

A white paper on emerging issues in the treatment of postprandial glucose in patients with type 2 diabetes

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Managing postprandial glucose levels in patients with diabetes

Program Goals

Epidemiologic and clinical studies suggest that postprandial glucose (PPG) levels correlate with an increased risk of cardiovascular disease in patients with impaired glucose tolerance and type 2 diabetes. This publication reviews the potential benefits to glycemic control and patient outcomes that may be obtained by targeting PPG levels in addition to fasting plasma glucose (FPG) levels in patients with diabetes.

Key Points and Recommendations

- All components of the glucose monitoring triad (HbA1c, FPG, and PPG levels) should be considered in the management of type 2 diabetes.
- In patients with type 2 diabetes, postprandial insulin secretion is not sufficient to suppress an excessive rise in PPG levels.
- Increasing evidence suggests that elevated PPG levels exert deleterious effects on the cardiovascular system.
- Recognition of the importance of PPG levels in addition to FPG levels and the availability of new pharmacologic options will provide new tools for diabetes management.
- These approaches may improve the overall success rate in achieving the target HbA1c levels known to improve patient outcomes.

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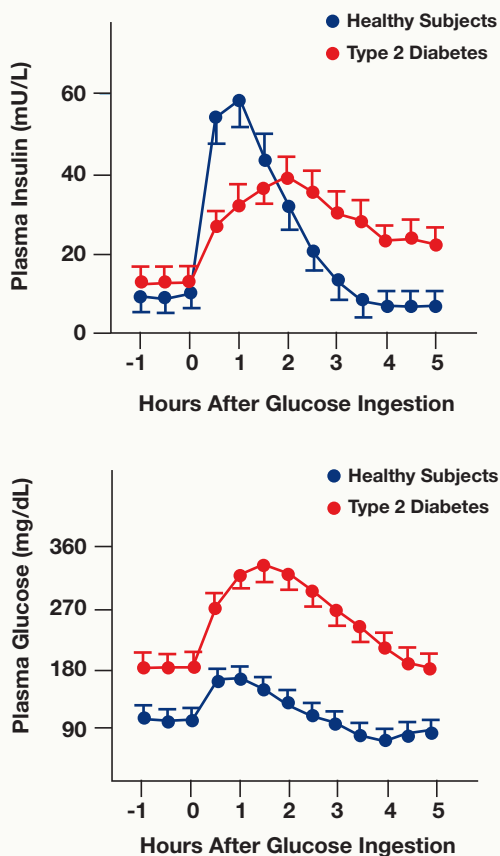
Of the many factors influencing insulin secretion, the most important treatment target is control of the amount of glucose transported from the blood into the beta cells of the pancreas. Even in healthy people, carbohydrate intake can lead to small increases in blood glucose and increased insulin secretion. If pancreatic beta cells can detect glucose levels and produce insulin, the insulin secretion usually is sufficient to maintain a fasting plasma glucose (FPG) level between 70 and 110 mg/dL and a postprandial glucose (PPG) level below 140 mg/dL. Diabetes leads to increasing resistance to insulin's effects and, early in the disease, greater output of endogenous insulin. Over time, beta cells fail to keep up; later, diabetes is characterized by both insulin resistance and insulin deficiency. Many patients are not diagnosed until both defects occur.

Is diagnosis based solely on fasting plasma glucose sufficient?

Nearly a third of affected individuals are unaware that they have type 2 diabetes.¹ FPG—the preferred method for diagnosis—may not identify all individuals with diabetes: 33% of patients diagnosed by PPG levels have normal FPG levels² and would

FIGURE 1

Type 2 diabetes: Blunted and delayed insulin response with higher and prolonged glucose excursions



Mean \pm arterial plasma glucose and insulin concentrations in nondiabetic (●; n = 10) and non-insulin-dependent diabetic (●; n = 10) subjects.

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have been missed by reliance on FPG measurements alone. Other diagnostic methods include a postprandial component or a postchallenge glucose measurement (75-g oral glucose tolerance test).²⁻⁴

Challenges in achieving glycemic control: Are current strategies adequate?

