



Clinical Decision Making: Managing Postprandial Hyperglycemia

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Abstract

The primary objective of treating all patients with diabetes is to establish and maintain near-normal blood glucose levels to prevent microvascular and macrovascular complications. The glycated hemoglobin (HbA_{1c}) is the accepted standard for monitoring overall glycemic control with treatments and management strategies traditionally targeting fasting and preprandial glucose levels. However, postprandial glucose levels also contribute to HbA_{1c}, and optimization of glycemic control may also require targeting these values. Exaggerated postmeal glucose excursions are common in patients with diabetes, and postprandial hyperglycemia (PPHG) is an independent risk factor for cardiovascular disease. Regular self-monitoring of blood glucose concentrations (SMBG) at appropriate times can detect PPHG, provide patient feedback regarding meals and lifestyle, and monitor response to therapy. SMBG can also help detect fluctuations in blood glucose levels, which may be an additional risk factor for complications, independent of HbA_{1c}. New therapeutic options that specifically target postprandial glucose levels may improve overall glycemic control and reduce the risk of microvascular and macrovascular complications. ©

INTRODUCTION

Establishing and maintaining tight glycemic control is important for minimizing the microvascular and macrovascular complications of diabetes.^{1,2} There is a close correlation between the risk of complications and the glycosylated hemoglobin (HbA_{1c}) value. HbA_{1c} provides a measure of overall mean glycemic exposure resulting from fasting, preprandial, and postprandial glucose concentrations and is the gold standard for monitoring control.

Although preprandial and fasting plasma glucose (FPG) concentrations have been considered the primary measures of daily glucose control, postprandial glucose (PPG) levels are equally, more important.³ Postprandial hyperglycemia (PPHG) has been linked to cardiovascular morbidity and mortality even when HbA_{1c} values are in the nondiabetic range,^{4,6} whereas elevated FPG concentrations are not independently associated with increased cardiovascular disease (CVD) risk.^{7,8} Additionally, acute glucose fluctuations appear to exhibit a more specific triggering effect on oxidative stress than does chronic sustained hyperglycemia.⁹ Such fluctuations can be detected by self-monitoring of

blood glucose (SMBG) but not by HbA_{1c}. Since therapies specifically targeting PPHG can reduce postprandial glucose levels, HbA_{1c} values, and CVD risk,^{10,11} strategies to reduce PPHG and excessive glycemic excursions may be particularly important in minimizing the risk of long-term complications. One important component of these strategies is SMBG, which, when used together with appropriate patient education, is effective for detecting and managing PPHG. SMBG can inform patients and their healthcare professionals about the effects of food choices, medications, exercise, and stress on glucose levels throughout the day, thus complementing information provided by HbA_{1c} values.¹² In addition, several new therapeutic options specifically targeting PPHG have expanded the ability to optimize glycemic control by tailoring therapy to the individual patient. This article will discuss the importance of detecting and managing PPHG and glycemic excursions, examine the role of SMBG, and review new and emerging treatment options.

Clinical Significance of PPHG

PPHG has been identified as an independent risk factor for CVD in patients with or without diagnosed diabetes, suggesting that PPHG may be a better predictor of risk than is FPG or HbA_{1c} alone (Table 1).^{4,6,10,13} PPHG, but not FPG, is a significant predictor of subsequent myocardial infarction (MI) and death in patients with newly diagnosed type 2 diabetes.⁵ In addition, reductions in carotid intima-media thickness

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Table 1 : Morbidity and mortality related to postchallenge and postprandial hyperglycemia

Study	Patients	Key Findings
DECODE study ¹³	10 prospective studies among 15,388 men and 7126 women not previously diagnosed with diabetes	2-hour blood glucose levels following 75-g OGTT better predictor of all-cause and cardiovascular deaths than FBG levels
Chicago Heart Association ⁶	12,220 men with diabetes or asymptomatic hyperglycemia	Increased risk of CVD mortality with higher postload glucose level (after 50-g OGTT)
Temelkova-Kurktschiev <i>et al</i> ⁴	582 men and women at risk for type 2 diabetes	2-hour blood glucose levels and spikes more strongly associated with CIMT than FPG or HbA _{1c}
Diabetes Intervention Study ⁵	1139 men and women with newly diagnosed type 2 diabetes	PPHG, but not FPG, significant risk factor for MI and mortality
Campanian Postprandial Hyperglycemia Study ¹⁰	93 men and 82 women with type 2 diabetes not previously drug-treated	Reduction of PPHG, but not FPG, associated with reductions in CIMT

DECODE, Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe; OGTT, oral glucose tolerance test; FBG, fasting blood glucose; CVD, cardiovascular disease; CIMT, carotid intima-medial thickness; HbA_{1c}, glycosylated hemoglobin; MI, myocardial infarction.

