The Management of Post-prandial Glucose

a report by
Antonio Ceriello, MD

Professor of Diabetes and Metabolic Medicine, University of Warwick

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Recently there has been considerable debate regarding the importance of post-prandial glucose (PPG) levels in patients with diabetes. Previously, therapeutic intervention focused on optimizing overall glycemic control as assessed by glycated hemoglobin (HbA_{1c}) levels, with a strong emphasis on fasting plasma glucose (FPG). There was concern in some quarters that setting PPG goals could be unrealistic and even unsafe because they carry an increased risk for hypoglycemia.[1] However, a growing body of evidence suggests that reducing PPG is as important, or even more important, for achieving HbA_{1c} goals.

Post-prandial blood glucose levels are generally <120mg/dl in healthy non-diabetic subjects and rarely exceed 140mg/dl, which reflects the World Health Organization (WHO) definition.[2] Post-prandial hyperglycemia is defined as a plasma glucose level exceeding 140mg/dl.[3] Development of post-prandial hyperglycemia coincides with an impairment or absence of the first-phase insulin response, a decrease in insulin sensitivity in the peripheral tissues, and decreased suppression of hepatic glucose output after meals due to insulin deficiency.[4] Post-prandial hyperglycemia is also one of the earliest abnormalities of glucose homeostasis associated with type 2 diabetes, and worsens—progressing to fasting hyperglycemia—as the condition progresses.[5] The relative contribution of PPG varies across the day: it is highest at HbA_{1c} levels of ~6.5%, when FPG levels are close to normal, and lowest at HbA_{1c} levels >8%, when the FPG level predominates.[6] Thus, a triad model of diabetes management in which all three parameters—HbA_{1c}, PPG, and FPG levels—are considered to be inter-related and therapeutic targets could potentially optimize glycemic control.[7]

Post-prandial hyperglycemia is common both in patients with diabetes and in those considered to have adequate glycemic control. A US study of individuals with type 2 diabetes found post-challenge glucose values of ≥200mg/dl in nearly 74% of patients.[8] Individuals with type 1 diabetes on intensive insulin therapy regimens also show elevations of PPG—levels of 140mg/dl were detected in 77% of one study patient population.[9] The Diabetes Control and Complications Trial (DCCT)[10,11] and the UK Prospective Diabetes Study (UKPDS)[12–14] clearly demonstrated a strong correlation between glycemic control and the incidence of late microvascular and macrovascular complications. Lowering of HbA_{1c} significantly delayed the onset or slowed the progression of diabetic retinopathy, nephropathy, and neuropathy, as well as myocardial infarction (MI). Since PPG has been shown to contribute to HbA_{1c} levels, targeting PPG should help reduce the risk for complications.

Several studies have found associations between PPG and cardiovascular risk.[15–17] Evidence suggests that acute hyperglycemia may increase cardiovascular risk by a variety of mechanisms at tissue, cellular, and biochemical levels, leading to the generation of oxidative stress.[18] Markers of cardiovascular risk have also been associated with elevated PPG levels. The one-hour PPG level has been linked to a rise in carotid intima-media thickness (CIMT), a marker of atherosclerosis.[19] PPG has also been linked to inflammation and endothelial dysfunction[20,21] and adhesion molecules.[22] It has been postulated that acute hyperglycemia, free fatty acids, and insulin resistance cause oxidative stress, protein kinase-C (PKC) activation, and advanced glycated end-product receptor (RAGE) activation, leading to vasoconstriction, inflammation, and thrombosis.[23]

Post-prandial and post-challenge hyperglycemia is associated with a variety of complications including nephropathy and retinopathy,[24] decreased myocardial blood volume/blood flow,[25] increased risk for cancer,[26–29] and impaired cognitive function in the elderly.[30] In MI patients both with and without diabetes, high levels of blood glucose at admission have been associated with an increased risk for death.[31]

