

# The Rationale for Prandial Glycemic Control in Diabetes Mellitus

Jennifer M. Perkins, MD

*Fellow, Division of Diabetes, Endocrinology and Metabolism, Vanderbilt University, Nashville, Tennessee*

Stephen N. Davis, MD, FRCP

*Chief, Division of Diabetes, Endocrinology and Metabolism; Mark Collie Professor of Medicine and Molecular Biology and Biophysics, Vanderbilt University, Nashville, Tennessee*

## ABSTRACT

**Background:** Diabetes mellitus (DM) is of epidemic proportions worldwide, and its microvascular and macrovascular complications have been well described. Achieving glycemic control has been demonstrated to reduce patients' risk of developing these complications.

**Objective:** The objective of this article was to examine how prandial hyperglycemia—especially postprandial hyperglycemia (PPHG)—affects overall glycemic control and the complications of DM and to discuss the pharmacologic agents available to reduce PPHG.

**Methods:** Materials used for this article were identified through a MEDLINE search of the literature (1975–2006). English-language randomized, controlled, prospective, cohort, and observational studies were chosen using the search terms *postprandial hyperglycemia, oxidative stress, cardiovascular disease, macrovascular disease, microvascular disease, lipidemia, and coagulation*.

**Results:** Data show that controlling prandial hyperglycemia reduces the risk of cardiovascular disease (CVD) and microvascular complications, lowers glycosylated hemoglobin levels, causes less oxidative stress, and leads to a more favorable coagulation and postprandial lipidemia profile. Guidelines for targeting PPHG are becoming standard, and various pharmacologic agents (eg,  $\alpha$ -glucosidase inhibitors, amylin analogues, incretin mimetics, rapid-acting insulins and insulin analogues, meglitinide analogues) that target PPHG may also improve overall glycemic control and reduce CVD risk.

**Conclusions:** Although the level of hyperglycemia that leads to microvascular and macrovascular complications in patients with DM remains to be elucidated, it appears prudent to address prandial hyperglycemia, especially PPHG, rather than focus solely on fasting glucose levels. Clinicians should consider incorporating agents that lower PPHG in their treatment of patients with DM. (*Insulin*. 2007;2:52–60) Copyright © 2007 Excerpta Medica, Inc.

**Key words:** postprandial hyperglycemia, oxidative stress, cardiovascular disease, macrovascular disease.

## INTRODUCTION

Diabetes mellitus (DM) affects ~21 million people in the United States, and an additional 45 million individuals have impaired blood glucose (BG) tolerance and are at high risk for developing DM.<sup>1</sup> DM is associated with microvascular and macrovascular complications; in fact, ~80% of patients with type 2 DM are expected to die of cardiovascular disease (CVD).<sup>1</sup> DM carries a 1.5- to 4.5-fold risk of cardiovascular (CV) mortality,<sup>2</sup> and the disease's microvascular complications (eg, retinopathy) can be devastating to quality of life. Although type 1 and type 2 DM differ in epidemiology and etiology, both cause similar complications. Cardiometabolic risk factors often coexist in patients with DM (predominantly those with type 2 DM) and include additional risk factors for CVD such as hypertension, low high-density lipoprotein (HDL), high low-density lipoprotein (LDL), and hypertriglyceridemia.

Although all these factors contribute to the complications of DM and the risk of CVD, hyperglycemia remains the hallmark of DM. The level of hyperglycemia that causes macrovascular disease remains to be elucidated. A number of large multicenter trials are currently under way to clarify the association between hyperglycemia and macrovascular disease. Post hoc analyses have shown that even relatively mild hyperglycemia is associated with macrovascular disease.<sup>3</sup> Similarly, hyperglycemia that occurs during an acute CV event is associated with worse outcomes in both myocardial infarction<sup>4</sup> and stroke.<sup>5</sup> Therefore, evidence exists that both chronic and acute hyperglycemia lead to unfavorable outcomes.

