

Targeting Plasma Glucose: Preprandial Versus Postprandial

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Over the past decade, a major interest in postprandial glucose (PPG) has emerged, in part because of a plethora of new medications that specifically target PPG. These include insulin analogs (lispro and aspart), insulin secretagogues (repaglinide and nateglinide), alpha-glucosidase inhibitors (miglitol and acarbose), and injectable amylin analogs and glucagon-like peptide receptor agonists.

Targeting plasma glucose has been an accepted practice. For example, in the Diabetes Control and Complication Trial (DCCT) involving type 1 diabetic patients, pattern analysis of pre-meal glucose values was targeted first. In the U.K. Prospective Diabetes Study (UKPDS), the fasting blood glucose (FBG) was targeted, and medications were titrated based on FBG.¹ Considering there are potentially seven points within a 24-hour glucose profile (pre-meals, post-meals, and at bedtime), the question of which glucose value(s) to target first and which will have the most impact on hemoglobin A_{1c} (A1C), is an important one for both patients and busy practitioners.

Normal and Abnormal Glucose Physiology

In people without diabetes, peak PPG occurs about 1 hour after a meal and generally does not exceed 140 mg/dl.¹ PPG values can change as a result of a multitude of variables, such as activity, insulin sensitivity, gastric emptying rate, and meal composition.² For example, carbohydrates contribute significantly more to PPG than do fats or protein. Hence, there is an accepted

practice of counting the grams of carbohydrate to be consumed, and administering supplemental insulin before the meal to cover the expected carbohydrate load.^{3,4}

In type 2 diabetic individuals, peak PPG occurs at about 2 hours after a meal and relates to inadequate glucose disposal.¹ The pathogenesis of PPG elevation in type 2 diabetic patients results from loss of first-phase insulin secretion, failure to control hepatic glucose production, and resistance of muscle to glucose uptake.⁵ In addition, postprandial hyperglycemia is driven by a lack of suppression of glucagon (hence, the interest in agents that antagonize glucagon).⁶

Normally, fasting glucose maintenance mostly depends on glucose production by the liver. In the progression of type 2 diabetes, insulin output is able to

increase with the increasing glucose level until the FBG reaches about 140 mg/dl, at which point the β -cell insulin output cannot keep pace with the increased glucose load, and the fasting insulin concentration decreases. This is sometimes referred to as "Starling's curve of the pancreas."⁷ At this time, hepatic glucose production begins to increase because insufficient insulin is available for suppression. This process is the major determinant of the FBG level.⁷

Mean Plasma Glucose

Most practitioners agree that A1C is the gold standard for glycemic control and that it best correlates with mean plasma glucose (MPG). Both pre- and post-meal glucose values are important because they both contribute to A1C, but the contribution of each has been debated.

Rohlfing et al.⁸ calculated the MPG for 1,439 type 1 diabetic patients in the DCCT by using a 7-point capillary glucose database (pre- and post-meal and bedtime). The importance of this association of MPG and A1C has been recognized by the American Diabetes Association (ADA) in its position statement "Standards of Medical Care in Diabetes"⁹ (Table 1).

The MPG, while providing general information about control, is not specific enough to allow practitioners to target glucose excursions during a specific time of day.

The Fasting Glucose Story

The ADA has recognized the fasting plasma glucose (FPG), instead of the 2-hour oral glucose tolerance test (GTT), as the diagnostic test of choice.⁹ The

IN BRIEF

Considering there are potentially seven points within a 24-hour glucose profile (pre-meals, post-meals, and at bedtime), the question of which of these values to target is important to both patients and busy practitioners. Appropriate targeting of plasma glucose may lead to less expense and less unnecessary testing for patients and may help patients and practitioners achieve glucose goals more expeditiously. This article suggests that targeting fasting plasma glucose is more beneficial when hemoglobin A_{1c} (A1C) results are very high, whereas targeting postprandial glucose is more effective when A1C results are lower.

