The Importance of Postprandial Plasma Glucose Control

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PROGRAM OVERVIEW
Several landmark clinical studies have demonstrated the relationship between type 2 diabetes and increased risk of both microvascular and macrovascular complications. Optimal glycemic control is vital to managing these risks in patients with type 2 diabetes. However, recent estimates indicate that only 57% of type 2 diabetes patients reach the American Diabetes Association glycemic target of A1C < 7%. Historically, glycemic control efforts have emphasized achievement of A1C and fasting plasma glucose (FPG) targets. It has recently become increasingly evident that postprandial increases in blood glucose levels also contribute significantly to overall glycemic control and to the development of diabetes complications. Consequently, postprandial plasma glucose (PPG) control is receiving recognition as an essential therapeutic target for optimizing glycemic control in patients with type 2 diabetes. This publication series will explore the science of PPG and its contribution to glycemic control, and highlight recent and emerging therapies that address this important target.

INTENDED AUDIENCE
This program is intended for endocrinologists, diabetologists, and other healthcare professionals (HCPs) who frequently treat patients with type 2 diabetes.

LEARNING OBJECTIVES
After completing this issue, participants should be able to:
- Describe the relative contribution of FPG and PPG to overall glycemic control among patients with type 2 diabetes, and explain how this relationship changes at different levels of glycemic control
- Explain the pathophysiologic defects that preclude the development of type 2 diabetes, and indicate when elevated PPG begins to play a contributing role
- Discuss the available evidence suggesting that elevated PPG leads to increased macrovascular complications

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INTRODUCTION
Diabetes can be defined as a state of chronic hyperglycemia that increases the risk of microvascular complications, namely retinopathy, nephropathy, and neuropathy. However, diabetes is also associated with increased risk of macrovascular complications including ischemic heart disease, stroke, and peripheral vascular disease, and in fact these are the leading causes of mortality in patients with diabetes. Type 2 diabetes is characterized by progressive β-cell failure and decreased production of the β-cell-derived glucoregulatory hormones, insulin and amylin. Compounding the insulin deficiency is a diminished responsiveness to insulin action, or insulin resistance, in peripheral tissues. The combined effect of these 2 physiologic abnormalities is hyperglycemia, both in the fasting state and after eating.

Landmark studies have demonstrated that therapies designed to lower average blood glucose (BG) to levels approaching the normal range reduce the risks that microvascular complications will develop or progress. The results of these studies have prompted the development of treatment guidelines for type 2 diabetes emphasizing goals for glycemic control that have been demonstrated to prevent the development of diabetes complications or limit their progression.

The pathophysiology of type 2 diabetes is complex and includes more than abnormalities of glucose metabolism. Patients with diabetes also have additional metabolic abnormalities such as hyperlipidemia and hypertension, and interventions that correct these abnormalities are also recommended to reduce microvascular and macrovascular complications in these patients. Moreover, while a substantial reduction in insulin action is central to diabetes, it is likely that other hormonal abnormalities contribute to the clinical picture of this condition.

Macrovascular disease has a multifactorial etiology, and the role of hyperglycemia in this process has been difficult to define. Several large, randomized, controlled trials failed to demonstrate that intensive treatment of BG reduced macrovascular complications associated with diabetes. Nonetheless, the increased risk of vascular complications shared by persons with types 1 and 2 diabetes suggests that dysregulated glucose contributes to this important complication, and dismissing treatment of hyperglycemia as unhelpful to limit macrovascular disease is an overly rigid interpretation of current evidence. For example, a recent meta-analysis of randomized trials comparing conventional treatment with interventions targeted to improve glycemic control demonstrated that improved glycemic control was associated with a decreased incidence of macrovascular events.
Plasma glucose (PG) levels can be assessed using several different measures that have specific uses and can provide insights into pathophysiology. For example, PG levels measured after an overnight fast have become the standard for diagnosing diabetes. Fasting glucose levels are a function of endogenous, mostly hepatic, glucose production, and elevated concentrations reflect some combination of insulin deficiency, glucagon excess, and hepatic insulin resistance.16-18 PG levels measured after consumption of a standardized meal or a fixed quantity of liquid glucose provide information as to how the glucose homeostatic system can respond to a challenge and give insights into the adequacy of insulin secretion and the degree of insulin sensitivity. The following sections describe and explain the use of several glycemic indicators that are commonly used in diabetes diagnosis and management: fasting plasma glucose (FPG), postchallenge plasma glucose (PCPG), glycosylated hemoglobin (glycated hemoglobin, hemoglobin A1C, HbA1c, or A1C), and PPG.

**Measuring plasma glucose for diabetes diagnosis**

Diagnostic criteria for diabetes may be based on FPG, oral glucose tolerance test (OGTT), or casual PG levels.1,4,5 FPG is measured after an extended period (eg, 8-12 hours) with no caloric intake.4,5 FPG is the measure preferred by the American Diabetes Association (ADA) for the diagnosis of diabetes because of its ease, relatively low cost, and extensive standardization.4 FPG levels ≥ 126 mg/dL (7 mmol/L) on 2 separate occasions constitute a diagnosis of diabetes. A BG level ≥ 200 mg/dL (11.1 mmol/L) 2 hours after the ingestion of 75 g liquid glucose solution, an OGTT, is also diagnostic of diabetes.1,4,5 OGTTs are more sensitive than FPG for diagnosing abnormalities of glucose metabolism, including diabetes, but are time consuming and more variable.4 Both of these diagnostic criteria are based in part on their association with microvascular complications.1,4,5,11 A third diagnostic indicator of diabetes is a random, or casual, glucose level ≥ 200 mg/dL (11.1 mmol/L) with symptoms of hyperglycemia (primarily polyuria and polydipsia).4,5

PPG is the BG level measured 1-2 hours after eating.7 Similar to an OGTT, PPG is a measure of PG level after glucose intake and indicates the patient’s ability to use glucose over time. However, because administration of a standardized glucose load is not required, PPG can be readily determined through self-monitoring of blood glucose (SMBG) and can therefore be used as an end point in the management of type 2 diabetes.4,5,19

The World Health Organization (WHO), ADA, and American Association of Clinical Endocrinologists (AACE) diagnostic criteria based on FPG and OGTT levels are provided in Table 1.1,4,5 Patients meeting 1 criterion receive the corresponding diagnosis, with the exception that patients must fulfill both criteria to receive a diagnosis of prediabetes according to WHO guidelines.1,4,5 In addition, ADA and AACE criteria provide for diagnosis of diabetes based on the presence of diabetes/hyperglycemia symptoms (polyuria, polydipsia, unexplained weight loss) and a casual PG level of ≥ 200 mg/dL.4,5 Table 1 also includes criteria for the diagnosis of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), conditions that are also referred to as prediabetes and are associated with increased risk for developing diabetes.1,4,5

**Monitoring plasma glucose levels for diabetes management**

A number of studies have revealed the importance of glycemic control in patients with type 2 diabetes. In the Kumamoto study, intensive glycemic control prevented and delayed the progression of retinopathy, nephropathy, and neuropathy in patients with type 2 diabetes.10 Based on analysis of the combined primary prevention and secondary intervention cohorts in this study, intensive glycemic control reduced the risks of worsening retinopathy and nephropathy by 69% and 70%, respectively.10 The United Kingdom Prospective Diabetes Study (UKPDS) similarly reported that lower glycemic exposure was associated with a 25% reduction in the risk of microvascular complications.8 Additional analyses of the data demonstrated that the risk of microvascular complications decreases 37% for each 1% reduction in A1C level.20
Current evidence regarding the general benefits of tight glycemic control on cardiovascular outcomes in patients with type 2 diabetes is not as convincing as the case for limiting microvascular disease. Among patients in the UKPDS who were allocated to sulfonylurea or insulin treatment, reduction in the risk of myocardial infarction (MI) was of borderline significance, while a significant 30% reduction in cardiovascular risk was reported for overweight patients treated with metformin. A subsequent analysis of UKPDS data revealed a 14% decrease in the risk of MI associated with each 1% decrease in A1C level.

