% of patients using this premix twice daily achieved A1C ≤7.0 and 52% achieved A1C ≤6.5%. In addition, 77% of those taking this premix 3 times per day achieved A1C ≤7% and 60% achieved A1C ≤6.5%.

Advancing basal insulin treatment

A summary of the approach for advancing a patient to basal-bolus insulin treatment is provided in the tear-off sheet at the end of the article. Several approaches can be taken to advance insulin therapy in a patient who has had basal insulin added to oral drugs. These include discontinuation of oral agents and initiation of treatment with a premixed insulin formulation or the addition of prandial insulin to basal insulin therapy. When basal insulin plus oral antihyperglycemic diabetic drugs are ineffective, a single dose of prandial insulin (ie, a rapidly acting analog) may be added before the largest meal of the day.

Additional prandial doses may be used to control postprandial hyperglycemia until the patient is

TABLE 1

Comparison of premixed human insulins and premixed insulin analogs

Outcome	Comparative efficacy	Strength of evidence
FPG	Similar	Moderate
PPG	Favors insulin analogs	High
A1C	Similar	High
Hypoglycemia	Similar	High
Weight	Similar	Moderate

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial glucose.

Qayyum R, et al. *Ann Intern Med.* 2008;149:549-559. © 2008 Adapted with permission from *Annals of Internal Medicine*. The American College of Physicians is not responsible for the accuracy of the translation.

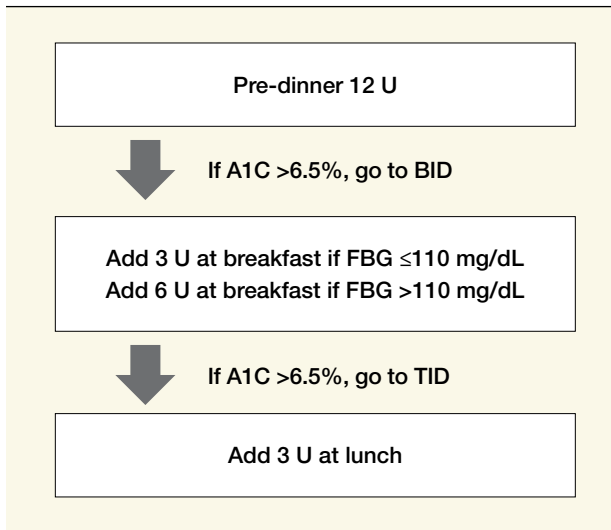
on 2 to 3 mealtime doses per day. These additions are made to keep postmeal glucose <180 mg/dL at midmorning or <140 mg/dL 2 hours after lunch or dinner.³⁷ Recommended starting doses of pre-meal rapid-acting insulins generally range from 5 to 10 U, or about 0.15 U/kg.

Several factors should be considered in subsequent dose titrations. For example, exercise improves insulin sensitivity; therefore, patients who engage in vigorous exercise within 3 hours of taking a dose of rapid-acting insulin may need to reduce that dose.^{38,39} Because this effect is highly variable, titration must be carefully tailored to reflect the needs of the individual patient.

Basal-bolus therapy

Basal-bolus therapy combines long- and rapid-acting insulin analogs; the long-acting agent is typically administered once daily and the rapid-acting agent is delivered at each meal.³⁷ The aim of this approach to treatment is to mimic normal physiologic insulin secretion and thus achieve near-normal glycemia.^{27,40}

Basal-bolus therapy may provide the best approach to treatment for patients who vary their meal-times and/or the contents of those meals, or for those who eat only twice daily. A basal-bolus regimen may be particularly suitable for individuals whose jobs mandate variable meal patterns (eg, individuals who

FIGURE 3**The 1-2-3 approach to dosing biphasic insulin aspart (BIAsp) in patients with type 2 diabetes**

FBG, fasting blood glucose (all doses should be taken pre-meal).

Garber AJ, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). *Diabetes Obesity and Metabolism*. 2006;8:38-66. Reproduced with permission from Blackwell Publishing Ltd.

must travel for work or have variable hours, shift workers). Many patients will prefer basal-bolus therapy because it provides increased flexibility with respect to the timing and content of their meals.²⁷

One aspect of basal-bolus therapy that may be difficult for some patients is determining the carbohydrate content for a given meal and adjusting their prandial insulin dose accordingly. It has been suggested that barriers to basal-bolus therapy related to carbohydrate counting include difficulties patients may have calculating mealtime carbohydrates and the education/resources needed to set the stage for this form of intensive insulin treatment.⁴¹ However, there are simple alternatives to carbohydrate counting for patients who have difficulty with this requirement. A recent study by Bergenstal et al⁴² showed that adjusting bolus insulin according to a simple algorithm based on whether mealtime glucose levels were above or below target (TABLE 2) was as effective as carbohydrate counting for controlling A1C and FPG in patients with type 2 diabetes. Furthermore, there were no significant differences between treatments in PPG levels.⁴² It is also worth noting that patients in this trial who counted carbohydrates were able to effectively adjust their

insulin doses and experienced less weight gain than the patients who used the simple algorithm.⁴²

Insulin pens and pumps

Insulin pens may facilitate both compliance and effective insulin treatment of patients with type 2 diabetes. These devices are either reusable with replaceable insulin cartridges or disposable. They typically feature dose selectors and a discreet appearance, and are generally viewed as being easy for patients to use and preferred by them over syringes and vials.⁴³