Currently, only 1 out of 3 patients achieves or maintains recommended glycemic levels.⁵ Treatment approaches that focus on FPG levels may

be inadequate. Type 2 diabetes results from both insulin resistance and impaired insulin secretion, primarily characterized by a gradual decline in insulin secretion in response to nutrient loads.⁶ Thus, it is a disorder of PPG regulation.² In the progression to diabetes, PPG levels often rise before FPG levels do. **FIGURE 1** shows the insulin curve, with increased time required for normalization of PPG.

Postprandial hyperglycemia (PPHG) may contribute significantly to overall glucose exposure in patients who can achieve normal or near-normal HbA1c levels. The lower the HbA1c level, the greater the contribution of PPG.⁷ For example, at HbA1c levels <7.3%, PPG contributes approximately 70% to elevated HbA1c levels; at HbA1c levels of 7.3% to 8.4%, approximately 50% of the HbA1c contribution comes from PPG. These findings may explain the inability of patients to achieve target HbA1c goals even when FPG levels appear to be controlled. Ideally, FPG and PPG levels should be determined at different time points during the day; many patients will not test often enough to reveal daily glucose patterns. It may be helpful for patients with higher HbA1c levels to measure their FPG levels more often, while those who are closer to achieving HbA1c goals measure mostly PPG levels.

The postprandial state is the norm for patients. The true fasting state typically exists only in the 2 hours before breakfast (for those who consume 3 meals a day at relatively fixed times).⁸ During the postprandial periods, insulin secretion in patients with type 2 diabetes does not fully compensate for insulin resistance. Monnier et al confirmed that worsening diabetes control is preceded by changes in daytime postprandial control, followed by changes during the morning (the dawn phenomenon, ie, the early morning rise in blood glucose, typically between 4 ' 1 and 8 ' 1), and finally by changes in nocturnal fasting control (**FIGURE 2**). As HbA1c levels exceed 6.5%, patients with near-normal FPG levels have abnormal elevations in PPG levels.⁹ This supports the

finding in recent treat-to-target trials that similar decreases in FPG levels did not result in similar improvements in HbA1c levels.^{10,11} In these trials, the use of a premixed insulin analog, which provides both fasting and postprandial coverage, resulted in superior HbA1c reductions compared with the combined use of basal insulin and oral agents. Whereas FPG reductions were similar, PPG reductions were greater when the premixed analog was used.^{10,11}

Although HbA1c level remains the primary target for glycemic control, the American Diabetes Association and the American Association of Clinical Endocrinologists have set specific goals for both FPG and PPG levels (TABLE).^{3,4} PPG

concentrations measured at midmorning will, for most patients, correspond to the highest glucose concentrations of daytime. Postprandial measurements taken 2 hours after lunch have been shown to provide an evaluation of overall glycemic control and to be excellent predictors of HbA1c levels (PPG <126 mg/dL predicts an HbA1c <7%).¹²

Summary

While normalizing FPG values may be an important goal of therapy in patients with type 2 diabetes, especially for those with very poorly controlled disease, there is strong evidence in support of monitoring and treating PPG elevations as well. ■

Effects of postprandial glucose levels on macrovascular complications

Optimal glycemic thresholds to prevent and slow progression of microvascular complications include an HbA1c level <6.5%, an FPG level <110 mg/dL, and a PPG level <180 mg/dL.¹³ The TABLE shows that these values roughly correlate with current association recommendations (AACE: HbA1c goal, ≤6.5%; FPG, <110 mg/dL; ADA: PPG goal, <180 mg/dL). Worsening of glycemic control, including elevated PPG levels, is correlated with microvascular complications.¹³ Evidence suggests additional metabolic and vascular implications of PPHG.

Epidemiologic and clinical studies show PPHG to be an independent risk factor for mortality, particularly cardiovascular.¹⁴⁻²² An 11-year follow-up of the Diabetes Intervention Study found a significantly greater incidence in mortality among patients with increased PPG levels (>200 mg/dL) at baseline, compared with patients who had good-to-borderline PPG levels (80-200 mg/dL).¹⁵ Another study group demonstrated that a 2-hour postchallenge glucose level after an oral glucose

tolerance test was a stronger predictor of risk for serious coronary heart disease events than were FPG levels.¹⁹ Over 17 years' follow-up, the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that patients receiving intensive treatment with basal and prandial insulin experienced significantly fewer cardiovascular events (ie, myocardial infarction, coronary revascularization, and confirmed angina) than those receiving conventional treatment (0.4 vs 0.8 events per 100 patient-years; $P = .007$). Intensive treatment showed a 42% risk reduction in the cumulative incidence of a first cardiovascular event ($P = .02$).²³ These data suggest that PPG may play an independent, modifiable role in cardiovascular disease.