As people age, their 2-hour postchallenge BG level typically increases, often independent of their fasting BG level. In fact, at diagnosis, 25% of patients with type 2 DM have relatively normal fasting BG levels. Furthermore, the incidence of isolated impaired glucose tolerance (IGT) is ~3 times

greater than isolated impaired fasting BG. Therefore, most patients with asymptomatic DM have isolated postchallenge hyperglycemia.<sup>6</sup> For years, clinicians have relied on the fasting plasma glucose (FPG) level for diagnosis and as a target for treatment, but increasing evidence shows that an elevated postprandial BG level is an independent risk factor for DM complications, especially CV morbidity and mortality.<sup>6</sup> A growing body of literature supports targeting postprandial hyperglycemia (PPHG) to lower glycosylated hemoglobin (A1C) levels and to reduce microvascular and macrovascular complications.

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The objective of this article was to examine how prandial hyperglycemia—especially PPHG—affects overall glycemic control and the complications of DM and to discuss the pharmacologic agents available to reduce PPHG.

## MATERIALS AND METHODS

Materials used for this article were identified through a MEDLINE search of the literature (1975–2006). English-language randomized, controlled, prospective, cohort, and observational studies were chosen using the search terms *postprandial hyperglycemia, oxidative stress, cardiovascular disease, macrovascular disease, microvascular disease, lipidemia, and coagulation*.

## POSTPRANDIAL GLUCOSE

### Definition

The postprandial profile is determined mainly by meal timing, quantity, and composition, including carbohydrate content, followed by the resulting secretion of insulin and inhibition of glucagon secretion. In healthy patients without DM, 2-hour postprandial BG levels are usually <120 mg/dL and seldom >140 mg/dL. BG levels begin to rise ~10 minutes postchallenge and peak at ~1 hour before returning to preprandial levels 2 to 3 hours postmeal.<sup>7</sup> Carbohydrate absorption continues for 5 to 6 hours postchallenge. This excursion of PPHG is mediated by the first-phase insulin response, which is characterized by a large endogenous release of insulin, typically within 10 minutes of nutrient intake. In patients with type 2 DM, the first-phase insulin response is severely blunted or absent and the postprandial BG level remains elevated throughout the day.<sup>8</sup> The 4 main determinants of postprandial BG level are: (1) influx of glucose from the gut; (2) availability of insulin; (3) deposition of glucose at the liver and peripheral tissues; and (4) hepatic glucose production.<sup>9</sup>

Patients with type 1 DM lack endogenous insulin; therefore, the time and height of peak insulin concentrations after

a glucose challenge depend on the amount, type, and route of insulin administration. In contrast, in patients with type 2 DM, peak insulin levels are delayed and insufficient to adequately control postprandial excursions. Patients with either type of DM have abnormal insulin and glucagon secretion, hepatic glucose uptake, suppressed hepatic glucose production, and peripheral glucose uptake; thus, they experience increased PPHG.<sup>7</sup>

## Implications

Until recently, PPHG has not received much attention as important in the sequelae of DM. Traditionally, researchers and clinicians have concentrated on FPG level as a measure of DM control. Recent studies<sup>10–15</sup> have identified PPHG as an independent risk factor for CVD and microvascular complications (eg, retinopathy). PPHG has been found to worsen postmeal lipidemia (eg, hypertriglyceridemia, oxidized LDL levels) and to increase inflammatory markers and oxidative stress. These effects increase atherosclerosis and endothelial damage. **Table I** summarizes the effects of PPHG.

## Effect on Overall Glycemic Control

Several studies have demonstrated that PPHG contributes greatly to overall glycemic control. Monnier et al<sup>16</sup> demonstrated the relative importance of PPHG to increased A1C level. In a study of 290 patients with type 2 DM, how much PPHG contributed to overall glycemic load varied, depending on degree of glycemic control. In patients with an A1C level <7.3%, PPHG contribution was >70%, whereas in patients with an A1C level >10.2%, PPHG contributed only 30% of glycemic load. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe study<sup>17</sup> found that ~33% of people classified as having type 2 DM based only on PPHG and >25% of people with IGT had normal FPG. This finding clearly illustrates that measuring only FPG underestimates the number of patients at