Table 1. Correlation Between A1C Level and MPG Levels

| A1C (%) | MPG | |
|---------|-------|--------|
| | mg/dl | mmol/l |
| 6 | 135 | 7.5 |
| 7 | 170 | 9.5 |
| 8 | 205 | 11.5 |
| 9 | 240 | 13.5 |
| 10 | 275 | 15.5 |
| 11 | 310 | 17.5 |
| 12 | 345 | 19.5 |

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FPG is more consistent and reproducible than PPG because there are more variables in the latter, such as timing and carbohydrate load.¹⁰ Likewise, FPG may be easier to control with medication than PPG. The variables of food intake and exercise, for example, are much less of a factor at night preceding measurement of the FPG, and this may enable a more consistent pattern of values for FPG.

It has been pointed out, however, that targeting FPG alone does not provide as good a degree of control as does targeting all pre-meal glucose values.¹¹ For example, the UKPDS, targeting just FPG, lowered A1C an average of ~ 1%, whereas the DCCT, targeting pre-meal lunch and supper values in addition to FPG, lowered A1C an average of ~ 2%.

DeFronzo has noted that, in type 2 diabetic individuals, fasting glucose contributes approximately three-fourths and postprandial glucose approximately one-fourth of mean glycemia.¹² Therefore, the phrase “fix the fasting first” has become an axiom of care for some practitioners, with the recommendation to use metformin and sulfonylureas first because they each lower the FPG by 60–70 mg/dl, whereas thiazolidinediones lower FPG by only 45–55 mg/dl, and alpha-glucosidase inhibitors lower FPG by 20–30 mg/dl.¹²

Carroll et al.¹³ evaluated the relationship of FPG to PPG and concluded that the FPG level predicts the degree of post-meal hyperglycemia and the magnitude

of the post-meal excursion from baseline. The authors noted a direct relationship between FPG and PPG elevation and concluded that, because FPG is a determinant of PPG excursion, “fixing the fasting” should precede PPG correction.

In a study of 371 type 2 diabetic patients, Bonora et al.¹¹ concluded that preprandial glucose measurements are more closely related to A1C than are PPG, but that the strongest correlation of A1C was to MPG. However, it was noted that many patients whose A1C indicated good control (A1C < 7%) still had PPG values > 160 mg/dl. This study suggests that “treating to goal” by attaining A1C < 7% may not ensure that PPG goals are also achieved.

The contribution of FPG to A1C was found to be dominant in patients with poorly controlled type 2 diabetes in a study by Monier et al.¹⁴ In this study of 290 patients, the contribution of FPG approached 70% as A1C neared 10%. It was also noted that, as glucose improves, PPG contribution dominates, so that with A1C values approaching 7%, the PPG contribution is about 70%.

The Postprandial Glucose Story

First written about in 1922,¹⁰ the GTT was described as currently used in 1979 by the National Diabetes Data Group. It is considered the gold standard for diagnosis of diabetes,¹⁵ in part because changes in PPG often precede FPG changes in the natural history of type 2 disease. In fact, the World Health Organization retains the 2-hour GTT as the diagnostic test of choice.¹⁶ Data from the Third National Health and Nutrition Examination Survey suggest that in about 10% of type 2 diabetic patients, the 2-hour value was > 200 mg/dl, when the FPG was < 126 mg/dl.⁵

In agreement with Monier et al.,¹⁴ Erlinger and Brancati⁵ showed that PPG elevations (> 200 mg/dl) occurred generally in 39% of patients whose A1C was optimal (< 7%). Looking at patients who were using oral agents, PPG elevation occurred in 63% of those with A1C results < 7%. Likewise, Soonthornpun et

al.¹⁷ noted that with normal or near-normal FPG and an A1C that remained high, the 2-hour PPG becomes a good index of glycemic control. Thus, PPG elevation is a frequent finding when “optimal” control is achieved. It follows that controlling PPG at this time would likely lead to an A1C reduction further below 7%.