The mechanisms by which PPHG may contribute to excess cardiovascular events in patients with diabetes remain unclear. However, studies indicate that PPHG may have a direct toxic effect on the vascular endothelium, mediated by oxidative

TABLE
Recommended preprandial and postprandial glucose goals

Guideline	Measure	Goal
American Diabetes Association	Peak postprandial capillary plasma glucose*	<180 mg/dL
	Preprandial capillary plasma glucose	90-130 mg/dL
American Association of Clinical Endocrinologists	2-hour postprandial glucose concentration	<140 mg/dL
	Fasting plasma glucose	<110 mg/dL

*Postprandial glucose measurements should be taken 1 to 2 hours after the beginning of a meal, at which time glucose levels generally peak in patients with diabetes. American Diabetes Association. *Diabetes Care*. 2007;30(suppl 1):S4-41; American Association of Clinical Endocrinologists. *Endocr Pract*. 2007;13(suppl 1):S3-S68.

HbA1c or mean daily glucose concentrations. These findings may explain those of the DCCT, which found that at the same level of HbA1c control, patients who received prandial and basal insulin had less retinopathy than did patients treated with conventional insulin therapy.²⁸

In addition to making a case for treating PPG excursions, Monnier's findings may point to a greater need for PPG monitoring in clinical practice. The risk

stress and independent of other cardiovascular risk factors.²⁴ PPHG has also been shown to be an independent risk factor for atherosclerosis and may amplify the effects of other risk factors, such as elevated triglycerides.²⁵ The Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes (RIAD) study suggests that post-challenge hyperglycemia relates more strongly with carotid intima-media thickness than does fasting hyperglycemia.²⁶ PPHG may exert its effects through its substantial contribution to total glycemic exposure.

Glycemic variability may contribute more strongly to the risk of diabetic complications than does total glycemic exposure.²⁷ Glucose fluctuation during postprandial periods has demonstrated greater triggering effects on oxidative stress than does chronic sustained hyperglycemia, as measured by

of stroke and death from heart disease among adults with type 2 diabetes is 2 to 4 times higher than for those without diabetes, and heart disease remains the number one cause of death in this patient population.¹ Therefore, aggressive early intervention to control hyperglycemia and PPHG—before the manifestation of complications—is a strategy likely to yield the best results in preventing diabetes sequelae.²⁹

Summary

Oxidative stress caused by PPHG may now be recognized as an important contributing factor in the development of diabetes complications. PPG control may hold the key to improving overall glycemic control, minimizing glycemic variability, and reducing the risk of diabetes-associated cardiovascular disease. ■

Effective therapeutic options for managing postprandial glucose

Current treatment approaches primarily target FPG levels and emphasize the use of oral antidiabetic agents (OADs) to reduce FPG and to lower HbA1c levels. Indirectly, they also affect PPG levels. Combination therapy with traditional agents also can benefit PPG levels. For example, the combination of glyburide and metformin, each at ~50% of the usual dose, reduces FPG, PPG, and HbA1c levels significantly more than either agent used alone, possibly by altering pharmacokinetics when used in combination.³⁰

Treatment strategies and specific agents can also reduce PPG levels directly. Lifestyle modification is effective in reducing PPG excursions and progression to diabetes. Foods with a low glycemic index as well as high-fiber or fiber-supplemented diets reduce PPG levels. Mixed meals that feature carbohydrate, fiber, and fat slow glucose absorption, thereby reducing PPG levels.³¹

Pharmacologic agents that counteract PPG excursions include rapid-acting insulin secretagogues (glinides, ie, repaglinide, nateglinide), alpha-glucosidase inhibitors (acarbose, miglitol), and rapid-acting insulin analogs. New agents—pramlintide, glucagon-like peptide-1 [GLP-1] agonists, and dipeptidyl peptidase [DPP]-4 inhibitors—effectively target PPG.