**Table I.** Effects of postprandial hyperglycemia (PPHG).

| PPHG                                     | Effect                                              |
|------------------------------------------|-----------------------------------------------------|
| Poor glycemic control                    | Increased A1C level                                 |
| Nonenzymatic glycation of proteins       | Increased CVD, microvascular disease, and mortality |
| Oxidative stress                         |                                                     |
| Dyslipidemia                             | Increased carotid intima-media thickness            |
| • Oxidized LDL<br>• Hypertriglyceridemia |                                                     |
| Effects on coagulation                   | Promotes thrombosis                                 |

A1C = glycosylated hemoglobin; CVD = cardiovascular disease; LDL = low-density lipoprotein.

increased risk of CVD due to either DM or IGT.<sup>11</sup> Avignon et al<sup>18</sup> studied the glycemic profiles of 66 patients with type 2 DM and found that compared with FPG or pre-lunch plasma glucose level, PPHG was more strongly correlated with A1C level.

Other studies have examined the effect of controlling PPHG on A1C reduction. Feinglos et al<sup>19</sup> reported that improving PPHG with insulin lispro in addition to a sulfonylurea markedly decreased 2-hour PPHG (18.6 to 14.2 mmol/L) and reduced the A1C level by 21%. The study also found that total cholesterol and triglyceride levels decreased and HDL increased in patients taking insulin lispro.

Reduction in A1C level decreases the risk of microvascular and macrovascular complications in patients with DM. The United Kingdom Prospective Diabetes Study (UKPDS)<sup>20</sup> demonstrated that each 1% reduction in A1C level was associated with a 21% reduction in risk for any end point related to DM, a 21% reduction in deaths related to DM, and a 37% reduction in microvascular complications. Similarly, the Diabetes Control and Complications Trial (DCCT)<sup>21</sup> and the Epidemiology of Diabetes Interventions and Complications study<sup>22</sup> demonstrated marked reductions of microvascular and macrovascular complications in patients with type 1 DM during and after periods of improved glycemic control.

**OXIDATIVE STRESS AND MARKERS OF INFLAMMATION**

It is well established that oxidative stress leads to endothelial dysfunction, which is an early manifestation of atherosclerosis. It is also known that endothelial dysfunction associated with oxidative stress increases the risk of CVD.<sup>23</sup> Studies have shown that acute hyperglycemia induces endothelial dysfunction, which is mediated by oxidative stress.<sup>24</sup> Patients with DM have enhanced production of reactive oxygen species (ROS) and an impaired antioxidant defense.<sup>25</sup> The mechanisms that cause endothelial damage involve several pathways (eg, activation of diacylglycerol and protein kinase C, decreased production of nitric oxide, increased production of nonenzymatic glycation products, glycosylation of certain proteins, increased generation of

free radicals), resulting in a proinflammatory response.<sup>26</sup> PPHG stimulates the production of ROS through these pathways.<sup>27</sup> LDL is more susceptible to oxidation after mealtime, and meal-induced oxidative stress is more prominent in patients with DM than in healthy controls.<sup>21</sup> Hyperglycemia has been found to induce overproduction of superoxide, resulting in downstream processes that stimulate acute endothelial dysfunction.<sup>28</sup> Overproduction of superoxide is thought to be the first and main event in the activation of all pathways involved in the pathogenesis of DM complications.<sup>29</sup>

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**CARDIOVASCULAR DISEASE AND POSTPRANDIAL HYPERGLYCEMIA**

Studies<sup>10-14</sup> have shown that PPHG increases the risk of atherosclerotic disease in patients with DM and IGT (**Table II**). Researchers have known for decades that hyperglycemia increases CVD risk. For instance, the UKPDS<sup>30</sup> demonstrated not only that a global reduction in A1C level was a good predictor of ischemic heart disease, but that each 1% reduction in A1C level yielded a 16% reduction in myocardial infarction. Although not statistically significant, this finding suggests a trend.