In a study by Bastyr et al.,¹⁸ 135 type 2 diabetic patients whose baseline mean A1C was > 10% were all prescribed glyburide. They were then divided into three groups depending on whether they received additionally lispro (targeting PPG), bedtime NPH (targeting FPG), or metformin (targeting pre-meal values). It was shown that the lispro group targeting PPG had the greatest A1C reduction. However, it was the FPG and pre-meal glucose values—not PPG values—that dictated dose titration.^{2,18} This study shows that FPG and pre-meal glucose values in patients with poorly controlled type 2 diabetes can successfully dictate titration of an agent specifically targeting PPG (lispro).

Supporters of PPG control laud its importance by noting that it is an independent risk factor for cardiovascular disease, over and above FBG, as demonstrated in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study.¹⁶ In the DECODE study, the plasma glucose value that defined increased risk was 140 mg/dl, 2 hours after a 75-g glucose load. This is the rationale for the American College of Endocrinology adopting this number (140 mg/dl) as its 2-hour PPG goal.²

PPG targets have been established in gestational diabetes with favorable reports. By monitoring and controlling PPG at 1 hour, DeVeciana et al.¹⁹ showed beneficial outcomes, such as reduced levels of macrosomia, in neonates.

ADA Consensus Statement

In January 2001, the ADA convened a consensus development conference, which led to publication of the consensus

Table 2. ADA-Recommended Glycemic Goals

| | |
|---------------------|----------------------------|
| A1C | < 7.0% (normal range 4–6%) |
| Preprandial glucose | 90–130 mg/dl |
| PPG | < 180 mg/dl |

statement “Postprandial Blood Glucose” in April of that year.¹ One of the outgrowths of this conference was the establishment of a 2-hour PPG goal of ≤ 180 mg/dl. This goal was chosen because it was associated with an A1C of ~ 7%.² In the DCCT, average post-breakfast values of 220 mg/dl and post-lunch and post-supper values of 180 mg/dl correlated with an A1C of about 7%.²⁰

In contrast, the American College of Endocrinology has recommended a PPG goal of < 140 mg/dl.^{12,21} A post-meal glucose of < 140 mg/dl would correlate with an A1C of 4.9–5.9%.^{2,20}

Achievement of such a goal would be rare and limited by the harmful effects of hypoglycemia, particularly in type 1 diabetic patients, as demonstrated in the DCCT. Proponents of the PPG goal of 140 mg/dl, however, point out that in a GTT, the ADA does recognize a 2-hour value between 140–199 mg/dl as an “impaired” state and a cardiovascular risk. Thus, 140 mg/dl would be a laudable goal, assuming side effects could be curtailed.

Under the ADA recommendations, preprandial glucose is targeted first. Only when preprandial glucose is at goal, but A1C is not, is PPG targeted.¹ However, PPG can be measured earlier when postprandial hypoglycemia is suspected. The goals for glycemic control, as recommended by the ADA, are listed in Table 2.⁹

A Unifying Concept

Despite seemingly contradictory studies, there may be a unifying concept as proposed by Monier et al.^{14,22} This is the notion that the contribution of a given glucose value varies depending on the A1C results. For example, with A1C results < 7.3%, PPG contributes ~ 70% of the A1C. However, with A1C results > 10.2%, FPG contributes 70% of the

value, and PPG contributes the remaining 30%.¹⁴ (Figure 1).

Conclusion

The roles of FPG and PPG continue to be debated. Table 3 lists various reasons to target each of these values. Because the FPG and pre-meal glucose levels are reflected in the PPG, it seems most practical to routinely control pre-meal glucose first, since it will likewise lower post-meal glucose levels, as well. When pre-meal glucose and A1C are markedly uncontrolled, the additional financial and personal burden of having patients check their PPG levels does not appear warranted at this time.⁵

Table 4 offers a targeting sequence that can help avoid unnecessary self-

monitoring of blood glucose by type 2 diabetic patients.

