Postprandial Blood Glucose

AMERICAN DIABETES ASSOCIATION

Individuals with diabetes are at increased risk of developing microvascular complications (retinopathy, nephropathy, and neuropathy) and cardiovascular disease (CVD). The Diabetes Control and Complications Trial (DCCT) (1) and U.K. Prospective Diabetes Study (UKPDS) (2) showed that treatment programs resulting in improved glycemic control, as measured by HbA_{1c}, reduced the microvascular complications of diabetes. The effect of these treatment programs on reducing CVD was less clear. However, some epidemiological studies suggest that there may be a relationship between glycemic levels and CVD.

In the management of diabetes, health care providers usually assess glycemic control with fasting plasma glucose (FPG) and premeal glucose measurements, as well as by measuring HbA_{1c}. Therapeutic goals for HbA_{1c} and preprandial glucose levels have been established based on the results of controlled clinical trials. Unfortunately, the majority of patients with diabetes fail to achieve their glycemic goals. Elevated postprandial glucose (PPG) concentrations may contribute to suboptimal glycemic control. Postprandial hyperglycemia is also one of the earliest abnormalities of glucose homeostasis associated with type 2 diabetes and is markedly exaggerated in diabetic patients with fasting hyperglycemia.

Several therapies targeted toward lowering PPG excursions are now available and have been shown to improve glycemic control as measured by HbA_{1c}. However, many questions remain unanswered regarding the definition of PPG and, perhaps most importantly, whether postprandial hyperglycemia has a unique role in the pathogenesis of diabetic complications and should be a specific target of therapy. To address these issues and to provide guidance to health care providers, the American Diabetes Association (ADA) convened a consensus development conference on 24–26 January 2001 in Atlanta, Georgia.

A seven-member panel of experts in diabetes, endocrinology, and metabolism heard selected abstracts and presentations from invited speakers. The panel was then asked to develop a consensus position on the following questions:

1. How is PPG defined?
2. What is the relationship among PPG, FPG, and HbA_{1c}?
3. What is the contribution of PPG to the long-term complications of diabetes?
4. Under what circumstances should people with diabetes be tested for PPG?
5. What are the benefits and risks of specifically lowering PPG in an effort to achieve better glycemic control?
6. What additional research needs to be performed to clarify the role of PPG in the medical management of diabetes?

QUESTION 1: HOW IS PPG DEFINED?

The word postprandial means after a meal; therefore, PPG concentrations refer to plasma glucose concentrations after eating. Many factors determine the PPG profile. In nondiabetic individuals, fasting plasma glucose concentrations (i.e., following an overnight 8- to 10-h fast) generally range from 70 to 110 mg/dl. Glucose concentrations begin to rise ~10 min after the start of a meal as a result of the absorption of dietary carbohydrates. The PPG profile is determined by carbohydrate absorption, insulin and glucagon secretion, and their coordinated effects on glucose metabolism in the liver and peripheral tissues.

The magnitude and time of the peak plasma glucose concentration depend on a variety of factors, including the timing, quantity, and composition of the meal. In nondiabetic individuals, plasma glucose concentrations peak ~60 min after the start of a meal, rarely exceed 140 mg/dl, and return to preprandial levels within 2–3 h. Even though glucose concentrations have returned to preprandial levels by 3 h, absorption of the ingested carbohydrate continues for at least 5–6 h after a meal.

Since people with type 1 diabetes have no endogenous insulin secretion, the time and height of peak insulin concentrations, and resultant glucose levels, are dependent on the amount, type, and route of insulin administration. In type 2 diabetic patients, peak insulin levels are delayed and are insufficient to control PPG excursions adequately. In type 1 and type 2 diabetic individuals, abnormalities in insulin and glucagon secretion, hepatic glucose uptake, suppression of hepatic glucose production, and peripheral glucose uptake contribute to higher and more prolonged PPG excursions than in nondiabetic individuals.

Because the absorption of food persists for 5–6 h after a meal in both diabetic and nondiabetic individuals, the optimal time to measure postprandial glucose concentration must be determined. Practical considerations limit the number of blood samples that can be obtained. In general, a measurement of plasma glucose 2 h after the start of a meal is practical, generally approximates the peak value in patients with diabetes, and provides a reasonable assessment of postprandial hyperglycemia. Specific clinical conditions, such as gestational diabetes or pregnancy complicated by diabetes, may benefit from testing at 1 h after the meal.

QUESTION 2: WHAT IS THE RELATIONSHIP AMONG PPG, FPG, AND HbA_{1c}?