Subsequent studies have yielded results that do not support the hypothesis that tighter glycemic control improves cardiovascular risk. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to demonstrate whether intensive diabetes treatment that targeted a hemoglobin A1C of less than 6% would reduce cardiovascular events compared with standard therapy. The ACCORD trial was terminated early due to an increased rate of death from any cause in the intensive therapy group compared with the standard therapy group. Analysis of the study data also revealed an increased death rate due to cardiovascular causes in the intensive therapy group compared with the standard group. There was no difference between the intensive and standard therapy groups in the primary composite cardiovascular outcome.

Like the ACCORD trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study and the VA Diabetes Trial (VADT) were large, long-term studies designed to determine whether intensive glycemic control improves cardiovascular outcomes compared with standard glycemic control in patients with established type 2 diabetes. The ADVANCE study and VADT were completed in 2008. Intensive glycemic control was not associated with a significant decrease in cardiovascular events in either study. The number of cardiovascular events was lower than expected for both the standard and intensive therapy groups in the VADT, but this may have been due to better control of hyperlipidemia and hypertension in both groups. In contrast with ACCORD, tighter glycemic control was not associated with increases in cardiovascular-related death or death due to any cause in the ADVANCE study and VADT.

While recent clinical trials of the effects of tight glycemic control on macrovascular disease have not demonstrated a benefit over the course of the study, recently published results from the UKPDS indicate a legacy effect of tight glycemic control. Ten years after the end of this study, the intensive glycemic control group had a lower risk of MI than the standard control group despite the fact that differences in glycemic control between the 2 groups were lost as early as 1 year after the end of the study. This observation serves to highlight the complexity of macrovascular disease, the potential for interventions to have different effects at different points in the natural history of this condition, and the need to be circumspect in the interpretation of specific trials.

In addition to the ACCORD and UKPDS findings, a meta-analysis of randomized controlled trials to compare glycemic interventions demonstrated that tight glycemic control decreased the incidence of macrovascular events, particularly stroke and peripheral vascular events, in patients with type 2 diabetes. The effect was most pronounced among younger patients with shorter disease duration, emphasizing the importance of individualizing interventions based on the patient’s clinical characteristics.

In light of the existing evidence, the ADA recommends glycemic goals that are near normal and acknowledges the importance of individualizing diabetes management so that glycemic goals can be safely achieved. Glycemic goals from treatment guidelines developed by the International Diabetes Federation (IDF), ADA, and AACE are presented in Table 2.

<table>
<thead>
<tr>
<th>Glycemic Target</th>
<th>IDF</th>
<th>ADA</th>
<th>AACE</th>
</tr>
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<tbody>
<tr>
<td>A1C (%)</td>
<td>&lt; 6.5%</td>
<td>&lt; 7.0%</td>
<td>≤ 6.5%</td>
</tr>
<tr>
<td>PrePG (mg/dL)</td>
<td>&lt; 110 mg/dL</td>
<td>70-130 mg/dL</td>
<td>&lt; 110 mg/dL</td>
</tr>
<tr>
<td>PPG (mg/dL)</td>
<td>&lt; 145 mg/dL*</td>
<td>&lt; 180 mg/dL*</td>
<td>&lt; 140 mg/dL*</td>
</tr>
</tbody>
</table>

IDF, International Diabetes Federation; ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists; A1C, glycated hemoglobin; PrePG, preprandial plasma glucose; PPG, postprandial plasma glucose.

*Measured 1-2 hours after start of meal; †measured 2 hours after start of meal.

Hemoglobin molecules inside red blood cells are glycosylated, covalently bound to glucose, in proportion to circulating glucose levels. There are several assays of glycosylated hemoglobin that have been used to monitor glycemic control in diabetic patients. The best established assay method, referred to as hemoglobin A1C or simply A1C, has become the gold standard because of its use in major clinical trials and because it is widely standardized.

Hemoglobin molecules are removed from circulation with aged red blood cells, so their lifespan is about 120 days. The degree of glycosylation increases over the red cell lifespan so that conditions that affect red cell lysis or production, such as hemolytic anemia or erythropoietic stimulation, can falsely reduce A1C. However, for most patients, A1C measurements provide a record of average PG levels over the previous 2 to 3 months.

Because it provides an integrated estimate of glycemia over time and has been the primary end point for the major diabetes intervention trials, A1C has become the primary clinical target for monitoring glycemic control. However, it is not currently recommended for diabetes diagnosis. Practice guidelines recommend measuring A1C every 2 to 6 months. Clinicians should have access to A1C results during a patient’s office visit to promote timely and appropriate therapy adjustment.
Results of a recent study affirmed a linear relationship between A1C and estimated average glucose (eAG). A list of A1C values and their corresponding eAG levels is presented in Table 3.27

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>eAG (mg/dL)*</th>
<th>eAG (mmol/L)*</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>97 (76-120)</td>
<td>5.4 (4.2-6.7)</td>
</tr>
<tr>
<td>6</td>
<td>126 (100-152)</td>
<td>7.0 (5.5-8.5)</td>
</tr>
<tr>
<td>7</td>
<td>154 (123-185)</td>
<td>8.6 (6.8-10.3)</td>
</tr>
<tr>
<td>8</td>
<td>183 (147-217)</td>
<td>10.2 (8.1-12.1)</td>
</tr>
<tr>
<td>9</td>
<td>212 (170-249)</td>
<td>11.8 (9.4-13.9)</td>
</tr>
<tr>
<td>10</td>
<td>240 (193-282)</td>
<td>13.4 (10.7-15.7)</td>
</tr>
<tr>
<td>11</td>
<td>269 (217-314)</td>
<td>14.9 (12.0-17.5)</td>
</tr>
<tr>
<td>12</td>
<td>298 (240-347)</td>
<td>16.5 (13.3-19.3)</td>
</tr>
</tbody>
</table>

The IDF, ADA, and AACE treatment guidelines also include target PG levels that correspond with the target A1C values.4,5,11 Preprandial plasma glucose (PrePG) and PPG levels are measured before and after a meal, respectively, and are applicable in the context of patient self-management.4,5,11,19 PrePG levels may be used interchangeably with FPG levels.5,19 SMBG can provide patients with information to assess their therapeutic response and adjust their treatment regimen.4 Results from SMBG also can complement A1C measurements.4,11 Because A1C is an average measure and does not reflect glycemic variability, a combination of SMBG and A1C may be appropriate to judge glycemic control in patients who experience glucose fluctuations.4 Timing and frequency of SMBG are generally determined by the patient’s needs.4 For example, an individual who is not reaching A1C goals despite good FPG levels may be advised to assess PPG levels to determine whether postmeal glucose fluctuations are high enough to be treated in order to improve overall glycemic control.4

Relative FPG and PPG contributions to A1C
Both FPG and PPG contribute to A1C, but the specific relationship among these glycemic indicators remains unclear.33 In a study of patients with good glycemic control (A1C < 7.0%) who were not treated with insulin, Bonora et al observed that A1C levels correlated most closely with mean plasma glucose (MPG) levels and less so with PrePG/ FPG levels. The poorest correlation was between A1C and PPG levels.34 In contrast, a study of patients receiving insulin therapy (mean A1C = 7.83%) demonstrated that A1C correlated better with PPG than FPG levels.35 In fact, the strongest correlations with A1C were noted for PPG levels measured after breakfast and dinner.