Although the UKPDS did not target PPHG, other studies have looked specifically at how PPHG affects CVD risk. In the Helsinki Policemen Study, Pyorala et al<sup>10</sup> showed that 1- and 2-hour BG levels during oral glucose tolerance testing better predicted the incidence of coronary heart disease than fasting BG values. Shaw et al<sup>11</sup> illustrated that isolated postchallenge hyperglycemia >200 mg/dL with a normal FPG level (<126 mg/dL) at least doubled the mortality risk in their study population. The Islington Diabetes Survey<sup>12</sup> demonstrated a linear relationship between 2-hour BG levels

**Table II.** Studies showing association of postprandial hyperglycemia with cardiovascular disease and mortality.

| Reference                    | Result                                                                                                   |
|------------------------------|----------------------------------------------------------------------------------------------------------|
| Pyorala et al <sup>10</sup>  | 1- and 2-h glucose levels during OGTT better predicted CHD than did FPG                                  |
| Shaw et al <sup>11</sup>     | Isolated postchallenge hyperglycemia doubled risk for mortality                                          |
| Jackson et al <sup>12</sup>  | 2-h glucose level better predicted CHD than A1C level                                                    |
| Meigs et al <sup>13</sup>    | 2-h glucose level better predicted CHD than A1C level                                                    |
| Hanefeld et al <sup>14</sup> | Postabsorptive glucose level (postbreakfast hyperglycemia) better predicted all-cause mortality than FPG |

OGTT = oral glucose tolerance test; CHD = coronary heart disease; FPG = fasting plasma glucose; A1C = glycosylated hemoglobin.

and A1C and coronary heart disease, but 2-hour BG level was a better predictor of coronary heart disease than was A1C level. Similar results were found in the Framingham Offspring Study,<sup>13</sup> which demonstrated that the 2-hour postchallenge BG level was a better predictor of CV events than was A1C level. In this study, fasting BG level was not associated with CVD risk.

Most studies have looked only at the effect of postchallenge BG level on CVD and mortality. The German Diabetes Intervention Study<sup>14</sup> was the only trial to investigate postabsorptive versus postchallenge hyperglycemia by measuring BG levels before and 1 hour after breakfast. The investigators confirmed that postbreakfast hyperglycemia was a better predictor than fasting hyperglycemia of all-cause mortality in 1139 patients with newly diagnosed type 2 DM. In this study, poor control of fasting hyperglycemia did not significantly increase risk of myocardial infarction or mortality, but poor control of PPHG level was associated with higher mortality. Another large meta-analysis involving PPHG and CVD risk included >95,000 patients from 22 studies and confirmed the progressive relationship between 2-hour postprandial BG level and CVD risk.<sup>3</sup>

### **MICROVASCULAR COMPLICATIONS DUE TO ELEVATED POSTPRANDIAL HYPERGLYCEMIA**

The Wisconsin Epidemiologic Study of Diabetic Retinopathy<sup>31</sup> demonstrated a relationship between A1C level and microvascular complications. The study followed up subjects for 10 years after stratification into younger or older onset DM groups (ie, type 1 and type 2 DM, respectively). The investigators found increased development of retinopathy related to baseline A1C levels in both groups. One of the best-known studies to show that glycemic control lowered the incidence of microvascular complications was the DCCT,<sup>21</sup> in which 1441 patients with type 1 DM were randomized to receive intensive (3–4 injections per day) or conventional (1–2 injections per day) insulin therapy. After 6.5 years of follow-up, patients receiving intensive insulin treatment showed reductions in the incidence of retinopathy (76%), nephropathy (39%), and neuropathy (60%) compared with patients receiving conventional treatment.

To show that the same benefits were true for patients with type 2 DM, the Kumamoto Study<sup>32</sup> used intensive therapy similar to that used in the DCCT.<sup>21</sup> This study's results demonstrated that tight glycemic control can effectively delay the onset and progression of microvascular complications in patients with type 2 DM. When Shichiri et al<sup>15</sup> reviewed the long-term results of the Kumamoto Study, they found PPHG to be a strong predictor of both retinopathy and nephropathy.