Insulin pumps provide another alternative for the delivery of intensive insulin therapy.⁴⁴ Insulin pumps have been used effectively in patients with type 2 diabetes and they may provide multiple benefits, including enhanced reproducibility of insulin delivery and attenuation of the “dawn” phenomenon (the increase in PG levels in the morning). In comparison to multiple daily injections, insulin pumps may provide greater flexibility with respect to the timing of meals and snacks, programmable basal rates to optimize overnight glycemic control, the ability to reduce the risk of exercise-induced hypoglycemia, and enhancement of the patient’s ability to control his or her own diabetes.⁴⁵ There is also evidence that pumps may permit achievement of lower A1C levels than do multiple daily insulin injections.⁴⁶ Furthermore, it appears that the benefits of continuous insulin delivery are enhanced with a rapid-acting insulin analog vs regular human insulin.⁴⁷ Results from one clinical trial that compared insulin pump treatment to multiple daily injections in patients with type 2 diabetes indicated that 93% of pump-treated patients preferred it to their previous injectable insulin regimen for reasons of convenience, flexibility, and ease of use.⁴⁸ There are potential disadvantages associated with insulin pumps. Patients may object to having an infusion device attached to their body. Successful insulin pump therapy requires appropriate patient selection, effective education, and patient commitment to intensive self-monitoring blood glucose (SMBG).⁴⁹

There are currently 3 continuous glucose monitoring (CGM) devices available for use, along with the insulin pumps available on the market. These pumps, which are sensor augmented, receive glucose data from a subcutaneous sensor every 5 minutes. A recent comparison of an insulin pump with CGM vs an insulin

TABLE 2

Simple approach to determining mealtime insulin dosing with a rapid-acting insulin analog in basal-bolus therapy

Mealtime dose	Pattern of mealtime blood glucose values below target^a	Pattern of mealtime blood glucose values above target^b
≤10 units	Decrease by 1 unit	Increase by 1 unit
>11-19 units	Decrease by 2 units	Increase by 2 units
≥20 units	Decrease by 3 units	Increase by 3 units

^a If more than one-half of the mealtime blood glucose values for the week were below target.

^b If more than one-half of mealtime blood glucose values for the week were above target.

Bergenstal RM, et al. Copyright © 2008 American Diabetes Association. From *Diabetes Care*, Vol. 31; 2008, 1305-1310. Reprinted with permission from The American Diabetes Association.

pump with SMBG indicated no significant difference between treatments with respect to decline in A1C levels, but there was an increased risk for hypoglycemia in the pump with SMBG group.⁵⁰

Other problems that have become less common with newer pumps and insulin preparations include catheter occlusions due to instability of insulin and formation of precipitates.⁵¹ Rapid-acting insulin analogs have good temperature stability and low risk for catheter occlusion.^{51,52} It has also been shown that overnight interruption of infusion with a rapid-acting insulin analog is not associated with a higher risk for metabolic decompensation vs regular human insulin.⁵³ Pump advocates contend that insulin pumps offer a more convenient way to deliver intensive insulin management than self-administration of multiple injections.

It should be noted that Medicare has relaxed the criteria for reimbursement for insulin pumps. A new pump patient must complete a diabetes education program, require ≥3 insulin injections per day, and make frequent self-adjustments of insulin for ≥6 months before initiating pump therapy. The patient must have documentation of need to self-monitor

BG ≥4 times a day for ≥2 months prior to pump treatment and meet at least one of the following criteria while on multiple daily injection treatment: A1C >7.0%, recurring hypoglycemic episodes, wide fluctuations of BG prior to meals, experience the “dawn” phenomenon (FBG >200 mg/dL, or a history of severe glycemic excursions). The C-peptide criterion for pump use is <110% of the laboratory’s lower limit of normal for patients with normal renal function.⁴⁵

Conclusions

Because of the progressive loss of β-cell function and the decline in the ability of the pancreas to produce insulin, most patients with type 2 diabetes eventually will require insulin therapy. There are several approaches for transitioning the patient from oral agents to insulin therapy, and the goal of insulin treatment for the patient who has made this switch is to provide exogenous insulin in a manner that mimics normal physiologic insulin secretion. Basal-bolus treatment with long- and rapid-acting insulin analogs is capable of achieving this goal. ■

TEAR-OFF SHEET

Suggestions for progressive insulin treatment: Basal-bolus therapy

Addition of basal insulin to oral therapy

A single dose of approximately 10 U of a long-acting insulin preparation may be added in the evening.

- Titrate upward weekly based on an FPG target of <100 mg/dL.
- In patients who experience hypoglycemia (FPG <72 mg/dL), titration should be discontinued for 1 week or the insulin dose reduced before being resumed.
- Once the target FPG level is obtained, titration can be maintained.

Progressive treatment intensification to basal-bolus therapy when basal insulin and oral drugs no longer provide glycemic control

A single dose of prandial insulin (ie, a rapidly acting analog) may be added before the largest meal of the day.

- Additional prandial doses may be used to control postprandial hyperglycemia until the patient is on 2 to 3 mealtime doses per day.
- Recommended starting doses of premeal rapid-acting insulins generally range from 5 to 10 U, or about 0.15 U/kg.
- Keep postmeal glucose <180 mg/dL at midmorning or <140 mg/dL 2 hours after lunch or dinner.

FPG, fasting plasma glucose.

Rosenstock J. Basal insulin supplementation in type 2 diabetes: refining the tactics. *Am J Med.* 2004; 116 (suppl):10S-16S.

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