In a study of patients with type 2 diabetes treated with diet and/or metformin, Monnier et al demonstrated that PPG levels make a greater relative contribution to A1C in patients with good glycemic control, and FPG levels have a greater impact on A1C in patients with poor glycemic control (Figure 1).36 The study by Monnier et al specifically excluded patients receiving acarbose or insulin because these treatments affect PPG excursions.36 For patients with poor glycemic control, PPG contributed approximately 30% to A1C, but the PPG contribution was 70% in patients with A1C values < 7.3%.36 The observations of Monnier et al suggest that achieving PPG control may be important to achieving near-normal glucose levels because of a disproportionate contribution of PPG to overall glycemic control as A1C levels approach the normal range.36

The Challenge of Meeting Glycemic Targets
Despite evidence supporting the benefits of tight glycemic control for patients with type 2 diabetes, a large number of patients do not meet recommended glycemic targets. Recent estimates indicate that 57% of type 2 diabetes patients reach the ADA glycemic target of A1C < 7%, and only 33% reach the AACE glycemic target of A1C ≤ 6.5%.28,29 It is essential to identify treatment approaches to improve glycemic control in order to prevent complications due to diabetes and to avoid the associated rise in health care costs.30 Historically, glycemic control efforts have emphasized achievement of A1C and FPG targets.31,32 However, it is becoming increasingly evident that postprandial increases in PG levels (also referred to as PPG excursions) also contribute significantly to overall glycemic control and to the development of diabetes complications.5,32,33 Consequently, PPG control is receiving recognition as an essential therapeutic target for optimizing glycemic control in patients with type 2 diabetes.4,5,32-34 Acceptance of PPG control as a therapeutic goal for type 2 diabetes has been facilitated by the introduction of agents that specifically target PPG.33
Data generated to date suggest that the relative contributions of FPG and PPG to overall glycemic control depend, to some extent, on a patient’s clinical characteristics. Consistent with these observations, treatment guidelines for type 2 diabetes include recommendations for personalizing diabetes management plans to include SMBG and PPG control as necessary.4,5,19

The importance of managing PPG to meet lower glycemic targets

Arguments can be made for measuring both FPG and PPG to achieve optimal glycemic control.33 Rationale supporting the use of each are listed in Table 4.33

Although PPG control is likely to improve overall glycemic control, a case can be made for targeting FPG first because PPG levels are elevated, in part, due to increased FPG levels.33 In addition, FPG is subject to fewer variables than PPG, which is affected by factors such as nutrient content of the meal and gastric emptying.33 According to this rationale, monitoring and correcting PPG levels would be considered appropriate for patients who have discrepant A1C and FPG measures.4 In these scenarios, monitoring and correcting PPG levels may have benefit on glycemic control in specific patients.

### Table 4. Reasons to Target FPG or PPG Values33

<table>
<thead>
<tr>
<th>FPG</th>
<th>PPG</th>
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<tbody>
<tr>
<td>• Contributes to A1C</td>
<td>• Contributes to A1C</td>
</tr>
<tr>
<td>• Determinant of PPG</td>
<td>• Better glucose control (A1C &lt; 8.4%)</td>
</tr>
<tr>
<td>• Poor glucose control (A1C &gt; 8.4%)</td>
<td>• Contributes ≈ 70% when A1C &lt; 7.3%</td>
</tr>
<tr>
<td>• Contributes ≈ 70% when A1C &gt; 10.2%</td>
<td>• Is frequently the earliest abnormality of type 2 diabetes</td>
</tr>
<tr>
<td>• More reproducible</td>
<td>• May represent an independent risk for cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>• Preprandial, but not A1C, at goal</td>
</tr>
<tr>
<td></td>
<td>• Gestational diabetes</td>
</tr>
<tr>
<td></td>
<td>• For patients using medications targeting PPG</td>
</tr>
<tr>
<td></td>
<td>• If postprandial hypoglycemia is expected</td>
</tr>
</tbody>
</table>

There is currently support for using all 3 glycemic measures — A1C, FPG, and PPG — to direct therapy necessary to achieve the glucose targets that have been demonstrated to reduce the risk of complications due to diabetes.4,5,19 This is particularly true for patients who are not meeting A1C goals or who are treated with multiple daily insulin injections.

It is now evident that a large number of patients with type 2 diabetes experience significant PPG excursions, even in the context of good control according to A1C and FPG measurements. A study by Bonora et al revealed that > 60% of patients with type 2 diabetes experienced PPG excursions higher than 160 mg/dL.34 This was true even in patients with A1C levels < 7.0. Erlinger and Brancati reported similar findings, with 74% of patients experiencing postchallenge hyperglycemia in response to an OGTT.37

PPG and the Pathophysiology of Type 2 Diabetes

There is general consensus that, for many patients, IGT is an early stage in diabetes pathogenesis.1,4,5,38,39 IGT is a specific instance of postprandial hyperglycemia, defined by a BG level of 140 to 200 mg/dL (7.8-11 mmol/L) 2 hours after oral glucose ingestion in persons who have normal fasting glucose concentrations.1,4,5 The risk for subjects with IGT to progress to diabetes is about 30% over 3 years.40 The state of IGT, an abnormality in PPG but not FPG, suggests that monitoring glycemia after a glucose challenge may be more sensitive than after a period of fasting. According to ADA criteria, IFG is defined by a BG concentration of 100 to 125 mg/dL (5.6-6.9 mmol/L) and can accompany IGT.4 Together, IGT, IFG, and IGT/IFG are considered to be prediabetic states.4

Even in instances where PPG elevation is not measured prior to a diabetes diagnosis, it is detectable early in the progression of the disease, and elevated PPG levels are considered to be a sensitive indicator for diagnosis.1,4,38 The progressive loss of β-cell function, insulin secretion, and insulin sensitivity contributes to the development of postprandial hyperglycemia (Figure 2).32,41
**Consequences of poor PPG control**

Individuals with diabetes have increased cardiovascular risk. Heart disease death rate and the risk for stroke are 2 to 4 times higher in adults with diabetes than adults without diabetes. In fact, recommendations of the National Cholesterol Education Program (NCEP) include diabetes as a coronary heart disease (CHD) risk equivalent because patients with diabetes have the same risk of experiencing major coronary events as individuals with CHD. The cardiovascular mortality rate among patients with type 2 diabetes has been estimated at 52%, making cardiovascular disease the leading cause of death in patients with type 2 diabetes.

Poor PPG control has been associated with development of surrogate markers for cardiovascular disease and has recently been proposed as a risk factor for cardiovascular disease. A number of studies have demonstrated an association between poor PPG control and the development of cardiovascular disease. The IDF Guideline for Management of Postmeal Glucose provides a good review of these studies.

In particular, the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study is 1 key study that demonstrated that PPG glucose levels better predicted excess mortality due to all causes and cardiovascular events than FPG levels.

Several mechanisms have been hypothesized to explain the increased cardiovascular risk that has been attributed to postprandial hyperglycemia, such as oxidative stress and free radical generation, inflammation, endothelial dysfunction, and hypercoagulability. For example, in a study comparing patients with type 2 diabetes and normal controls, Monnier et al measured excretion of urinary 8-iso-PGF to assess oxidative stress over 24 hours. Oxidative stress was higher for patients with type 2 diabetes and correlated most strongly with the amplitude of postprandial glucose excursions.

Perhaps the most convincing evidence that elevated PPG contributes to cardiovascular risk in patients with type 2 diabetes comes from studies in which amelioration of postprandial hyperglycemia improves cardiovascular outcomes. Although no completed studies have demonstrated that controlling PPG levels decreases the risk of macrovascular disease in patients with type 2 diabetes, data suggest that this may be the case. For example, treatment with acarbose, an α-glucosidase inhibitor that decreases PPG excursions, has been associated with decreased risk of MI, improved lipid profiles, decreased blood pressure, and slower progression of intima-media thickness (a surrogate marker for atherosclerosis) compared with placebo.

Esposito et al compared the effects of repaglinide, an agent that targets PPG control, with glyburide, an agent that has greater effects on FPG. Both groups generated the same decrease in A1C, but carotid intima-media thickness (CIMT) decreased to a greater extent in the repaglinide group than the glyburide group. In addition, repaglinide treatment was associated with greater decreases in several markers of inflammation, namely interleukin-6 (IL-6), IL-18, and C-reactive protein (CRP). Findings such as these raise the possibility that the use of interventions to target PPG levels can achieve cardiovascular benefits in addition to better glycemic control. However, it is important to note that this hypothesis has not been conclusively established in well-controlled trials or widely accepted into clinical medicine.

**Intervening to address PPG fluctuations**

Consumption of foods that are low in dietary fiber content and contain higher proportions of readily digestible carbohydrates are associated with development of type 2 diabetes and CHD. In addition, physical inactivity increases insulin resistance, which in turn exacerbates PPG excursions. Diet and exercise can improve PPG and A1C levels and are recommended as first-line therapeutic approaches for patients with type 2 diabetes. However, even compliant patients with an initial positive response to diet and exercise are unable to maintain glycemic control with lifestyle modification alone and will require therapeutic intensification using a combination of pharmacologic antihyperglycemic agents. Because a majority of patients with type 2 diabetes will eventually require pharmacologic agents, and in the interest of space limitations, this review will focus on pharmacologic agents that target PPG control. Specifically, incretin-based therapies are reviewed in depth because they are the newest agents to address PPG.