### **EFFECTS OF POSTPRANDIAL HYPERGLYCEMIA ON COAGULATION**

DM is a prothrombotic disease state. Several studies have demonstrated that acute hyperglycemia can alter the coagu-

lation process, increasing the risk for thrombosis.<sup>33–37</sup> Half-life of fibrinogen is shortened<sup>33</sup> while fibrinopeptide A,<sup>34</sup> factor VII,<sup>35</sup> and other coagulation factors are increased. Overproduction of thrombin has been documented in response to acute hyperglycemia.<sup>36</sup> The intracellular adhesion molecule 1 (ICAM-1) is a possible accelerator of atherogenesis. In patients with DM with or without vascular disease, ICAM-1 increases with acute glycemia,<sup>37</sup> again suggesting a role for PPHG in accelerated atherogenesis. Alterations in the coagulation cascade suggest that controlling acute hyperglycemia and PPHG may reduce the incidence of thrombotic events.

### **EFFECTS OF POSTPRANDIAL HYPERGLYCEMIA ON LIPIDEMIA**

Hyperglycemia is not the only risk factor for DM sequelae. The cardiometabolic risk factors of obesity, hypertension, and dyslipidemia also play a significant role in the macrovascular complications of DM. Hypertriglyceridemia commonly occurs in insulin-resistant patients with DM.<sup>38</sup> Major contributing factors are increased very-low-density lipoprotein (VLDL) production and competition for the removal mechanisms of chylomicron and VLDL (eg, reduced lipoprotein lipase activity).<sup>38</sup> Even patients with normal fasting triglyceride levels often exhibit postprandial hypertriglyceridemia. Heine and Dekker<sup>39</sup> studied 100 patients with type 2 DM and normal fasting triglycerides and found that triglyceride levels increased 2 to 3 times during the day, with peak values after dinner and at bedtime. A study investigating the effects of postprandial hypertriglyceridemia on carotid intima-media thickness found that postprandial triglyceride levels had a stronger association with carotid intima-media thickness than did PPHG and fasting LDL levels.<sup>40</sup>

### **OFFICIAL RECOMMENDATIONS FOR MEASUREMENT AND TREATMENT OF POSTPRANDIAL HYPERGLYCEMIA**

Guidelines are now being revised in response to increasing evidence that PPHG affects A1C level and CVD risk, and postprandial BG targets are becoming standardized. In 2003, the American Diabetes Association (ADA) added a target postprandial BG level <180 mg/dL and recommended targeting PPHG for therapy if A1C goals were not reached, even if FPG goals were reached.<sup>41</sup> European guidelines on CVD prevention set postprandial BG targets lower than did the ADA—between 70 and 135 mg/dL.<sup>42</sup> The American College of Endocrinology (ACE)<sup>43</sup> has published guidelines defining desired targets for fasting, preprandial (<110 mg/dL), and 2-hour postprandial (<140 mg/dL) BG levels. ACE defines target A1C levels as <6.5% for overall glycemic control.

The optimal target for postprandial BG level remains to be clarified. Additional studies are needed to determine what glycemic targets would provide the most protection from microvascular and macrovascular complications of DM.

In addition, the best time to measure postprandial BG level remains to be elucidated. The ADA recommends monitoring BG levels 1 to 2 hours after meals.<sup>41</sup>

## TREATMENT MODALITIES

If diet and lifestyle changes are not sufficient to achieve postprandial glycemic control, various pharmacologic agents target PPHG (Table III). These agents include  $\alpha$ -glucosidase inhibitors (eg, acarbose, miglitol), amylin analogues (eg, pramlintide), incretin mimetics (eg, exenatide), rapid-acting insulins and insulin analogues (eg, insulins aspart, lispro, and glulisine; regular human insulin [RHI]; premixed insulins), meglitinide analogues (eg, repaglinide, nateglinide), and dipeptidyl peptidase-IV (DPP-IV) inhibitors. In patients with type 2 DM, the effectiveness of these agents depends on several factors, including patients' residual  $\beta$ -cell function. Although traditional oral antidiabetic drugs (OADs) such as the sulfonylureas, biguanides, and thiazolidinediones have some effect on PPHG, they are not prescribed specifically to control PPHG. In patients with early DM in whom  $\beta$ -cell function is better preserved, these OADs have a considerable effect on PPHG. However, as  $\beta$ -cell function deteriorates, these OADs may not sufficiently control PPHG. Risks of aggressively treating PPHG include hypoglycemia and adverse drug reactions.<sup>9</sup>