Measurement of Post-prandial Glucose

The oral glucose tolerance test (OGTT) was once widely used as the first-choice test for the diagnosis of diabetes, gestational diabetes, impaired glucose tolerance, or reactive hypoglycemia. The OGTT involves measurement of baseline fasting plasma glucose, then plasma glucose is measured again at two hours following a glucose 'challenge.' Glucose tolerance is defined as normal (NGT), impaired (IGT), or indicative of overt diabetes. The test has the advantage of simplicity; however, it is expensive and not considered physiological because the 75–100g of glucose used in the challenge is rarely consumed during a meal. Since 1997, the American Diabetes Association (ADA) has recommended that FPG testing replace OGTT as the first-choice test for the diagnosis of diabetes or IGT.[32] It has

Antonio Ceriello, MD, is a Professor of Diabetes and Metabolic Medicine at the University of Warwick in the UK, and an Adjunct Professor of Medicine at the University of Oklahoma City. Until March 2006 he was Chair of Internal Medicine and Director of the Specialty School of Geriatrics at the University of Udine in Italy. Professor Ceriello is an active member of numerous diabetes associations, including the American Diabetes Association (ADA), the American Heart Association (AHA), the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD). He is also Associate Editor of *Diabetes Care* and *Diabetic Medicine* and a regular reviewer for the *American Journal of Physiology*, *Circulation*, *Circulation Research*, *Diabetes*, *Diabetes Care*, *Diabetic Medicine*, *Diabetologia*, and *The Lancet*. He was the winner of the 2004 Castelli Pedroli Prize of the EASD.

E: Antonio.Ceriello@warwick.ac.uk

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been demonstrated, however, that the level of glycemia reached two hours after an OGTT correlates strongly to the level reached after a standardized meal, particularly among those with IGT, suggesting that among this group the two-hour OGTT glucose level provides valuable information on altered carbohydrate metabolism during a meal.[33]

Findings from two large-scale epidemiological studies—the European DECODE and the Asian DECODA—have shown that serum glucose level at least two hours after oral challenge with glucose is a more powerful predictor of cardiovascular risk than fasting glucose.[15,16] Furthermore, a meta-analysis demonstrated a linear increase of cardiovascular risk within a wide range of two-hour plasma glucose values, but demonstrated a threshold effect for fasting plasma glucose values up to ~100mg/dl.[17]

> The two-hour timescale for measurement of post-prandial glucose/post-challenge glucose is generally used because it is consistent with the guidelines published by most of the leading diabetes organizations and medical associations.

The two-hour timescale for measurement of PPG/post-challenge glucose is generally used because it is consistent with the guidelines published by most of the leading diabetes organizations and medical associations. However, in recent years a focus on glucose fluctuations has led to the definition of new parameters in the assessment of PPG. It has been demonstrated that a single fluctuation in blood glucose is almost always accompanied by an alteration in endothelial function, and oscillating glucose over 24 hours has been shown to cause more endothelial dysfunction than a stable constant high level of glucose.[34] The glucose 'spike'—i.e. the difference between the baseline glucose level before an OGTT and the 'peak' value during an OGTT—has been found to be a more powerful predictor of CIMT in those with IGT than the glycemic peak at two hours, regardless of the time after glucose challenge and the level of FPG.[35] The effect of acute glycemia on endothelial function is dependent on glucose concentration, and in diabetic patients this does not depend on the basal level of glycemia already present.[34]

A recent study of 611 patients with diabetes in normal daily life defined the term incremental glucose peak (IGP) as the maximal incremental increase in blood glucose obtained at any point following a meal, and also showed a correlation with CIMT. Moreover, IGPs tend to occur at the same time: 95% of the diabetic population studied had an IGP occurring within one hour after the start of the meal, and timing was not influenced by diet or drugs. It has been suggested that of the glycemic parameters usually used to identify both chronic and post-prandial hyperglycemia, IGP is the best predictor of CIMT.[36]