In type 2 diabetes, postprandial hyperglycemia is the consequence of a collection of physiologic abnormalities, including:

- Insulin resistance, which impedes glucose uptake by peripheral tissues like skeletal muscle and fat.
- Decreased β-cell function with insufficient insulin secretion to compensate for insulin resistance. In patients with diabetes, insulin secretion is lower in absolute terms and delayed in response to eating or hyperglycemia.
- Impaired suppression of glucagon and endogenous hepatic glucose production.
- Faster glucose delivery due to more rapid gastric emptying, a characteristic of many patients with early diabetes.
Agents that target postprandial glycemic control affect 1 or more of these underlying pathophysiologic characteristics. Classes of agents available for managing PPG levels include fast-acting insulin analogs, glinides, α-glucosidase inhibitors, amylin analogs, and incretin-based therapies. Fast-acting insulin analogs have rapid onset, peak, and short duration of action. They were developed to provide insulin replacement in a manner that is more physiologic, and more convenient for patients. The glinides are rapid-acting insulin secretagogues that stimulate β-cell activity. The α-glucosidase inhibitors inhibit a key enzyme in carbohydrate digestion to slow carbohydrate absorption and decrease the PPG peak.

Because insulin and amylin have multiple roles in glucose regulation, replacing these hormones addresses several physiologic abnormalities. For example, exogenous insulin can promote peripheral glucose uptake and utilization, even in insulin-resistant patients, and suppresses endogenous glucose production by the liver directly and by reducing glucagon release. Amylin replacement slows gastric emptying, suppresses glucagon secretion, and increases satiety to reduce food intake. The intestinal hormone glucagon-like peptide 1 (GLP-1) also has multiple activities that promote glycemic regulation. GLP-1 enhances glucose-dependent insulin secretion, suppresses glucagon secretion, slows gastric emptying, and reduces food intake. Similar to therapies that replace insulin and amylin, incretin-based therapies address multiple physiologic deficits.

INCRETIN-BASED THERAPIES: ADDRESSING PPG AND FILLING A THERAPEUTIC NEED

The studies of Bonora et al and Erlinger and Brancati revealed that the majority of patients with type 2 diabetes experience postprandial hyperglycemia. Most outpatients in the Bonora study had a PPG level > 160 mg/dL (8.9 mmol/L) with average levels ≥ 180 mg/dL (10 mmol/L). In the Erlinger and Brancati study, 74% of patients with type 2 diabetes experienced a 2-h postmeal glucose level ≥ 200 mg/dL (11 mmol/L). Even among patients with A1C < 7%, the percent of patients who experienced postprandial hyperglycemia ranged from 39% to nearly 100%, depending on the particular study group. Evidence suggests that improving PPG control is useful for achieving therapeutic targets, and it has been hypothesized that minimizing wide swings in BG may reduce the damaging vascular effects of hyperglycemia. As concerns about the negative consequences of PPG excursions have been raised, practice guidelines that provide recommendations for the management of PPG have been developed, including the use of therapeutic agents that target PPG.

What are incretin-based therapies?

It has long been known that ingestion of glucose causes a greater insulin response than intravenous administration of glucose. This enhancement of glucose-stimulated insulin secretion is due to the release of gastrointestinal hormones during nutrient ingestion and is called the incretin effect. In particular, 2 hormones, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), are thought to account for most of the incretin effect. The incretins, GIP and GLP-1, are essential for normal glucose regulation, and interference with either GIP or GLP-1 action causes glucose intolerance.

The incretin effect is abnormal in patients with type 2 diabetes who have been shown to have only a small enhancement of insulin secretion with oral compared to intravenous glucose. While the explanation for an impaired incretin effect in diabetes is not clear, there is good evidence that the insulinotropic action of GIP is reduced in diabetic patients. GLP-1 remains a potent β-cell stimulus in persons with type 2 diabetes, although compared with subjects without type 2 diabetes, sensitivity to GLP-1 is decreased. While some studies have demonstrated that plasma GLP-1 levels are reduced in persons with diabetes, this finding has not been consistent. Moreover, where decrements of GLP-1 secretion have been demonstrated in patients with diabetes, the absolute decrease is relatively modest. Based on current evidence, it seems unlikely that a deficiency of circulating GLP-1 contributes to the pathogenesis of type 2 diabetes.

Administration of pharmacologic amounts of GLP-1 to diabetic subjects has impressive effects on PG. Intravenous infusion of GLP-1 reduced fasting glucose to near-normal levels and resulted in PPG similar to individuals without diabetes (Figure 3). In a 6-week study, continuous subcutaneous administration of GLP-1 to poorly controlled subjects with type 2 diabetes improved glycemia by increasing insulin secretion and reducing plasma glucagon and also caused weight loss. Together, these studies demonstrated the potential for GLP-1 signaling to effectively lower glucose in type 2 diabetes, both acutely and over extended treatment, and to engage multiple mechanisms to have these effects.

**FIGURE 3. GLP-1 normalizes postprandial hyperglycemia in patients with type 2 diabetes**

![Figure 3. GLP-1 normalizes postprandial hyperglycemia in patients with type 2 diabetes](image-url)
Because GLP-1 is rapidly degraded by the ubiquitous enzyme dipeptidyl peptidase-4 (DPP-4), continuous infusion of the native peptide, which is both expensive and impractical, is required to achieve clinical efficacy in patients with type 2 diabetes. To overcome this key limitation of GLP-1, alternative strategies have been employed to utilize GLP-1 receptor signaling in the treatment of diabetes. Two general approaches have been pursued. The first is development of DPP-4-resistant GLP-1 receptor agonists that have an extended half-life after injection. The second is the synthesis of orally available small molecules that inhibit DPP-4 and increase levels of endogenous GLP-1 by preventing its degradation.

GLP-1 receptor agonists available or in advanced stages of clinical development include exenatide, exenatide long-acting release (LAR), liraglutide, taspoglutide, and AVE0010. Each of these therapies is administered by subcutaneous injection. Exenatide is a synthetic version of a naturally occurring reptilian peptide, exendin-4, that has considerable homology with GLP-1 but is resistant to degradation by DPP-4, and is a potent GLP-1 receptor agonist. Exenatide is approved for twice-daily dosing and has been in wide usage for more than 3 years. Exenatide LAR, a microsphere formulation with delayed release after subcutaneous injection, has a pharmacokinetic profile consistent with once-weekly dosing and is in phase 3 clinical trials. Phase 3 clinical trials also have begun for AVE0010, another exendin-based GLP-1 receptor agonist that is administered 1 to 2 times daily. Unlike exenatide and AVE0010, liraglutide and taspoglutide are synthetic versions of human GLP-1 with amino acid changes that confer resistance to degradation. Liraglutide, which has demonstrated benefit with once-daily administration in clinical trials, is now being considered for regulatory approval in the US, Europe, and Japan. Taspoglutide is formulated for once-weekly administration and is currently in phase 3 clinical trials.

There are currently 5 DPP-4 inhibitors either on the market or in late-stage clinical development. Sitagliptin has been available in the US for 2 years and is approved for use as monotherapy or in combination with other antidiabetic drugs to lower BG in adults with type 2 diabetes. Although it has not received regulatory approval in the US, vildagliptin is approved for use in the European Union, and in other countries outside the US. Discussions continue regarding steps needed for US approval, but resubmission is not planned at this time. Alogliptin is also awaiting regulatory approval, and phase 3 clinical trials are under way for saxagliptin and BI-1356.

As listed in Table 5, GLP-1 engages a range of physiologic systems that counter the pathophysiology of type 2 diabetes. Consistent with its release after meals and role in postprandial metabolism, many of the effects of GLP-1 promote PPG normalization. The information in Table 5 also indicates that, in general, both classes of incretin-based therapies share some of the beneficial actions of GLP-1. Unlike the GLP-1 receptor agonists, the DPP-4 inhibitors appear to have minimal effects on deceleration of gastric emptying and do not promote weight loss, but all of the incretin-based therapies counter multiple pathophysiologic characteristics of type 2 diabetes that contribute to postprandial hyperglycemia.

