Is Postprandial Glucose Control Important? Is It Practical In Primary Care Settings?

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There has been much debate about the effect of postprandial glucose levels on diabetes outcomes and the necessity of treating postprandial hyperglycemia in patients with type 2 diabetes.

Current recommendations of the American Diabetes Association (ADA), which have been used predominantly in the United States, present goals for fasting/preprandial and bedtime glucose levels but do not define a target for postprandial glucose.[1] The ADA guidelines also present a glycated hemoglobin (A1C) goal of <7%, with "additional action suggested" when A1C is >8%. (See Table 1.) The International Diabetes Federation (IDF) and the American College of Endocrinology (ACE) have each published guidelines that define targets for both fasting/preprandial and 2-h postprandial blood glucose and present ≤6.5% as their A1C goal for glycemic control.[2,3] (See Table 1.)

Many clinicians argue that these new guidelines are necessary in order to address the significant and growing incidence of microvascular and macrovascular complications caused by poorly controlled diabetes and to clear up confusion among health care providers regarding glycemic targets. Other clinicians, however, fear that the new targets may be unrealistic and even unsafe because they carry an increased risk of hypoglycemia.

The latest study of American adults (>20 years of age) with diabetes revealed that ~37% had A1C concentrations >8%; 14% had concentrations >10%.[4] These findings support the results of a recent, unpublished survey of 100 primary care providers in which ~58% of respondents indicated that they would not start pharmacological therapy until a patient's A1C reached 8.0% or higher.[5] This may explain why A1C levels in many patients are often well above the ADA target of <7%.

In the remainder of this article, we will discuss some of the key issues associated with the role and treatment of postprandial glucose in type 2 diabetes by addressing the following questions:

- Does tighter glycemic control matter?
- How does postprandial glucose relate to overall glycemic levels?
- Is postprandial glucose control an independent contributor to diabetes outcomes?
- Is postprandial glucose control safe for most patients?
- Is postprandial glucose control practical in primary care settings?

IN BRIEF

Large interventional studies have shown that achieving and maintaining near-normal glycemic levels reduces the risk for microvascular and macrovascular complications in type 2 diabetes. The impact of postprandial glucose on glycemic control has become a topic of much discussion among clinicians. This article examines the literature related to the role of postprandial glucose in type 2 diabetes, both as a contributor to overall glycemia and as an independent risk factor for diabetes complications, and discusses the practicality of managing postprandial hyperglycemia in primary care settings.

Does tighter glycemic control matter?

Large, randomized, prospective trials[6–8] have demonstrated that reductions in hyperglycemia and management of diabetes-related risk factors significantly reduce microvascular and macrovascular complications in patients with either type 1 or type 2 diabetes. These trials demonstrated a 30–35% reduction in microvascular complications per 1% absolute reduction of glycated hemoglobin. Epidemiological data from the United Kingdom Prospective Diabetes Study (UKPDS)[9] also showed a 14–16% decrease in macrovascular complications for every 1% absolute reduction in glycated hemoglobin—with no glycemic threshold for a substantive change in the risk for any of the clinical outcomes studied. In other words, risk reduction extended into the normal range for glycated hemoglobin. To achieve maximum benefit from treatment, many researchers and clinicians now believe that A1C values must be kept close to ≤6.5%, which is slightly above the normal range in nondiabetic patients (<6%).[9]

How does postprandial glucose relate to overall glycemic levels?

In healthy, nondiabetic subjects, 2-h postprandial blood glucose levels are usually <120 and rarely >140 mg/dl. Glucose levels peak at ~1 h after the start of the meal and then return to preprandial levels within 2–3 h.[10,11] This rise and fall of postprandial glucose levels is mediated by the first-phase insulin response, in which large amounts of endogenous insulin are released, usually within 10 min, in response to nutrient intake. In individuals with type 2 dia-

Table 1. Glycemic Goals for Diabetes Control

	ADA[1]	IDF[2]	ACE[3]
Glycated hemoglobin (%)	<7.0	≤6.5	≤6.5
Fasting/preprandial (mg/dl) *(plasma equivalent)*	80–120	<100	<110
2-h postprandial (mg/dl)	—	<135	<140

betes, the first-phase insulin response is severely diminished or absent, resulting in persistently elevated postprandial glucose throughout most of the day.[12]

There is some disagreement among researchers as to the level of significance of postprandial glucose in affecting and/or predicting overall glycemic control, as measured by glycated hemoglobin. In a recent study of patients with non-insulin-treated type 2 diabetes, Bonora et al.[13] showed that A1C levels are more closely related to preprandial than to postprandial glucose levels, even though the majority of patients studied had extremely elevated glucose excursions with meals and extended periods of postprandial hyperglycemia.