Managing Post-prandial Glucose

There is much evidence to suggest that although treatment of type 2 diabetes always carries a risk of hypoglycemia, fears regarding the safety of PPG control have proved unfounded.[1] Management of PPG using the short-acting insulin analog aspart reduces oxidative stress and improves arterial function.[37] The STOP-NIDMM trial indicated that treatment of patients with IGT with the alpha-glucosidase inhibitor acarbarose, a compound that specifically reduces PPG, causes a reduction in the risk for progression to diabetes, development of hypertension, and cardiovascular events.[38,39] Acarbarose treatment has been associated with a significant decrease in CIMT.[40]

Other agents that affect PPG include the alpha-glucosidase inhibitor miglitol and the rapid-acting insulin secretagogs repaglinide and nateglinide. Diets with a low glycemic load are also beneficial in controlling PPG. Future studies of non-pharmacological and pharmacological therapies should greatly increase our understanding of the relative benefits of pre- and post-prandial glucose as therapeutic targets. In any therapeutic regime, it is important that each therapy be appropriately matched to a patient's ability to recognize and respond to hypoglycemia when it does occur.

Guidelines

Previous guidelines published by the ADA defined targets for fasting and bedtime glucose levels but not for PPG.[41] The International Diabetes Federation's (IDF's) guidelines previously defined a level for two-hour PPG of <135mg/dl.[42] The guideline development group has stated that the goal of diabetes therapy should be to achieve near-normal glycemic status by the safest possible means in all three measures of glycemic control: HbA_{1c}, FPG, and PPG.[43] The IDF and other organizations define normal glucose tolerance as <140mg/dl two hours following ingestion of a 75g glucose load, thus a two-hour PPG level of <140mg/dl is consistent with this definition. Furthermore, because PPG usually returns to basal level two to three hours following food ingestion, a plasma glucose goal of <140mg/dl would seem to be a reasonable and conservative target.

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The IDF, following an extensive, systematic search of the literature published over the past 20 years, proposed the following recommendations in the IDF Guideline for Management of Postmeal Glucose:[42]

- post-prandial hyperglycemia is harmful and should be addressed;
- implement treatment strategies to lower post-prandial plasma glucose in people with post-prandial hyperglycemia;
- a variety of both non-pharmacological and pharmacological therapies should be considered to target post-prandial plasma glucose;
- two-hour post-prandial plasma glucose should not exceed 140mg/dl as long as hypoglycemia is avoided;

- self-monitoring of blood glucose (SMBG) should be considered because it is currently the most practical method for monitoring post-prandial glycemia; and
- the efficacy of treatment regimens should be monitored as frequently as needed to guide therapy toward achieving post-prandial plasma glucose target.

Following this report, guidelines published by most of the leading diabetes organizations and medical associations have been revised, adding recommendations for PPG. A summary of the various guidelines is given in *Table 1*. The two-hour timescale for measurement of plasma glucose concentrations is the most commonly recommended. It is the safest timescale for those treated with insulin, particularly if they are inexperienced or have been poorly advised, as they may respond inappropriately to an elevated one-hour plasma glucose level by taking an additional insulin bolus without waiting for the initial bolus to take effect.[43] This can lead to severe hypoglycemia.

SMBG is currently considered the optimal method for assessing glucose levels. In contrast to periodic HbA_{1c} testing, which indicates the mean value of blood glucose over the preceding two to three months, SMBG provides immediate feedback to patients regarding glucose levels throughout the day. Both tests are essential for assessing glycemic control, with HbA_{1c} considered the preferred standard for predicting long-term micro- and macrovascular complications. Specific protocols remain variable, however, particularly among non-insulin-using patients.[44–49] SMBG can lead to improved glycemia by revealing the immediate effect of patient behavior on blood glucose levels.