### Table 5. Actions of GLP-1 and Incretin-Based Therapies in Correcting Postprandial Hyperglycemia

<table>
<thead>
<tr>
<th>Characteristic of type 2 diabetes</th>
<th>GLP-1 action</th>
<th>GLP-1 receptor agonists?</th>
<th>DPP-4 inhibitors?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defective β-cell glucose sensing</td>
<td>Improved insulin response to increased BG</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Delayed and attenuated insulin secretion after meals</td>
<td>Improved postprandial insulin release</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyperglucagonemia</td>
<td>Suppression of glucagon secretion</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Normal, decelerated, or accelerated gastric emptying</td>
<td>Deceleration of gastric emptying</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hyperphagia/obesity</td>
<td>Satiety/anorexia/weight loss</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Inappropriate HGP</td>
<td>Suppression of HGP</td>
<td>Possibly</td>
<td>Possibly</td>
</tr>
<tr>
<td>Impaired glucose disposal</td>
<td>Increased glucose utilization</td>
<td>Possibly</td>
<td>Possibly</td>
</tr>
</tbody>
</table>

HGP, hepatic glucose production.

*Agent is not yet approved for clinical use.
**Incretin-based therapies improve PPG control**

There is now ample evidence from clinical trials that demonstrate the efficacy of incretin-based therapies for improving glycemic control. A summary of clinical trial data published in 2007-2008, which includes PPG control as an outcome, is summarized in Table 6. Studies with fewer than 100 participants are not included, with the exception of the trial by Covington et al, which was the only study that was identified as having information regarding the effects of alogliptin on PPG.

### Table 6. Selected Clinical Study Results: Effects of Incretin-Based Therapies on PPG Levels in Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>PPG (mg/dL, unless otherwise indicated)</th>
<th>A1C (%)</th>
<th>Cardiovascular risk factors or surrogate markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP-1R Agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exenatide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Moretto 2008<sup>87</sup>  
N = 232<sup>c</sup>  
EXE mono vs PBO  
24 weeks | **Daily mean PPG excursions**  
(Change from BL to EOS)  
5 mcg EXE: −21.3*  
10 mcg EXE: −24.7*  
PBO: −8.3 | (Change from BL to EOS)  
5 mcg EXE: −0.7*  
10 mcg EXE: −0.9*  
PBO: −0.2 | Improved systolic and diastolic BP for EXE* |
| Brodows 2008<sup>88</sup>  
N = 414  
26 weeks | **PPG excursions**  
(AUC calculation)  
EXE:  
BL: 17.7 ± 1.1 mmol∙h/L  
End: 8.8 ± 0.7 mmol∙h/L<sup>1</sup>  
GLAR:  
BL: 15.4 ± 0.9 mmol∙h/L  
End: 16.4 ± 1.0 mmol∙h/L | **EXE:**  
BL: 8.2 ± 0.9  
End: 7.1 ± 1.1  
GLAR:  
BL: 8.3 ± 0.9  
End: 7.1 ± 0.9 | None reported |
| Barnett 2007<sup>89</sup>  
N = 138<sup>c</sup>  
EXE 10 mcg vs GLAR + MET or SU  
Crossover study  
2 × 16-week periods | **2-h PPG excursions**  
(Mean differences  
EXE – GLAR)  
−39.6<sup>†</sup> (morning)  
−9<sup>†</sup> (midday)  
−37.8<sup>†</sup> (evening)  
Lower daily mean glucose excursion for EXE vs GLAR (mean diff. = −30.6<sup>†</sup>) | (Change from BL to EOS)  
10 mcg EXE: −1.36<sup>‡</sup>  
GLAR: −1.36<sup>‡</sup> | None reported |
| Nauck 2007<sup>90</sup>  
N = 501<sup>c</sup>  
EXE 10 mcg vs ASPART + MET and SU  
52 weeks | **PPG excursions**  
Larger reductions in PPG vs ASPART  
(values not reported)<sup>†</sup> | (Change from BL to EOS)  
10 mcg EXE: −1.04  
ASPART: −0.89 | (Change from BL to EOS)  
1.2 mg LIR: −41.4<sup>‡</sup>  
1.8 mg LIR: −46.8<sup>‡</sup>  
4 mg GLIM: −45<sup>‡</sup>  
PBO: −10.6 | Greater reduction in LDL for EXE<sup>†</sup>  
Similar improvement in systolic and diastolic BP for both groups<sup>‡</sup> |
| **Exenatide LAR** | | | |
| Drucker 2008<sup>91</sup>  
N = 295  
EXE LAR vs EXE  
30 weeks | **2-h PPG**  
(Change from BL to EOS)  
EXE LAR: −95.4<sup>‡</sup>  
EXE: −124.2<sup>‡</sup> | (Change from BL to EOS)  
2 mg EXE LAR: −1.9<sup>‡</sup>  
10 mcg EXE: −1.5<sup>‡</sup> | Greater reduction in LDL for EXE LAR group<sup>†</sup>  
Fasting triglycerides reduced in both groups  
Similar improvements in systolic and diastolic BP for both groups<sup‡</sup> |
| **Liraglutide** | | | |
| Nauck 2008<sup>71</sup>  
N = 1087<sup>c</sup>  
LIR, GLIM, and PBO + MET  
26 weeks | **Mean PPG**  
(Change from BL to EOS)  
0.6 mg LIR: −30.6<sup>‡</sup>  
1.2 mg LIR: −41.4<sup>‡</sup>  
1.8 mg LIR: −46.8<sup>‡</sup>  
4 mg GLIM: −45<sup>‡</sup>  
PBO: −10.6 | (Change from BL to EOS)  
0.6 mg LIR: −0.7<sup>‡</sup>  
1.2 mg LIR: −1.0<sup>‡</sup>  
1.8 mg LIR: −1.0<sup>‡</sup>  
4 mg GLIM: −1.0<sup>‡</sup>  
PBO: 0.1 | Greater reduction in systolic BP for 1.2 and 1.8 mg LIR compared with GLIM<sup>‡</sup> |
<table>
<thead>
<tr>
<th>Trial</th>
<th>PPG (mg/dL, unless otherwise indicated)</th>
<th>A1C (%)</th>
<th>Cardiovascular risk factors or surrogate markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-4 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sitagliptin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Raz 2008</strong>&lt;sup&gt;92&lt;/sup&gt;</td>
<td>2-h PPG (Change from BL to EOS)</td>
<td>(Change from BL to EOS)</td>
<td>No significant treatment differences in fasting lipid levels</td>
</tr>
<tr>
<td>N = 190&lt;sup&gt;c&lt;/sup&gt;</td>
<td>100 mg SIT: −68.4*</td>
<td>100 mg SIT: −1.0*</td>
<td></td>
</tr>
<tr>
<td>SIT vs PBO</td>
<td>PBO: −14.4</td>
<td>PBO: 0</td>
<td></td>
</tr>
<tr>
<td>+ MET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nonaka 2008</strong>&lt;sup&gt;93&lt;/sup&gt;</td>
<td>2-h PPG (Change from BL to EOS)</td>
<td>(Change from BL to EOS)</td>
<td>None reported</td>
</tr>
<tr>
<td>N = 151</td>
<td>100 mg SIT: −69.3*</td>
<td>100 mg SIT: −0.65*</td>
<td></td>
</tr>
<tr>
<td>SIT vs PBO</td>
<td>PBO: 12.0</td>
<td>PBO: 0.4</td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vildagliptin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Garber 2007</strong>&lt;sup&gt;94&lt;/sup&gt;</td>
<td>2-h PPG (Change from BL to EOS)</td>
<td>(Adjusted mean change)</td>
<td>No significant between-group differences in lipid measurements</td>
</tr>
<tr>
<td>N = 398&lt;sup&gt;c&lt;/sup&gt;</td>
<td>50 mg VILDA - PBO: −34.2</td>
<td>50 mg VILDA: −0.8*</td>
<td></td>
</tr>
<tr>
<td>VILDA vs PBO</td>
<td>100 mg VILDA - PBO: −46.8*</td>
<td>100 mg VILDA: −1.0*</td>
<td></td>
</tr>
<tr>
<td>+ PIO</td>
<td>PBO: −0.3</td>
<td>PBO: −0.3</td>
<td></td>
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<tr>
<td>24 weeks</td>
<td></td>
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<tr>
<td><strong>Alogliptin</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Covington 2008</strong>&lt;sup&gt;86&lt;/sup&gt;</td>
<td>4-h PPG (Change from BL to EOS)</td>
<td>(Change from BL to EOS)</td>
<td>None reported</td>
</tr>
<tr>
<td>N = 56</td>
<td>Breakfast 25 mg ALO: −32.5*</td>
<td>25 mg ALO: −0.22*</td>
<td></td>
</tr>
<tr>
<td>ALO mono vs PBO</td>
<td>100 mg ALO: −37.2*</td>
<td>100 mg ALO: −0.40*</td>
<td></td>
</tr>
<tr>
<td>+ 2 weeks</td>
<td>400 mg ALO: −65.6*</td>
<td>400 mg ALO: −0.28*</td>
<td></td>
</tr>
<tr>
<td>PBO: 8.2</td>
<td>PBO: 0.05</td>
<td>PBO: 0.05</td>
<td></td>
</tr>
<tr>
<td>Lunch 25 mg ALO: −15.8*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>100 mg ALO: −29.2*</td>
<td></td>
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<tr>
<td>400 mg ALO: −27.1*</td>
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<tr>
<td>PBO: 14.3</td>
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<tr>
<td>Dinner 25 mg ALO: −21.9*</td>
<td></td>
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<tr>
<td>100 mg ALO: −39.7*</td>
<td></td>
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</tr>
<tr>
<td>400 mg ALO: −35.3*</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PBO: 12.8</td>
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</tr>
<tr>
<td><strong>Saxagliptin</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Rosenstock 2008</strong>&lt;sup&gt;73&lt;/sup&gt;</td>
<td>1-h PPG (Change from BL to EOS)</td>
<td>(Change from BL to EOS)</td>
<td>None reported</td>
</tr>
<tr>
<td>N = 338 (low-dose cohort)</td>
<td>Low dose 2.5 mg SAX: −24.42</td>
<td>Low dose 2.5 mg SAX: −0.72*</td>
<td></td>
</tr>
<tr>
<td>N = 85 (high-dose cohort)</td>
<td>5 mg SAX: −35.30</td>
<td>5 mg SAX: −0.90*</td>
<td></td>
</tr>
<tr>
<td>SAX mono vs PBO</td>
<td>10 mg SAX: −41.04</td>
<td>10 mg SAX: −0.81*</td>
<td></td>
</tr>
<tr>
<td>12 weeks (low-dose cohort)</td>
<td>20 mg SAX: −27.54</td>
<td>20 mg SAX: −0.74*</td>
<td></td>
</tr>
<tr>
<td>6 weeks (high-dose cohort)</td>
<td>40 mg SAX: −33.98</td>
<td>40 mg SAX: −0.80*</td>
<td></td>
</tr>
<tr>
<td>PBO: −1.41</td>
<td>PBO: −0.27*</td>
<td>PBO: −0.27*</td>
<td></td>
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<tr>
<td></td>
<td>Breakfast 25 mg SAX: −24.42</td>
<td>High dose 100 mg SAX: −1.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg SAX: −35.30</td>
<td>100 mg SAX: −0.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg SAX: −41.04</td>
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<td></td>
<td>20 mg SAX: −27.54</td>
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<td>40 mg SAX: −33.98</td>
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<td></td>
<td>PBO: −1.41</td>
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<tr>
<td></td>
<td>100 mg SAX: −17.22</td>
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<tr>
<td></td>
<td>Lunch 25 mg SAX: −24.42</td>
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<td></td>
<td>5 mg SAX: −35.30</td>
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<td>40 mg SAX: −33.98</td>
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<tr>
<td></td>
<td>PBO: −1.41</td>
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<td></td>
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<tr>
<td></td>
<td>100 mg SAX: −17.22</td>
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</tr>
</tbody>
</table>