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### $\alpha$ -Glucosidase Inhibitors

After carbohydrates are digested by amylases, they are split further by glucosidases into monosaccharides in the jejunal brush border for absorption. Inhibition of  $\alpha$ -glucosidase by acarbose and other  $\alpha$ -glucosidase inhibitors causes a more gradual and delayed absorption of carbohydrates, reducing the peak of postprandial glucose.<sup>44</sup> Acarbose is the most widely studied  $\alpha$ -glucosidase inhibitor for its effect on CVD and PPHG. In a study of 1368 patients with IGT and a mean age of 54.5 years, patients were randomly divided to receive placebo or acarbose 100 mg 3 times daily.<sup>45</sup> The primary end point was development of major CV events. The study found a relative risk reduction of 49%, with risk of myocardial infarction most reduced. The Study to Prevent Noninsulin-Dependent Diabetes Mellitus<sup>46</sup> demonstrated that acarbose significantly reduced the incidence of myocardial infarction and progression of carotid intima-media thickness. In another study,<sup>47</sup> acarbose modestly reduced FPG and A1C levels. Miglitol, another  $\alpha$ -glucosidase inhibitor available in the United States, has demonstrated similar results.<sup>48</sup> These drugs' most common adverse effect is gastrointestinal upset, particularly flatulence.

**Table III.** Pharmacologic agents that target postprandial hyperglycemia.

| Class                              | Agent                              |
|------------------------------------|------------------------------------|
| $\alpha$ -Glucosidase inhibitors   | Acarbose, miglitol                 |
| Amylin analogues                   | Pramlintide                        |
| Meglitinide analogues              | Repaglinide, nateglinide           |
| Regular and premixed agents        | Humulin <sup>®</sup> 70/30*        |
| Insulin analogues                  | Insulins lispro, aspart, glulisine |
| Inhaled insulin                    | Exubera <sup>®†</sup>              |
| Incretin mimetics                  | Exenatide                          |
| Dipeptidyl peptidase-IV inhibitors | Vildagliptin, sitagliptin          |

\*Eli Lilly and Company, Indianapolis, Indiana.

<sup>†</sup>Insulin human (rDNA origin) inhalation powder, Pfizer Inc., New York, New York.

### Amylin Analogues

Amylin is a pancreatic  $\beta$ -cell hormone cosecreted with insulin in response to various insulin secretagogues. Its mechanisms of action include regulating gastric emptying, suppressing postprandial glucagon secretion, and replenishing hepatic glycogen stores. SC injections of pramlintide, a human amylin analogue, reduced postmeal BG excursions in individuals with type 1 and type 2 DM.<sup>49</sup> In a 4-week double-blind, placebo-controlled crossover study, Nyholm et al<sup>49</sup> studied the effect of adding 30  $\mu$ g of pramlintide 4 times daily to premeal insulin in 14 patients with type 1 DM. Compared with the placebo group, 60-minute glucagon levels and postprandial serum glucose AUC were significantly lower ( $P < 0.01$ ) in the pramlintide group after breakfast and lunch. In a study by Ceriello et al,<sup>50</sup> pramlintide in addition to mealtime insulin in patients with type 1 DM significantly reduced postprandial BG excursions, nitrotyrosine (a marker for oxidative stress), and oxidative LDL (all,  $P < 0.03$ ). Patients receiving pramlintide experienced more mild to moderate hypoglycemia than those receiving placebo (28% vs 16%, respectively) and more mild nausea, which is consistent with what other studies<sup>51,52</sup> have reported for adverse reactions.