In contrast, Avignon et al.[14] found that post-lunch plasma glucose and extended post-lunch plasma glucose was more reliable in predicting poor glycemic control than pre-breakfast or pre-lunch plasma glucose. Several other studies[15–17] have shown that postchallenge and postprandial glucose values correlate better with glycated hemoglobin levels than do fasting/preprandial glucose values. Soonthornpun et al.[17] demonstrated that postprandial hyperglycemia, specifically the 2-h postprandial glucose level, is associated with high A1C levels.

The question now becomes: Does targeting postprandial hyperglycemia improve overall glycemic control? In a study of patients with type 2 diabetes with secondary failure of sulfonylurea therapy, Feinglos et al.[18] showed that improvement of postprandial hyperglycemia, using insulin lispro (Humalog) at mealtime in combination with a sulfonylurea, not only reduced 2-h postprandial glucose excursions, but also reduced both fasting glucose and A1C levels from 9.0% to 7.1% ($P < 0.0001$). Subjects in the lispro group also benefited from significantly decreased total cholesterol levels and improved HDL cholesterol concentrations.

Improvements in A1C levels were also reported in a study by Bastyr et al.,[19] which showed that therapy focused on lowering postprandial glucose versus fasting glucose may be better for lowering glycated hemoglobin levels. Further, in a study of patients with gestational diabetes, De Veciana et al.[20] demonstrated that targeting treatment to 1-h postprandial glucose levels rather than fasting glucose reduces glycated hemoglobin levels and improves neonatal outcomes.

Regardless of whether postprandial glucose is a better predictor of A1C than fasting/preprandial glucose, most researchers agree that the *best* predictor of A1C is mean blood glucose, which is a composite of both fasting/preprandial and postprandial glucose. Therefore, it is reasonable to conclude that achieving near-normal postprandial glucose levels is essential to achieving overall glycemic control.

Is postprandial glucose control an independent contributor to diabetes outcomes?

There is continuing debate about whether and to what degree postprandial glucose contributes to the development of microvascular and macrovascular complications. The report from the ADA consensus conference on postprandial glucose reiterated findings from the Diabetes Control and Complications Trial, the Kumamoto study, and the UKPDS, which demonstrated that therapies directed at achieving normal glycemia reduce the development and delay the progression of long-term microvascular complications.[10] Further, as mentioned earlier, epidemiological analysis of UKPDS data showed that macrovascular outcomes were also improved by lowering glycemic levels.[9] Therefore, if postprandial glucose is a contributor to overall glycemia, then postprandial glucose control must be a contributor to the development of diabetes complications. It is still not clear, however, whether postprandial glucose is an *independent* contributor to diabetes complications.

Numerous epidemiological studies have shown elevated postprandial/postchallenge glucose to be independent and significant risk factors for macrovascular complications and increased mortality risk. The Honolulu Heart Study[21] found a strong correlation between postchallenge glucose levels and the incidence of cardiovascular mortality. The Diabetes Intervention Study,[22] which followed newly diagnosed patients with type 2 diabetes, found moderate postprandial hyperglycemia to be more indicative of artherosclerosis than was fasting glucose, and found postprandial but not fasting glucose to be an independent risk factor for cardiovascular mortality. The DECODE Study,[23] which followed more than 25,000 subjects for a mean period of 7.3 years, showed that increased mortality risk was much more closely associated with 2-h post–glucose load plasma levels than with fasting plasma glucose. Similar to these findings, de Vegt et al.[24] found that the degree of risk conferred by the 2-h postprandial glucose concentration was nearly twice that conferred by A1C level. Further, recent studies have demonstrated that even moderate postprandial hyperglycemia (148–199 mg/dl) is not only more indicative of artherosclerosis than is fasting glucose, but also may have direct adverse effects on the endothelium.[25,26]

No adequate randomized clinical trials have demonstrated a causal relationship between postprandial glucose treatment and reduction of diabetes

complications. However, strong evidence shows that a relationship does exist between postprandial glucose and mean glucose, which, in turn, affects overall glycemic levels.[13]

Although the ADA consensus panel did not specify a postprandial glucose target, it did recommend postprandial monitoring and therapy for type 2 diabetic patients with *suspected* postprandial hyperglycemia.[10] As mentioned earlier, Bonora et al.[13] and others have clearly shown that the majority of patients with type 2 diabetes have exaggerated glucose excursions at meals with subsequent 2-h postprandial hyperglycemia. If monitoring and treatment of postprandial glucose is recommended in patients with type 2 diabetes, what is the goal for this therapy? The ADA has left this question unanswered pending future study.[1,10] The IDF and ACE guidelines recommend <135 and <140 mg/dl, respectively, for blood glucose concentrations 2 h after the start of a meal.[2,3]

Is postprandial glucose control safe for most patients?