Glinides. Although the pharmacologic effect of the rapid-acting insulin secretagogues repaglinide and nateglinide is similar to that of the sulfonylureas, the short half-life of the glinides and their capacity to stimulate acute-phase insulin release permit their use as mealtime medications. Esposito et al demonstrated that treatment with repaglinide was more effective at controlling PPHG to <140 mg/dL than was a sulfonylurea (glyburide).³² Improved PPHG was achieved with the additional outcome of regression in carotid atherosclerosis

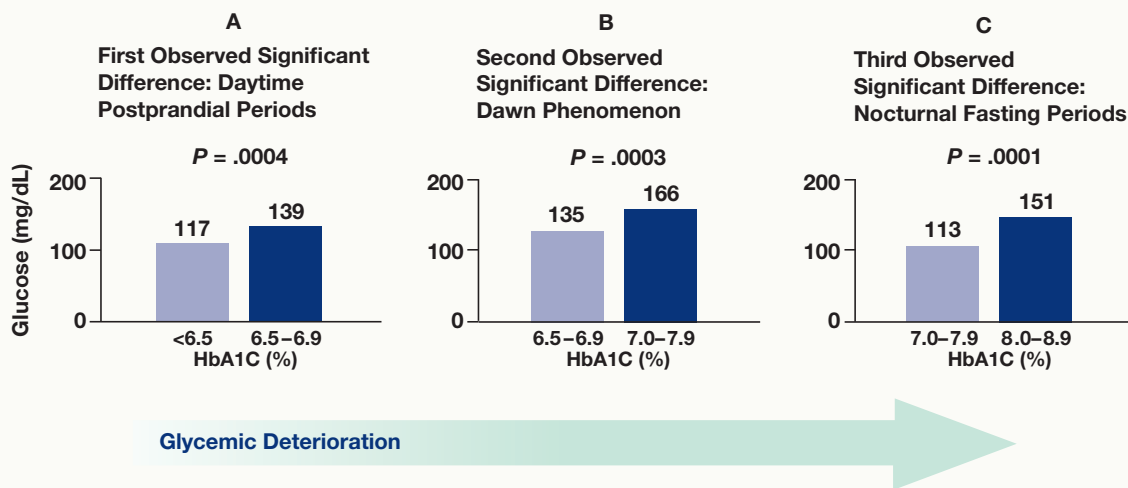
as measured by carotid intima-media thickness. Other inflammatory markers (eg, interleukin-6 and C-reactive protein) were also decreased.

Alpha-glucosidase inhibitors. Also known as disaccharidase inhibitors, these agents reduce PPG levels but have limited effects on FPG; overall reductions in HbA1c levels tend to be modest. The Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial found that treatment with acarbose reduced PPHG and resulted in a 49% relative risk reduction (2.5% absolute risk reduction) for any cardiovascular event.³³ This effect was attributed primarily to a major risk reduction for myocardial infarction in patients with impaired glucose tolerance.³³

Short-acting and rapid-acting insulins. Insulin remains the most powerful tool for optimal glucose control. Limitations include weight gain and the risk of hypoglycemia (although this risk is lower in type 2 diabetes than in type 1 diabetes).³⁴ Therapy is generally initiated with basal insulin, which will not address PPG. Basal-bolus insulin therapy mimics normal physiology more accurately but requires 4 or more daily injections. Premixed formulations provide FPG and PPG coverage and can be used initially as a single injection before the largest meal but may require injection BID or even TID.³⁵

The practical use of regular human insulin to control PPG is limited by its pharmacokinetics. Slower onset of action of regular human insulin requires injection 30 to 60 minutes prior to a meal to ensure that peak concentrations coincide with increased PPG levels. Patients, however, tend to inject their insulin at mealtime. The rapid-acting insulin analogs (aspart, lispro, glulisine) are designed to provide PPG coverage more physiologically to achieve higher postprandial insulin levels and more

FIGURE 2
Stepwise glycemetic deterioration in diabetes: Loss of postprandial control precedes other defects



HbA1C, glycosylated hemoglobin level.

Progressive deterioration of glycemetic profiles according to glycosylated hemoglobin (HbA1C) levels in the 3 study periods: daytime postmeal period (A), morning period (dawn phenomenon) (B), and nocturnal fasting period (C). Data are geometric means of glucose concentrations and superior value of 95% confidence interval. Only the initial differences in mean glucose concentrations reaching statistical significance are indicated. Statistical comparisons were considered significant for $P < .05/n$ (n = comparison number, Bonferroni correction).