ALO, alogliptin; ASPART, biphasic insulin aspart; BL, baseline; BP, blood pressure; EOS, end of study; EXE, exenatide; GLAR, glargine; GLIM, glimepiride; LAR, long-acting release; LIR, liraglutide; MET, metformin; mono, monotherapy; PBO, placebo; PIO, pioglitazone; SAX, saxagliptin; SIT, sitagliptin; SU, sulfonylurea; VILDA, vildagliptin.

*Published trial results for taspoglutide were not available for inclusion; †EXE administered twice per day; ‡intent-to-treat population; §EXE LAR administered once per week.

*Significant difference vs PBO; †significant difference vs comparator; ‡significant difference vs baseline.
CURRENT TREATMENT GUIDELINES REGARDING PPG

Recent practice guidelines from the ADA, AACE, and IDF all reflect increased awareness of the importance of PPG control, although their recommendations differ slightly. Glycemic targets, according to each set of guidelines, are presented in Table 2.

The ADA guidelines acknowledge that PPG levels contribute to overall glycemic control, measured by A1C, and that elevated PPG levels have been associated with increased cardiovascular risk. However, because studies demonstrating the relationship between A1C and diabetes complications have relied heavily on FPG levels, the ADA recommends that FPG levels should be measured routinely. According to the ADA guidelines, though, it is reasonable to include PPG measurements if a patient achieves PrePG/FPG levels but does not meet A1C goals.

The AACE guidelines place more emphasis on addressing PPG levels. The authors of these guidelines propose that approaches addressing both FPG and PPG levels are prudent because of the potential increased cardiovascular risk associated with elevated PPG levels. They were also considered appropriate because the relative contribution of PPG to overall hyperglycemia increases as a patient nears target glucose level. At A1C levels between 7.3% and 8.0%, FPG and PPG levels each contribute equally (50%) to overall glycemia, and the FPG contribution drops to 30% as the A1C decreases below 7.3%. The validity of these assumptions will need to be reconsidered in light of the results of the ACCORD and ADVANCE trials. However, to facilitate the treatment of both FPG and PPG by clinicians, the AACE guidelines include practical recommendations for combinations of agents that achieve both pre- and postprandial glucose targets based on the A1C level. Furthermore, the appropriate target, FPG or PPG, relative to A1C level, is specifically indicated on the ACE/AACE Diabetes Road Map, which provides a diagrammatic algorithm for treating patients with type 2 diabetes.

The IDF has developed a specific approach for the management of postmeal glucose with the stated understanding that to achieve A1C goals, controlling PPG excursions is at least as important, and perhaps more important, than lowering FPG levels. The IDF guidelines provide a rationale for treating PPG, a summary of PPG targets, a discussion of therapies such as diets with low glycemic load, and recommendations for pharmacologic agents that specifically target PPG levels. The list of agents includes α-glucosidase inhibitors, amylin analogs, glinides, insulins, GLP-1 receptor agonists, and DPP-4 inhibitors. The IDF guidelines state, in conclusion, that “…optimal glycaemic control cannot be achieved without adequate management of postmeal glucose.”

SUMMARY

Improving glycemic control to an A1C of at least 7.0%, and perhaps lower, has clear benefits in decreasing the risk of microvascular complications in patients with type 2 diabetes. There is also a growing body of evidence indicating that intensive glycemic control may decrease the risk of macrovascular complications, although this position is under revision given the results of recent clinical trials. Overall glycemic control, assessed by A1C levels, is determined by FPG and PPG. As patients with type 2 diabetes achieve near-normal glucose levels, the contribution of PPG to A1C levels is greater. Postprandial hyperglycemia also appears to be a prominent characteristic of glycemic dysregulation in patients at early stages of diabetes progression.