The safety of postprandial glucose control is both dependent upon the therapy used and specific to each patient's ability to recognize and treat hypoglycemia when it does occur. Although severe hypoglycemia is rare in patients with type 2 diabetes, *fear* of hypoglycemia (among patients and providers) remains a major obstacle to achieving postprandial glucose control and, presumably, tighter overall glycemic control.

Is this fear justified? The VA Cooperative Study[27] showed severe hypoglycemic reactions to be extremely rare among intensively treated patients and not significantly different from those among conventionally treated patients. The Kumamoto study[7] showed no severe hypoglycemia over 8 years in either the intensively or the conventionally treated group. Conversely, the UKPDS did show severe hypoglycemia in intensively treated patients, from 0.1 to 2.3% per year, depending on the therapy.[8,28] However, severe hypoglycemia (0.03% per year) was also reported by patients treated with diet therapy alone, which raises some question about the actual incidence of true severe hypoglycemia.

Regardless of the differences in reported hypoglycemia in these studies, all of them have shown that the risk of severe hypoglycemia in type 2 diabetes is significantly less than in type 1 diabetes.[6–8] One reason for this reduced risk is that, unlike type 1 diabetes, deficits in secretion of counter-regulatory hormones (glucagon and epinephrine) are less prominent in type 2 diabetes. Further, recent studies have shown that the glucose thresholds for counter-regulatory hormone secretion are altered in patients with both well-controlled and poorly controlled type 2 diabetes, so that both symptoms and counter-regulatory hormone release occur at normal glucose values.[29,30] Spyer et al.[29] concluded that this effect may protect patients with type 2 diabetes against severe hypoglycemia, yet makes the achievement of tight glycemic control more challenging in clinical practice.

While it may be difficult to achieve tighter postprandial glucose control in patients with type 2 diabetes, today's new insulin preparations and oral therapies may provide part of the solution to this challenge. Rapid-acting insulin analogs, such as insulin aspart (Novolog) and insulin lispro, produce higher serum insulin levels earlier and have a shorter duration of action than regular human insulin, resulting in lower postprandial glucose excursions with shorter durations of postprandial hyperglycemia, as well as reduced incidence of severe hypoglycemia in patients with type 2 diabetes.[31,32]

A double-blind, double crossover study of 25 insulin-requiring type 2 diabetic patients (mean age of 59.7 years) by Rosenfalck et al.[31] demonstrated that immediate pre-meal administration of insulin aspart resulted in improved postprandial glucose control compared to regular human insulin injected immediately before the meal, with no concerns about safety. Anderson et al.[32] also found that mealtime therapy with lispro reduced postprandial hyperglycemia compared with regular human insulin therapy, and that it may decrease the rate of mild hypoglycemic episodes in patients with type 2 diabetes.

Additionally, studies that have looked at the effects of rapid-acting insulin analogs combined with intermediate-acting insulins (free-mixed and premixed preparations) in patients with type 2 diabetes have shown improved postprandial glucose control with reduced hypoglycemia.[33–35] These results indicate that the improvements in glucose control and reductions in the frequency/severity of hypoglycemia previously demonstrated in type 1 diabetic patients treated with insulin aspart or insulin lispro also apply to insulin-treated type 2 diabetic patients.

In addition to rapid-acting insulin therapy, there are also rapid-acting oral secretagogues, such as repaglinide (Prandin) and nateglinide (Starlix), which have been shown to be safe and effective in controlling postprandial glucose excursions.[36,37]

While it can be argued that the incidence and severity of hypoglycemia reported in the UKPDS may have been lower if patients had used the new insulin analogs and oral agents in combination with home glucose monitoring technology (which was not widely available when the study started), the risk of hypoglycemia in type 2 diabetes cannot be discounted. All hypoglycemic therapies (secretagogues and insulin) have the potential to cause severe hypoglycemia. Therefore, it is important that health care providers understand the level of risk associated with each therapy utilized and that each therapy be appropriately matched to each patient's ability to recognize and respond to hypoglycemia when it does occur.

Is postprandial glucose control practical in primary care settings?

Achieving and maintaining tight postprandial glucose control without

increased incidence of severe hypoglycemia may, indeed, be challenging in primary care settings. However, it can be achieved in most patients with type 2 diabetes through informed and thoughtful utilization of the various therapeutic options, in combination with appropriate blood glucose monitoring regimens and comprehensive patient education in diabetes self-management. Providers may find the following strategies useful in initiating more aggressive postprandial glucose management with their patients.

1. ***Make appropriate use of qualified diabetes education programs.*** Diabetes management is ultimately driven by patients. Therefore, it is important that patients fully understand and are able to manage all aspects of their self-care. Diabetes instruction should cover meal planning; exercise/physical activity; safe and appropriate use of pharmacological therapies (including insulin injection); self-monitoring of blood glucose (SMBG); utilization of pattern management to adjust therapy; prevention/treatment of hypoglycemia; and general health maintenance (foot exams, skin care, dental care, etc.).