Although SMBG is recommended in the daily management of type 1 diabetes and insulin-treated type 2 diabetes, worldwide healthcare guidelines have not generally advised SMBG for non-insulin-using patients. This is due to the high cost of frequent SMBG and the tradition of evaluating SMBG use in terms of HbA_{1c}.[49] However, the correlation between glycemic spikes and oxidative stress previously discussed has led to suggestions that all patients with diabetes perform SMBG to monitor glycemic variability.[35,50] In a large managed care study, an association between frequent monitoring of blood glucose and clinically and statistically better glycemic control was observed regardless of diabetes type or therapy.[51] During pregnancy, regular post-prandial monitoring is accepted, supported by evidence that patients using post-prandial glucose goals have improved fetal outcomes.[52] It must be remembered that SMBG is only one component of diabetes management, and its benefits require training of patients to perform SMBG, interpret their test results, and appropriately adjust their treatment regimens to achieve glycemic control. Moreover, clinicians should be familiar with interpreting SMBG data, prescribing appropriate medications, and closely monitoring patients in order to make timely adjustments to their regimens as needed.

> Strategies that target both fasting plasma glucose and post-prandial glucose are needed to optimize glycemic control, and treatment of both should be initiated simultaneously at any HbA_{1c} level.

Table 1: Summary of Post-prandial Glucose Guidelines

Organization, Year		HbA_{1c} (%)	FPG (mg/dl)	PPG (mg/dl)	PPD Timing
IDF, 2007[3]		<7	<110	<140	1–2 hours post-prandially
ESC/EASD, 2007[56]	Type 1 diabetes	≤6.5	≤108	135–160	'Peak'
	Type 2 diabetes	≤6.5	≤108		
ADA, 2007[57]		≤6.5	70–130	<180	1–2 hours post-prandially
AACE, 2007[58]		≤6.5	110	<140	2 hours post-prandially

AACE = American Association of Clinical Endocrinologists; ECS/EASD = European Society of Cardiology/European Association for the Study of Diabetes; IDF = International Diabetes Federation; HbA_{1c} = glycated hemoglobin; FPG = fasting plasma glucose; PPG = post-prandial glucose.

On the basis of the new guidelines, it has been recommended that people treated with insulin perform SMBG ≥3 times a day; SMBG frequency for people who are not treated with insulin should be individualized to each person's treatment regimen and level of glycemic control.[43] Given that glycemic status is the sum of the fasting, post-prandial, and post-absorptive states, at least one test per day from each of these periods would be ideal. In reality, though, over 65% of patients with non-insulin-treated type 2 diabetes practice SMBG less than once daily, due in part to cost, inadequate patient education, and/or poor patient motivation.[53] While these obstacles require long-term solutions, a possible interim measure is to target either FPG or PPG, depending on HbA_{1c} level.

New techniques for glucose monitoring are emerging: these include continuous glucose monitoring (CGM), in which a sensor measures glucose at intervals of up to 10 minutes and transmits this reading to a data storage device.[54] Results can be downloaded retrospectively by the physician, or displayed in realtime in the monitor. Markers for post-prandial hyperglycemia such as 1,5-anhydroglucitol (1,5-AG), a naturally occurring dietary polyol, have also been studied.[55]

Conclusions

Post-prandial and post-challenge hyperglycemia are associated with cardiovascular and other risks. The importance of PPG is now widely accepted, and this is reflected in the new guidelines. Strategies that target both FPG and PPG are needed to optimize glycemic control, and treatment of both should be initiated simultaneously at any HbA_{1c} level. Subject to available therapies and technologies, a two-hour PPG <140mg/dl is both reasonable and achievable. SMBG is currently the most practical method for monitoring PPG. The efficacy of treatment regimens should be monitored as frequently as needed to guide therapy toward achieving PPG target. Large epidemiological studies have shown not only that type 2 diabetes is often under-managed, but also that diabetes is now becoming a worldwide epidemic. Since the greatest increase in prevalence of type 2 diabetes is among adults 30–39 years of

age, there will be more people living longer with type 2 diabetes.[1] It is therefore imperative that healthcare providers find ways to improve their effectiveness in treating hyperglycemia. Although cost will remain an important factor in determining appropriate treatments, controlling glycemia is ultimately much less expensive than treating the complications of diabetes. ■

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