The majority of patients with type 2 diabetes will require pharmacologic intervention to maintain glucose control. Medications like metformin and long-acting insulins are proven to be effective in controlling FPG and are the cornerstones of pharmacologic therapy for type 2 diabetes. However, it is now possible to augment these traditional treatments using several classes of agents with enhanced effects on PPG. These include fast-acting insulin analogs, glinides, α-glucosidase inhibitors, amylin analogs, and incretin-based therapies. In recognition of growing evidence regarding the importance of PPG control, clinical practice guidelines from the ADA and AACE have been revised to address PPG control and to include recommendations for the use of the relatively new categories of incretin-based therapies. Subsequent issues of the Peak Issues series will address the clinical use of incretin-based therapies to achieve near-normal glycemic control and improve outcomes for patients with type 2 diabetes.
The 2-hour postprandial glucose (2-h PPG) level is currently used to describe postmeal glycemic peaks and has been associated with macrovascular outcomes. The incremental glucose peak (IGP), another measure of PPG, is defined as the maximal incremental increase in blood glucose (BG) obtained at any point after the meal. Because IGP is defined as a difference and does not reflect premeal glucose levels as 2-h PPG does, it may be a good measure of postmeal glycemic spikes. The authors set out to assess the size and timing of postmeal glucose peaks in everyday life of patients with type 2 diabetes and to determine the relationship with carotid atherosclerosis. In addition, they compared 2-hour PPG and IGP in the context of PPG monitoring.

The observational study included 644 patients with type 2 diabetes who attended diabetes clinics in the vicinity of Campania County, South Italy. Study participants had disease durations of 6 months to 10 years, A1C levels ≥ 6.5%, and were treated with oral antidiabetic agents or diet. Patients treated with insulin were excluded from the study.

Participants were requested to follow their normal therapeutic regimen and diet for the month of their study involvement. Study participants completed specified home BG measurements over the course of 1 month. All participants were provided with the same model of glucose monitor and were instructed to measure BG around their main meal (just before and every 30 minutes after for 2 hours) for 3 nonconsecutive days. Participants were also asked to measure fasting plasma glucose (FPG) on 2 nonconsecutive days. Carotid intima-media thickness (CIMT) was assessed by B-mode ultrasound. The following glucose parameters were examined: IGP, A1C, FPG, premeal glucose, 2-h PPG, and absolute glucose peak (the highest glycemic peak recorded at any time after the meal). Statistical analyses included only results from those patients with 3 complete BG profiles and CIMT measurements.

A summary of glycemic and CIMT results, by IGP quintiles, is presented in the accompanying table. Home BG profiles were reproducible for each patient. In addition, 95% of patients experienced IGP within 1 hour from the start of the meal, regardless of their therapeutic regimen. Results are summarized in the table below and indicate that all examined measures of glycemic control correlated with IGP, although the correlation with premeal glucose level was negative. A positive correlation between IGP and triglyceride level was also reported.

<table>
<thead>
<tr>
<th>Glycemic and CIMT Outcomes by IGP Quintile</th>
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</thead>
<tbody>
<tr>
<td>IGP Quintiles (mg/dL)</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
</tr>
<tr>
<td>IGP</td>
</tr>
<tr>
<td>Fasting</td>
</tr>
<tr>
<td>Premeal</td>
</tr>
<tr>
<td>2-h PPG</td>
</tr>
<tr>
<td>Absolute peak</td>
</tr>
<tr>
<td>A1C (%)</td>
</tr>
<tr>
<td>CIMT (mm)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD) unless otherwise specified.
IGP, impaired glucose response; PPG, postprandial plasma glucose; CIMT, carotid intima-media thickness.
Of the glycemic control markers, IGP had the strongest positive, statistically significant, linear correlation with CIMT \((r = .40; P = .006)\). Correlations were also observed for absolute glucose peak \((r = .35; P = .01)\), 2-h PPG \((r = .24; P = .02)\), and A1C \((r = .21; P = .03)\). Age also demonstrated a strong correlation with CIMT \((r = .38; P = .001)\). Levels of fasting insulin, FPG, total cholesterol, HDL-cholesterol, and triglycerides did not correlate with CIMT.

When results were considered by A1C level (< 7.0, 7.0-8.5, > 8.5), significant trends for increase in CIMT with increasing IGP were observed for each level (see accompanying figure).

The results of this study demonstrate that postchallenge hyperglycemic spikes measured at home correlate more strongly with CIMT than 2-h PPG, A1C, and FPG levels. In addition, based on the timing of the IGP, 2-h PPG should not be considered equivalent with IGP. The correlation between IGP and CIMT exists regardless of A1C level. These findings suggest that home monitoring of postmeal glucose peaks may provide additional benefits in managing patients with type 2 diabetes.


Woerle et al reported the results of a prospective interventional study performed to assess the relative contributions of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) control in reaching target A1C levels. The trial included 164 patients with unsatisfactory glycemic control as indicated by A1C levels ≥ 7.5%.

Prior to beginning the 3-month interventional portion of the study, participants provided 7-point diurnal PG profiles, including 3 preprandial measurements (7 AM, 1 PM, 7 PM), 3 PPG measurements 90 minutes after completion of each meal, and 1 bedtime measurement. Participants then entered a 2-week assessment period to titrate, intensify, and optimize their therapeutic regimens. Therapeutic optimization followed a stepwise process, beginning with treatment intensification to achieve FPG levels < 100 mg/dL, followed by further titration to achieve PPG levels < 140 mg/dL. The target A1C level was ≤ 7.0%.

Treatments were individualized for each patient and included a range of regimens, including:
- Diet
- Metformin (MET)
- Sulfonylurea (SU)
- MET + SU
- Neutral protamine Hagedorn insulin (NPH)
- NPH twice daily
- NPH + short-acting insulin
- NPH + MET
- NPH + SU
- NPH + short-acting insulin + MET
- NPH + short-acting insulin + MET + SU

Following the 2-week therapeutic titration period, participants entered a 3-month study period. A second set of diurnal measurements was obtained at the end of this study period. By the end of the 3-month study period, participants did not experience significant weight change, and there were no cases of severe hypoglycemia. Significant decreases in mean A1C, FPG, PPG, and daylong glucose levels were measured following the intervention phase of titrated therapy and are summarized in the accompanying table.

### Glycemic Parameters Before and After Titrated Therapy

<table>
<thead>
<tr>
<th>Glycemic Parameter</th>
<th>Pre-intervention</th>
<th>Post-intervention</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>8.7 (0.1)</td>
<td>6.5 (0.1)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>174 (4)</td>
<td>117 (2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>PPG (mg/dL)</td>
<td>224 (4)</td>
<td>159 (3)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Daylong glucose (mg/dL)</td>
<td>199 (4)</td>
<td>141 (2)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD) unless otherwise specified.

The target A1C of ≤ 7.0% was achieved by 73% of participants. Among participants achieving the FPG target (< 100 mg/dL), 64% also reached the A1C target. By comparison, 94% of patients achieving the PPG target (< 140 mg/dL) reached the A1C target.
FPG was nearly identical for patients who did and did not achieve A1C targets. However, all other measurements on diurnal glucose curves were significantly higher for those who did not achieve A1C ≤ 7.0%. Diurnal plasma glucose curves revealed that, for patients who did not achieve A1C ≤ 7.0%, PG levels did not return to premeal levels following meals, resulting in a progressive, stepwise increase in PG levels throughout the day (see accompanying figure).

Multiple linear regression analysis, with A1C level changes as the dependent variable and FPG and daylong hyperglycemia as independent variables, revealed partial regression coefficients of 0.22 and 0.40 for FPG and daylong hyperglycemia, respectively. This indicates that daylong hyperglycemia contributed nearly twice as much to A1C as FPG. In addition, PPG contribution was estimated at ≈ 90% for A1C levels < 6.2% and ≈ 40% for A1C levels > 9.0%.

Results of this study confirm earlier findings regarding the relative contributions of FPG and PPG to overall hyperglycemia. In particular, PPG contributes more to A1C as A1C levels decrease. Sequential optimization of FPG and PPG control permitted investigators to demonstrate that control of PPG, in addition to FPG, is needed to achieve A1C targets specified in current treatment guidelines. Furthermore, good glycemic control, using individualized treatment plans targeting FPG and PPG, can be attained without weight gain or severe hypoglycemia. The results of this study underscore the importance of attention to PPG goals when A1C targets are not achieved despite optimal FPG control.