   Because most primary care practices do not have the intensive educational resources available to teach these skills, it is important to identify and utilize the services of a qualified diabetes educator to provide self-management instruction. Qualified educators both enable and encourage patients to take a more active role in their diabetes management, thereby enhancing safety, efficacy, and adherence to the diabetes regimen.

2. ***Establish aggressive, but realistic glycemic goals for each patient.*** Targets for glycemic control must be individualized based on each patient's clinical status, which includes socioeconomic circumstances, cognitive abilities, level of motivation, and many other factors. Elderly patients whose diabetes is relatively well controlled or who have minimal complications, for example, may not be appropriate candidates for more aggressive therapy. This individualization of therapeutic goals is recommended by the American Academy of Family Physicians.[38]

   It is important, however, that health care providers do not let their own attitudes about glycemic targets influence their patients' performance. A recent study[39] showed that metabolic control is strongly related to provider beliefs regarding tight glycemic control in patients with type 1 or type 2 diabetes. Patients whose providers stressed more aggressive glucose targets achieved lower glycated hemoglobin values and reduced rates of complications compared to patients whose providers set higher glycemic goals.

   A1C test results should be shared and discussed with patients regularly to provide feedback and reinforcement for managing their diabetes.

3. ***Match and continuously adjust therapy to the each patient.*** Type 2 diabetes is a progressive disease characterized by persistent insulin resistance and relentless loss of β-cell function. Therefore, therapy must not only address each patient's current level of β-cell function, but also be continuously monitored and adjusted to accommodate ongoing β-cell deterioration.

4. ***Utilize laboratory and SMBG data to determine appropriate therapy, then make therapeutic adjustments on a timely basis.*** SMBG data combined with A1C test results provide key information about overall glycemic control, postprandial glucose excursions, and the effectiveness of current therapy. This information enables clinicians to more accurately monitor and adjust therapy. It also provides patients with the ability (and enhanced motivation) to make more informed decisions regarding their meal planning, exercise regimens, and, if appropriate, insulin dosages. While it is unrealistic to expect patients with type 2 diabetes to test their blood glucose before and after every meal on a daily basis, a staggered SMBG regimen including testing 2–3 times per day can provide a clear pattern of control. Figure 1 presents one of many options for staggered SMBG.

5. ***Monitor and treat all diabetes risk factors.*** Approximately 92% of all patients with type 2 diabetes are insulin resistant, which puts them at risk for a number of disorders, including cardiovascular disease, hypertension, dyslipidemia, and obesity. Monitoring and managing blood pressure, lipid levels, renal function, and obesity are crucial to the prevention of diabetic complications. Table 2 presents recommendations for management of these risk factors.

	Breakfast		**Lunch**		**Supper**		**Bed**
	Pre	Post	Pre	Post	Pre	Post	
Monday	X	X					X
Tuesday	X		X	X			
Wednesday					X	X	
Thursday	X	X					X
Friday	X		X	X			
Saturday					X	X	
Sunday	X	X					X

Figure 1. One option for staggered SMBG.

Table 2. Goals for Blood Pressure, Lipids, and Microalbumin

Blood Pressure[1]	<130/80 mmHg
Lipids[40]	
LDL cholesterol	<100 mg/dl
HDL cholesterol	>60 mg/dl
Triglycerides	<150 mg/dl
Microalbumin[1]	<30 μg/mg creatinine (spot collection)

Conclusions

Large, randomized interventional studies have provided conclusive evidence that achieving and sustaining tight glycemic control (<6.5% A1C) significantly reduces the risk of diabetic microvascular and macrovascular complications. Unfortunately, large epidemiological studies have shown not only that type 2 diabetes is often *undermanaged*, but also that diabetes in the United States is now an epidemic. Because 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. It is, therefore, imperative that health care providers find ways to improve their effectiveness in treating diabetes in order to prevent years of debilitating complications and an enormous financial burden on the health care system.

To argue that the new glycemic goals are inappropriate because they are unsafe or too difficult to achieve is contrary to sound clinical judgment. The focus should be on achieving the best possible glycemic control for each patient because *any* reduction in A1C significantly reduces the risk for diabetes complications. Helping patients achieve their best possible level of glycemic control will require the utilization of appropriate therapy, appropriate monitoring, and comprehensive instruction in diabetes self-management.

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Note of disclosure: *Mr. Parkin is a paid consultant for Eli Lilly and Company and Bayer Diagnostics. Dr. Brooks sits on advisory boards for Eli Lilly and Company, Aventis Pharmaceuticals, and Pfizer Pharmaceuticals. These companies manufacture or market pharmaceutical products for the treatment of postprandial hyperglycemia.*