### Meglitinide Analogues

Repaglinide, a nonsulfonylurea insulin secretagogue, is a benzoic acid derivative that has high affinity for adenosine triphosphate-sensitive potassium channels on  $\beta$ -cells and acts at a different site from sulfonylurea to stimulate insulin release.<sup>53</sup> Repaglinide has a quick onset and short duration of action and peaks at 1 to 2 hours; by 6 hours, insulin levels return to fasting concentrations. Despite its favorable pharmacokinetic profile, repaglinide causes frequent hypoglycemia.

In a study of antihyperglycemic agent-naïve patients, mean A1C levels decreased from 9.3% at baseline to 7.6% and 7.6% at 24 weeks for groups receiving 1 and 4 mg of repaglinide, respectively.<sup>54</sup> Nateglinide, another meglitinide analogue, causes less hypoglycemia than repaglinide but is 50% to 60% less effective at lowering A1C levels than repaglinide and sulfonylureas.

### Insulin Analogues

The 3 rapid-acting insulin analogues available in the United States are designed to mimic the body's physiologic insulin response to meals. Research has shown that rapid-acting insulin analogues can reduce arterial oxidative stress and improve endothelial dysfunction.<sup>55</sup> Insulin lispro has been shown in 2 studies to improve overall glycemic control and PPHG. Ashwell et al<sup>56</sup> studied patients with type 1 DM over 32 weeks and found that A1C levels were lower in patients taking insulins glargine and lispro than in patients taking neutral protamine Hagedorn (NPH) insulin and RHI (7.5% vs 8.0%, respectively). In addition, postprandial BG AUC was 15% lower. When comparing insulin glargine alone with insulins glargine and lispro to reduce postprandial BG level, Kazda et al<sup>57</sup> found that A1C levels decreased by 0.3% and 1.1%, respectively. Insulins lispro and aspart provide improved control of PPHG and can be used within 10 to 20 minutes of eating, unlike RHI.

Insulin glulisine, a newer rapid-acting insulin analogue, was developed to provide a more physiologic prandial insulin replacement compared with RHI. In a study of 876 patients with type 2 DM, Dailey et al<sup>58</sup> found that NPH plus insulin glulisine reduced PPHG significantly compared with NPH plus RHI ( $P < 0.05$ ). Unlike RHI, insulin glulisine can be taken with or right after a meal. Its peak effect occurs in 1 hour and its duration of action is 4 hours, leading to superior PPHG control.<sup>59</sup> Garg et al<sup>60</sup> found that insulin glulisine taken before a meal was more effective at lowering A1C levels than insulin glulisine taken after a meal but that the drug controlled PPHG when taken at either time.

### Inhaled Human Insulin

Exubera<sup>®</sup> (insulin human [rDNA origin] inhalation powder; Pfizer Inc., New York, New York) is the first approved inhaled human insulin (IHI). Several studies have demonstrated its effects on A1C and PPHG levels. Barnett et al<sup>61</sup> studied patients with type 2 DM for 24 weeks who took IHI plus a sulfonylurea or metformin plus a sulfonylurea and found that those taking IHI experienced a greater reduction in A1C level compared with the metformin group. The IHI group experienced more cough and a slight increase in hypoglycemic events.

Similar results were demonstrated by DeFronzo et al,<sup>62</sup> who studied patients with type 2 DM and an A1C level between 8% and 11% even after changes in diet and exercise. Patients were then treated for 3 months with IHI before meals or rosiglitazone 4 mg twice daily. More patients in the IHI group achieved an A1C level <8.0% (83% vs 58%) or

<7.0% (44% vs 18%). IHI is an option for prandial glycemic control but cannot be used by smokers or certain patients with decreased forced expiratory volume in 1 second or carbon dioxide-diffusing capacity.