The United Kingdom Prospective Diabetes Study (UKPDS) compared outcomes following conventional glucose control (dietary restriction) or intensive glucose control (either sulfonylurea or insulin [SU-insulin]) or, in overweight patients, metformin (MET) in patients newly diagnosed with type 2 diabetes. Compared with the conventional therapy group, the UKPDS revealed significantly decreased risks for microvascular complications in the SU-insulin group and for any diabetes-related end point, myocardial infarction (MI), and death from any cause in the MET group. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study of patients with type 1 diabetes, macrovascular risk was not reduced for the intensive glucose therapy group compared with the conventional group at the end of the study, but decreased cardiovascular risk became evident during the 8-year postintervention follow-up period. Posttrial monitoring was also conducted for the UKPDS to ascertain whether glycemic control was maintained and to determine macrovascular outcomes.

A subset of 3277 UKPDS participants entered posttrial monitoring. The posttrial participants were asked to attend annual UKPDS clinics for 5 years and complete annual questionnaires in years 6 to 10. Posttrial monitoring examined 7 aggregate clinical outcomes prespecified by the UKPDS according to previous randomization categories. The outcomes included:

- Any diabetes-related end point (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photoacoagulation, blindness in 1 eye, or cataract extraction)
- Diabetes-related death (sudden death or death from MI, stroke, peripheral vascular disease, renal disease, hyperglycemia, or hypoglycemia)
- Death from any cause
- MI (sudden death or fatal or nonfatal MI)
- Stroke (fatal or nonfatal)
- Peripheral vascular disease (amputation of at least 1 digit or death from peripheral vascular disease)
- Microvascular disease (vitreous hemorrhage, retinal photoacoagulation, or renal failure)

Posttrial follow-up continued for a median of 8.5 years for participants in the SU-insulin group and 8.8 years for those in the MET group. Overall mortality across both groups was the leading cause of death. Baseline differences in A1C levels between intensive- and conventional-therapy groups were no longer evident after 1 year. Results related to aggregate outcomes are summarized in the accompanying table.
### Aggregate Outcomes for Patients During Follow-Up

<table>
<thead>
<tr>
<th>Aggregate Outcome</th>
<th>Absolute Risk*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive Therapy</td>
<td>Conventional Therapy</td>
</tr>
<tr>
<td><strong>SU-insulin group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any diabetes-related end point</td>
<td>48.1</td>
<td>52.2</td>
</tr>
<tr>
<td>Diabetes-related death</td>
<td>14.5</td>
<td>17.0</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>26.8</td>
<td>30.3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16.8</td>
<td>19.6</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>11.0</td>
<td>14.2</td>
</tr>
<tr>
<td><strong>MET group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any diabetes-related end point</td>
<td>45.7</td>
<td>53.9</td>
</tr>
<tr>
<td>Diabetes-related death</td>
<td>14.0</td>
<td>18.7</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>25.9</td>
<td>33.1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14.8</td>
<td>21.1</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.0</td>
<td>6.8</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>12.4</td>
<td>13.4</td>
</tr>
</tbody>
</table>

MET, metformin; SU, sulfonylurea.*The absolute risk is the number of events per 1000 patient-years.

In the SU-insulin group, significant risk reductions for any diabetes-related end point (relative risk reduction [RRR], 9%) and for microvascular disease (RRR, 24%) were maintained. Significant risk reductions emerged for diabetes-related death (RRR, 17%), MI (RRR, 15%), and death from any cause (RRR, 13%). No risk reductions were observed for stroke or peripheral vascular disease. Significant reductions for any diabetes-related end point (RRR, 21%), diabetes-related death (RRR, 30%), MI (RRR, 33%), and death from any cause (RRR, 27%) were maintained in the MET group. No additional risk reductions emerged; there was no observed risk reduction for stroke, peripheral vascular disease, or microvascular disease.

The data indicate a legacy effect for intensive glycemic control such that earlier periods of intensive glucose control result in long-standing risk reduction. Ten years after the end of the UKPDS, participants who received intensive control experienced benefits beyond those who received conventional control, even though the gap in A1C levels between groups was closed soon after the study ended. These data support implementing intensive glycemic control as early as possible in the progression of type 2 diabetes to prevent the development of microvascular and cardiovascular complications.
REFERENCES


64. Roche moves investigational diabetes drug, taspoglutide, into phase III clinical trials.


66. After one year, type 2 diabetes patients taking exenatide once weekly sustained improvements in glycemic control and weight; DURATION-1 presented at ADA 2008.


69. A study to compare the glycemic effects, safety, and tolerability of exenatide once weekly to those of sitagliptin and a thiazolidinedione in subjects with type 2 diabetes treated with metformin (DURATION -2).


**Posttest Questions**

1. A patient's _____ level provides a record of average blood glucose levels over several months, but it is not a good indicator of glycemic variability.
   a. A1C
   b. fasting plasma glucose (FPG)
   c. postprandial plasma glucose (PPG)
   d. preprandial plasma glucose (PrePG)

2. PPG is typically measured ______ following a meal.
   a. immediately
   b. 1-2 hours
   c. 5-6 hours
   d. 7-8 hours

3. PPG levels have a relatively ______ influence on overall glycemic control at near-normal plasma glucose levels and contribute approximately ______ when A1C is < 7.3%.
   a. small, 10%
   b. small, 30%
   c. large, 50%
   d. large, 70%

4. The American Diabetes Association (ADA) recommends a therapeutic PPG target of ________, and the American Association of Clinical Endocrinologists (AACE) recommends ________.
   a. < 200 mg/dL, < 180 mg/dL
   b. 70-130 mg/dL, < 110 mg/dL
   c. < 180 mg/dL, < 140 mg/dL
   d. < 160 mg/dL, < 120 mg/dL

5. A study by Bonora et al revealed that ______ of patients with type 2 diabetes experience PPG levels > 160 mg/dL.
   a. < 10%
   b. < 50%
   c. > 60%
   d. > 90%

6. Postprandial hyperglycemia in the range of 140 to 200 mg/dL is referred to as impaired glucose tolerance (IGT) and is considered to be a prediabetic state with a risk of progression to diabetes of ________.
   a. 30% over 1 year
   b. 10% over 3 years
   c. 30% over 3 years
   d. 30% over 5 years

7. Agents that ameliorate PPG excursions may provide cardiovascular benefits as demonstrated by their ability to ________.
   a. slow the progression of atherosclerosis
   b. increase inflammation
   c. increase blood pressure
   d. decrease A1C

8. Postprandial hyperglycemia is a consequence of several physiologic abnormalities including insulin resistance, decreased β-cell function, and ________.
   a. increased insulin secretion
   b. slowed gastric emptying
   c. impaired glucagon suppression
   d. decreased hepatic glucose production

9. Which of the following is not an agent or class of agents that targets PPG levels?
   a. α-glucosidase inhibitors
   b. fast-acting insulin analogs
   c. incretin-based therapies
   d. metformin

10. Incretin-based therapies improve PPG control by ________.
    a. suppressing glucagon secretion
    b. accelerating gastric emptying
    c. decreasing postprandial insulin release
    d. inhibiting α-glucosidase
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What is your professional title? ☐MD ☐DO ☐RN ☐PA ☐Other ________________________________

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LEARNING OBJECTIVES
Rating Scale: 1=Poor  2=Fair  3=Good  4=Very Good  5=Excellent
Please evaluate how well the following learning objectives were met:
• Describe the relative contribution of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) to overall glycemic control among patients with type 2 diabetes, and explain how this relationship changes at different levels of glycemic control
• Explain the pathophysiologic defects that precede the development of type 2 diabetes, and indicate when elevated PPG begins to play a contributing role
• Discuss the available evidence suggesting that elevated PPG leads to increased macrovascular complications

BALANCE AND OBJECTIVITY
• Were all data reported objectively and with appropriate referencing?  
• Was the overall content of this educational activity presented objectively and free of bias?
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• Was the educational format an effective learning method?
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ACTIVITY PLANNING AND NEEDS ASSESSMENT
What one question remains unanswered after having participated in this activity?

Cite one new piece of information learned from this activity.

What related topics would you like to have offered as future CME activities?

What are your preferred learning methods? (check as many as applicable)
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☐ I do not want to receive further information regarding CaringForDiabetes activities

Additional comments:

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THANK YOU FOR PARTICIPATING IN THIS EDUCATIONAL ACTIVITY.