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rapid declines in 2-hour PPG levels.³⁶ Markers of oxidative stress (eg, nitrotyrosine) are reduced with rapid-acting insulin analogs. Thus, the addition of prandial insulin to basal insulin effectively targets PPG.²⁴

Inhaled insulin. The only inhaled insulin marketed in the United States was recently withdrawn for commercial reasons; however, similar products are in development. Inhaled insulin (insulin human [rDNA origin] inhalation powder) could be used with OADs and/or a single injection of basal insulin, or as part of a basal/bolus regimen to provide prandial coverage, with PPG control comparable to or better than that of regular human insulin.³⁷⁻³⁹ In randomized studies, use of inhaled human insulin before meals improved PPHG in both type 1 and type 2 diabetes.³⁷⁻⁴³

Inhaled insulin should not be used in patients with chronic, unstable, or poorly controlled lung

disease; smokers; or those who quit smoking <6 months earlier. If smoking is resumed, treatment should be discontinued immediately.⁴⁴

Pramlintide. This amylin agonist is an adjunct treatment in patients who have not achieved glucose control despite optimal prandial insulin therapy. Coadministration with prandial insulin reduces PPG excursions by 75% to 100% versus treatment with prandial insulin alone.^{45,46} Pramlintide, 60 or 120 mcg BID or TID, also reduced mean PPG increments by 24 mg/dL in patients who had achieved suboptimal control with basal insulin with or without OADs.⁴⁷ The PPG reductions achieved with pramlintide are associated with decreases in markers of oxidative stress and with prevention of elevations in such markers.⁴⁸ The weight loss effect of pramlintide may counterbalance the weight gain often seen with insulin therapy.⁴⁷

Incretin mimetics. The GLP-1 agonists (eg, exenatide) and DPP-4 inhibitors (eg, sitagliptin) offer new approaches to PPG control. Exenatide blunts, and thereby improves, PPG excursions. These effects are mediated by glucose-dependent stimulation of insulin secretion and suppression of inappropriately elevated glucagon levels typical of patients with type 2 diabetes. Clinical trials with exenatide have demonstrated sustained improvement in blood glucose control associated with weight loss of up to 11 pounds after 1 year.⁴⁹⁻⁵² Durable reductions in HbA1c, progressive weight loss, and improvements in cardiovascular risk factors (lipid profiles and blood pressure) have been observed. As a component of combination therapy with oral antidiabetic agents, targeting PPG levels have allowed an increased number of patients to achieve glycemic goals (HbA1c \leq 7%).⁴⁹⁻⁵¹

The antidiabetic effect of the DPP-4 inhibitors depends mainly on prolonging activity of the 2 principal incretin hormones—GLP-1 and glucose-dependent insulinotropic peptide (GIP). DPP-4 inhibitors prevent the rapid degradation of GLP-1 and GIP by the enzyme DPP-4, thereby having a greater effect on decreasing PPG than on decreasing FPG. Thus, whereas treatment with sitagliptin monotherapy was shown to decrease FPG by about 20 mg/dL, PPG was decreased by about 50 mg/dL.⁵³ In patients inadequately controlled on glimepiride alone or with glimepiride and metformin, the addition of sitagliptin reduced FPG by 20 mg/dL and PPG by 36 mg/dL, and increased beta-cell function by 12%.⁵⁴ Treatment with metformin

plus a DPP-4 inhibitor improved FPG and PPG and resulted in significant improvements in insulin secretion and indices of beta-cell function.⁵⁵ These data support a role for combination therapy targeting both FPG and PPG levels to improve glycemic control in patients with type 2 diabetes.

Summary

Therapeutic strategies to enhance PPG control include oral agents and injectable agents such as insulin, exenatide, and pramlintide. The ability of these agents, when used in combination with agents that target FPG, to help more patients reach their HbA1c goals supports the use of combination strategies to improve overall glycemic control.

Conclusions

By focusing solely on controlling FPG levels, clinicians may miss opportunities to help patients meet glycemic targets, minimize glucose variations, and control PPG excursions, with negative effects on long-term patient outcomes. Physicians should consider targeting PPG levels to more effectively treat diabetes and, thereby, reduce the risk of complications. Studies are indicating that ideal diabetes management will likely require therapies that improve not only FPG levels but also PPG levels in order to achieve overall optimal glycemic control and outcomes. ■

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