Hemoglobin A_{1c} is a measure of the degree to which hemoglobin is glycosylated in erythrocytes and is expressed as a percentage of total hemoglobin concentration. It reflects the exposure of eryth-

Address correspondence and reprint requests to Richard Kahn, PhD, American Diabetes Association, 1701 N. Beauregard St., Alexandria, VA 22311.

Abbreviations: ADA, American Diabetes Association; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; MPG, mean plasma glucose; OGTT, oral glucose tolerance test; PPG, postprandial glucose; PPGE, postprandial glucose excursion; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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rocytes to glucose in an irreversible and time- and concentration-dependent manner. HbA_{1c} levels provide an indication of the average blood glucose concentration during the preceding 2–3 months, incorporating both pre- and postprandial glycemia.

Because blood glucose concentrations vary widely during a 24-h period and from day to day in diabetes, the measurement of HbA_{1c} is the most accepted indicator of long-term glycemic control. However, the HbA_{1c} level does not provide a measure of the magnitude or frequency of short-term fluctuations of blood glucose, which are particularly great in type 1 diabetes.

The relative contributions of FPG and PPG to HbA_{1c} have been studied only recently. Data from several large cohorts with either type 1 or type 2 diabetes were presented at the conference. In general, FPG, PPG, and especially mean plasma glucose (MPG) concentrations, defined by the average of multiple measurements of glucose taken throughout the day, are highly correlated with HbA_{1c}. In contrast, postprandial glucose excursions (PPGEs), defined as the change in glucose concentration from before to after a meal, and the incremental glucose area, defined as the area under the glucose curve that is above the premeal (or pre–oral glucose tolerance test [OGTT]) value, are poorly correlated with HbA_{1c}.

Several analyses have shown a strong correlation between HbA_{1c} and MPG ($r \approx 0.81–0.95$), with each 1% change in HbA_{1c} corresponding to a change in MPG of ~35 mg/dl. The relationship between timed blood glucose measurements and HbA_{1c} in type 1 diabetic patients was examined in recent analyses of DCCT data presented at the conference. Small differences were detected in the relationship between HbA_{1c} and plasma glucose at different times during the day ($r \approx 0.66–0.76$), with bedtime and postlunch plasma glucose correlating most strongly with HbA_{1c}, and fasting and postbreakfast plasma glucose correlating less well. No specific time point or combination of time points, including mean preprandial or mean postprandial glucose levels, correlated as well with HbA_{1c} as the MPG.

In type 2 diabetes, a study performed in Pima Indians showed that correlations of HbA_{1c} with FPG and PPG measured 1 and 2 h after an oral glucose load or a test meal were indistinguishable ($r \approx 0.6–0.7$). Similar results from a European population were presented at the conference. In another study in type 2 diabetic patients, the effects of different glucose lowering therapies on the relationship among HbA_{1c}, FPG, and PPG were analyzed in a 24-week randomized clinical trial involving three treatment groups (a rapid-acting insulin secretagogue, an insulin sensitizer, and a combination of both agents) and a placebo group. FPG was found to correlate best with HbA_{1c} ($r \approx 0.62–0.67$); the correlation with PPG was weaker ($r \approx 0.22–0.56$) and was inconsistent across the three treatment and placebo groups. There was no significant correlation between HbA_{1c} and PPGE.

In summary, there are insufficient data to determine accurately the relative contribution of the FPG and PPG to HbA_{1c}. It appears that FPG is somewhat better than PPG in predicting HbA_{1c}, especially in type 2 diabetes.

QUESTION 3: WHAT IS THE CONTRIBUTION OF PPG TO THE LONG-TERM COMPLICATIONS OF DIABETES?

Controlled clinical trials, such as the DCCT (1) and the Stockholm Diabetes Study (3) in type 1 diabetes and the Kumamoto Study (4) and UKPDS (2) in type 2 diabetes, have established that therapies directed at achieving normal glycemia are effective in reducing the development and delaying the progression of long-term microvascular diabetic complications.

Even before these clinical trials were completed, observational studies demonstrated a positive association between retinopathy and hyperglycemia. The epidemiological studies relied predominantly on measures of chronic glycemia, such as HbA_{1c}. In the relatively few studies in which HbA_{1c}, FPG, and 2-h OGTT value were measured, all were similarly associated with the risk for retinopathy. Considering the interrelationships among these glycemic measures (described in the previous section), these results are not surprising.