Various studies have suggested that PPG is an independent risk factor for cardiovascular disease. Because impaired glucose tolerance (2-hour values of 140–199 mg/dl) and impaired fasting glucose (FBG of 100–125 mg/dl) are associated with macrovascular disease, whereas micovascular disease appears to be more related to the FPG of > 126 mg/dl,⁹ it is suggested that a lower glycemic threshold may exist for macrovascular disease. Thus, there is adequate rationale to attempt to lower the A1C even further below 7%.

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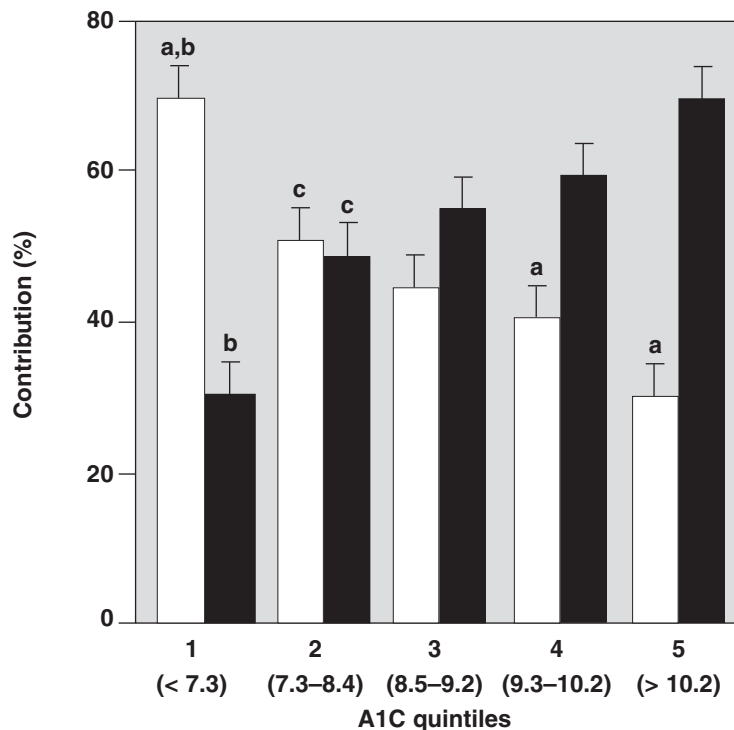


Figure 1. Relative contributions of postprandial and fasting hyperglycemia (%) to the overall diurnal hyperglycemia over quintiles of A1C. Reprinted with permission from Ref. 14.

Table 3. Reasons to Target FPG or PPG Values

| FPG | PPG |
|---|--|
| <ul style="list-style-type: none"> • Contributes to A1C • A determinant of PPG¹³ • Poor glucose control (A1C > 8.4%)¹⁴ • Contributes ~ 70% when A1C > 10.2%¹⁴ • More reproducible | <ul style="list-style-type: none"> • Contributes to A1C • Preprandial glucose, but not A1C, at goal¹ • Better glucose control (A1C < 8.4%)¹⁴ • Contributes ~ 70% when A1C < 7.3%¹⁴ • Is frequently the earliest abnormality of type 2 diabetes • May represent an independent risk for cardiovascular disease^{17,22} • Gestational diabetes¹⁹ • For patients using medications targeting PPG¹ • If postprandial hypoglycemia is suspected¹ |

Table 4. Suggested Glucose Targeting Sequence for Type 2 Diabetes

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|--|
| <ol style="list-style-type: none"> 1. With poor glucose control (A1C in the 9–10% range or greater), titrate medication according to FPG. 2. With improving control of the FPG (A1C in the range of 8–9%), look for patterns for pre-lunch, pre-supper, and bedtime glucose levels, and target these. 3. With pre-meal glucose values coming into target range (A1C ~ 7–8% or even less) but A1C results still not optimal, look for patterns of PPG elevation, and target these. |
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