### Incretin Mimetics

Exenatide is a 39-amino acid peptide incretin mimetic that exhibits glucoregulatory effects similar to those of glucagon-like peptide-1 (GLP-1). Administered SC twice a day, exenatide enhances glucose-dependent insulin secretion, suppresses inappropriately elevated glucagon secretion, slows gastric emptying, and suppresses appetite.<sup>63</sup> Several studies have demonstrated that exenatide reduces PPHG in healthy individuals and patients with type 2 DM. In a recent study, Fehse et al<sup>64</sup> demonstrated that exenatide augments first- and second-phase insulin secretion in response to IV glucose in patients with type 2 DM. Longer term clinical studies ( $\leq 2$  years) showed reductions in A1C level (1.0%–1.3%) and weight (~3.0 kg) in patients with type 2 DM.<sup>65</sup> In a study by Ozyazgan et al,<sup>66</sup> exenatide improved vascular tone in streptozotocin/nicotinamide-induced diabetic rats. Exenatide is generally well tolerated but may cause transient nausea in ~20% to 50% of patients.

### Dipeptidyl Peptidase-IV Inhibitors

GLP-1 helps regulate postprandial BG levels by enhancing glucose-dependent insulin secretion, suppressing glucose-dependent glucagon secretion, and slowing gastric emptying.<sup>67</sup> Because GLP-1 is rapidly degraded in the circulation by the proteolytic activity of DPP-IV inhibitors, DPP-IV inhibition is a potential therapeutic option for glycemic control.

DPP-IV inhibitors are taken PO once or twice daily. Preliminary results<sup>68</sup> have demonstrated that they reduce A1C levels ~1.0% and are well tolerated. The DPP-IV inhibitor vildagliptin (currently in development and not yet approved by the US Food and Drug Administration) has been reported to reduce postprandial, fasting, and 24-hour mean BG levels and increase basal and postprandial active GLP-1 concentrations.<sup>69</sup> The DPP-IV inhibitor sitagliptin improved glycemic control and  $\beta$ -cell function in patients with diet-controlled type 2 DM.<sup>70</sup> The DPP-IV inhibitors appear to be well tolerated, with no effects on weight.

### DISCUSSION AND CONCLUSIONS

The prevalence of DM is reaching epidemic proportions worldwide.<sup>1</sup> Hyperglycemia is the hallmark of DM as a result of  $\beta$ -cell dysfunction and insulin resistance. Glycemic control has been shown to reduce the incidence of microvascular and macrovascular complications in patients with either type 1 or type 2 DM.<sup>21,22</sup> Traditionally, clinicians have targeted FPG level as reflecting glycemic control. More clinicians now realize the importance of glycemic control throughout the day and, in particular, the importance of controlling PPHG.<sup>7</sup> PPHG has been shown to increase CVD risk, promote oxidative stress, worsen postprandial hypertriglyceridemia, exacerbate microvascular disease, and cause

alterations in the coagulation cascade that promote a prothrombotic state. The evidence strongly supports treating PPHG, especially in patients whose A1C level is not at goal.

**T**raditionally, clinicians have targeted FPG level as reflecting glycemic control. More clinicians now realize the importance of glycemic control throughout the day and, in particular, the importance of controlling PPHG.

Different organizations have now published postprandial BG goals. Traditional OADs such as metformin, sulfonylureas, and thiazolidinediones have a substantial effect on PPHG in patients with type 2 DM. However, as patients'  $\beta$ -cell function deteriorates and first- and second-phase insulin responses to

glucose challenge diminish, these traditional OADs may fail to adequately reduce PPHG. Several therapies that specifically target PPHG have been found to improve overall glycemic control and reduce CVD risk.

Although the level of hyperglycemia that leads to microvascular and macrovascular complications in patients with DM remains to be elucidated, it appears prudent to address prandial hyperglycemia, especially PPHG, rather than focus solely on fasting glucose levels. Clinicians should consider incorporating agents that lower PPHG in their treatment of patients with DM.

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**Address correspondence to:** Stephen N. Davis, MD, FRCP, Division of Diabetes, Endocrinology and Metabolism, Vanderbilt University Medical Center, 715 Preston Research Building, 2201 Pierce Avenue, Nashville, TN 37232-6303. E-mail: [steve.davis@vanderbilt.edu](mailto:steve.davis@vanderbilt.edu)