The interventional studies in type 1 diabetes aimed to lower glucose levels with the goal of maintaining HbA_{1c} as close to the nondiabetic range as safely possible. In the DCCT, the primary focus of intensive therapy was to lower preprandial (up to 1 h before meals) and bedtime self-monitored blood glucose levels. If HbA_{1c} goals were not achieved, further attention was focused on lowering the 90- to 120-min postprandial levels. In type 2 diabetes, the UKPDS adjusted glucose-lowering therapy to attain fasting glucose goals. Epidemiological analyses of the DCCT (5) and UKPDS (6) results reinforce the relationship between chronic glycemia, as measured by HbA_{1c}, and risk for developing long-term complications. No clinical trial data address whether PPG, independent of other measures of glycemia, plays a unique role in the pathogenesis of diabetes-specific complications. Similarly, no clinical trial data outside of studies in gestational diabetes have examined the need to treat postprandial glucose levels specifically to prevent complications.

Interventional studies have not demonstrated a convincing beneficial effect of glucose lowering on CVD outcomes (1,2), and no clinical trials have examined whether treatments that primarily lower PPG decrease cardiovascular events. Associations of CVD and CVD risk factors with glycemia have been demonstrated over a broad range of glucose tolerance, from normal to diabetic, in several epidemiological studies. Whether the FPG or a postchallenge (OGTT) glucose level is an independent risk factor for CVD in these studies is controversial and requires further study.

QUESTION 4: UNDER WHAT CIRCUMSTANCES SHOULD PEOPLE WITH DIABETES BE TESTED FOR PPG?

The only setting in which PPG monitoring has been shown to improve outcomes is gestational diabetes. In one study, women with gestational diabetes were randomly assigned either to a treatment program in which therapy was adjusted to achieve predefined FPG and PPG levels or to one targeting premeal and bedtime glucose levels (7). The women assigned to postprandial monitoring achieved a lower HbA_{1c} and required fewer Caesarian sections for cephalopelvic disproportion, and their babies suffered less frequently from macrosomia and neonatal hypoglycemia. Whether similar outcomes could have been achieved with premeal monitoring if lower premeal targets had been selected is unknown. There are no comparable randomized clinical studies in people with type 1 or type 2 diabetes examining whether PPG monitoring improves outcomes.

Are there other clinical situations in

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which PPG monitoring should be considered part of the overall treatment plan? There are no adequate randomized clinical trial data to answer this question, but the following are clinical situations in which PPG monitoring could be considered:

A. Suspected postprandial hyperglycemia. In patients who achieve their premeal glucose targets, but whose overall glycemic control as determined by HbA_{1c} is inappropriately high, PPG monitoring and therapy to minimize PPGEs may be beneficial.
B. Monitoring treatment aimed specifically at lowering PPG. In patients with type 1 or type 2 diabetes who are treated with glucose-lowering agents expected primarily to reduce PPG, monitoring may be useful in titrating these treatments or in confirming that patients have responded to the intervention. It is also possible that PPG monitoring may be beneficial to evaluate the effect of changes in nutrition or exercise patterns.
C. Hypoglycemia. Hypoglycemia in the postprandial period is rare except in response to exercise or rapid-acting insulin analogs.

There are insufficient data either to support or to refute the need for extensive or routine PPG monitoring in diabetes, except in the setting of pregnancy. Since self-monitoring of blood glucose represents a significant financial and personal burden for patients, decisions regarding PPG monitoring should be based on the needs and responses of individual patients. The decision to recommend a glucose monitoring plan should be made judiciously, accompanied with specific patient education, and reviewed and modified regularly by the health care team.

QUESTION 5: WHAT ARE THE BENEFITS AND RISKS OF SPECIFICALLY LOWERING PPG IN AN EFFORT TO ACHIEVE BETTER GLYCEMIC CONTROL?

Randomized clinical trials have demonstrated that a reduction in the long-term complications of diabetes is proportional to average glycemia as determined by HbA_{1c}. However, it is unclear whether reducing PPG provides additional improvements in HbA_{1c}.

What, if any, are the documented benefits of specifically lowering PPG? The definitive answer to this question can only come from well-designed, randomized, controlled clinical trials. The availability of oral agents and insulin analogs that specifically target postprandial glucose levels has provided tools to perform such studies.

Alpha-glucosidase inhibitors, rapid-acting oral insulin secretagogues, and rapid-acting insulin analogs predominantly lower PPG. They also reduce HbA_{1c}. It is unclear, however, to what extent HbA_{1c} is lowered by these drugs because of their effects on PPG as compared with their effects on FPG. Furthermore, it is not clear whether therapies that target PPG provide unique benefits relative to other pharmacological therapies that lower HbA_{1c} comparably. Performing such studies will be important.

It has been suggested that agents that specifically lower PPG may decrease the risk of hypoglycemia and weight gain. These claims have not been consistently supported by randomized, controlled studies. There appear to be no unique risks associated with the specific lowering of PPG to achieve HbA_{1c} goals.

QUESTION 6: WHAT ADDITIONAL RESEARCH NEEDS TO BE PERFORMED TO CLARIFY THE ROLE OF PPG IN THE MEDICAL MANAGEMENT OF DIABETES?

There are several issues that should be considered when designing studies to examine PPG. Studies should be performed in well-defined patient groups; at a minimum, separation of patients by type of diabetes is necessary. It is also quite likely that results of studies in patients with impaired fasting glucose and/or impaired glucose tolerance may be different from those in patients with type 2 diabetes and different degrees of fasting hyperglycemia. In particular, elderly patients, in whom postprandial hyperglycemia may be the most prevalent abnormality in glucose homeostasis, may warrant special attention. In studies of the impact of PPG on diabetic complications, it is important to differentiate between microangiopathy and macroangiopathy as end points. Finally, attention must be paid to differences in therapeutic programs (e.g., nutrition therapy versus oral antihyperglycemic agents versus insulin) and type of oral glucose-lowering drugs used. Given these general principles, the following specific questions should be addressed:

A. How do we best assess postprandial hyperglycemia and the relationships among FPG, PPG, and HbA_{1c}? The term postprandial hyperglycemia is used very loosely because its assessment has not been standardized. Some of the most obvious unresolved issues related to the definition of PPG include: *1*) use of a carefully defined meal test versus the OGTT; *2*) variations in size and macronutrient content of test meals; *3*) timing of blood sampling after standard meals or glucose challenge; and *4*) how often any of these measurements should be made in order to provide meaningful information. Resolving these issues, in the appropriate experimental setting, will provide information to define more precisely the nature of the relationships among FPG, PPG, and HbA_{1c}. This information is also necessary to address broader issues, such as the relative importance of PPG and FPG in assessing glycemic control and/or predicting the risk for diabetic complications.
B. What is the clinical utility of using measurements of PPG to improve glycemic control? At present, HbA_{1c} measurements are the "gold standard" for assessing long-term glycemic control. The fundamental question to be answered is whether measuring premeal glucose, FPG, or PPG, alone or in combination, will be most helpful in adjusting treatment to achieve HbA_{1c} goals while minimizing hypoglycemia. Although useful insights concerning these issues have been gained from retrospective analyses, definitive answers require intervention studies. These studies should determine whether treatments aimed at controlling FPG and PPG result in lower HbA_{1c} than do treatments that predominantly affect FPG and/or premeal glucose levels.
C. In the presence of equivalent HbA_{1c} values, does an excessive rise in PPG uniquely affect chronic diabetic complications? It is unclear whether excessive excursions of PPG have a significant impact on the development of diabetic microvascular or macrovascular complications independent of

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HbA_{1c} levels. To address this fundamental question, studies must be designed to control FPG versus PPG levels while aiming to achieve similar and acceptable HbA_{1c} levels.

Because CVD is the major cause of morbidity and mortality in patients with diabetes, and in type 2 diabetes in particular, understanding the impact on CVD events of treatments directed at specifically lowering PPG is crucial. Furthermore, the relationship between PPG excursions and both the well-established risk factors and the more recently identified putative mechanisms for CVD should be examined.

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APPENDIX

Consensus Panel

David M. Nathan, MD,* Chair; John B. Buse, MD, PhD, CDE*; Edward S. Horton, MD*; Harold Lebovitz, MD*; Gerald Reaven, MD; Robert A. Rizza, MD*; and Bruce R. Zimmerman, MD*. *These Panel members disclosed that within the past year they have received honoraria, consulting fees, or research grant support, or hold stock in one or more of the companies providing support for this conference.

Speakers at the Conference

Paul J. Beisswenger, MD; Antonio Ceriello, MD; William C. Duckworth, MD; William C. Knowler, MD, DrPH; James B. Meigs, MD, MPH; Michele Muggeo, MD; and F. John Service, MD, PhD.

Oral Abstract Presenters at the Conference

Enzo Bonora, MD, PhD; Frederick L. Brancati, MD; Michael M. Engelgau, MD; Thomas Erlinger, MD, MPH; David E. Goldstein, MD; Francine Ratner Kaufman, MD; M. Sue Kirkman, MD; Elizabeth Koller, MD; Romano Nosadini, MD; and Thomas M.S. Wolever, MD, PhD.

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