(CIMT) have been linked to changes in postprandial but not fasting hyperglycemia or HbA_{1c}¹⁰ and PPHG has been associated with the development of diabetic nephropathy and retinopathy.^{14,15}

Many complex biochemical and molecular events have been implicated in hyperglycemia-induced tissue damage.^{8,16,17} At least 4 biochemical pathways are thought to be involved in vascular damage, and hyperglycemia-induced mitochondrial superoxide production is thought to be the unifying mechanism for all 4 pathways (Table 2).¹⁶ A recent study suggests that acute glucose fluctuations lead to increased urinary excretion of 8-iso-prostaglandin F_{2α}, a marker of oxidative stress.⁹

Treatment of PPHG Improves Glycemic Control and Reduces Diabetic Complications

Therapies focusing on PPHG have successfully reduced PPG levels,¹⁸ enhanced glycemic control (HbA_{1c}),^{19,20} and may improve clinical outcomes as suggested by studies showing regression of CIMT¹⁰ and a reduced risk of cardiovascular events.¹¹ For example, targeting of PPHG with a sulfonylurea plus insulin lispro resulted in better glycemic control than did a sulfonylurea alone or therapies targeting fasting or preprandial glucose.^{19,20} Patients with type 2 diabetes treated with the insulin secretagogue repaglinide, which increases insulin secretion following meals, had a greater decrease in peak and area-under-the-curve glucose levels than did those who received the sulfonylurea

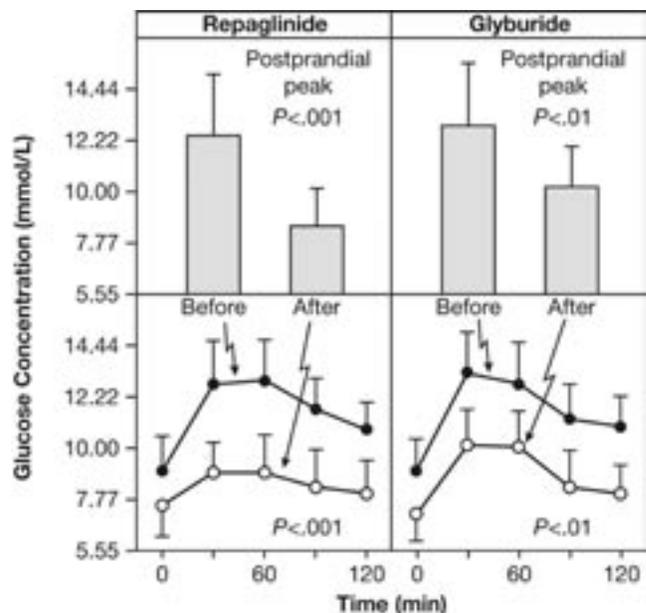


Fig. 1 : Effect of therapy specifically targeting postprandial glucose. Glucose peaks (top) and curves (bottom) after main meal of the day, before and after study completion in patients treated with repaglinide or glyburide. Adapted with permission from Esposito K *et al.* *Circulation*. 2004;110:214-219.¹⁰

glyburide (Fig. 1). Regression of CIMT occurred in 52% of subjects receiving repaglinide versus 18% of those receiving glyburide ($P=.01$), suggesting an association between regression of CIMT and reductions in PPHG, but not FPG.¹⁰

In patients with impaired glucose tolerance, treatment with the α -glucosidase inhibitor acarbose, which delays or prevents absorption of carbohydrates by the gut, resulted in a 49% relative risk reduction in overall cardiovascular events compared with placebo (2.5% absolute risk reduction, $P=.03$).¹¹ This reduction was primarily due to a reduced risk of MI (91% relative risk reduction, $P=.02$). Although this study did not actually measure PPG levels, other studies have shown that acarbose has an effect on these values.¹⁸

Table 2 : Postprandial hyperglycemia and tissue damage: proposed pathophysiological mechanisms¹⁶

Hyperglycemia-induced mitochondrial superoxide production leads to:
- Increased flux in polyol pathway
- Increased intracellular formation of advanced glycation end-products
- Protein kinase C activation
- Increased flux through hexosamine pathway

SMBG HELPS IDENTIFY PATIENTS AT GREATEST RISK FOR POSTPRANDIAL GLYCEMIC EXCURSIONS

It is important to identify patients at risk of PPHG or excessive glycemic excursions and to regularly monitor their PPG levels. Excessive postprandial glycemic excursions are common in patients with type 2 diabetes, even those considered well controlled according to HbA_{1c} values and FPG levels (Fig. 2).²¹⁻²⁴ PPHG is one of the earliest defects in diabetes and is the predominant contributor to HbA_{1c} at values below 8.4% (Fig. 3).²⁵

HbA_{1c} is an integrated measure of glycemic exposure over the previous 2 to 3 months. Although PPHG may contribute more at lower HbA_{1c} values, it is still not possible to use HbA_{1c} to identify patients with

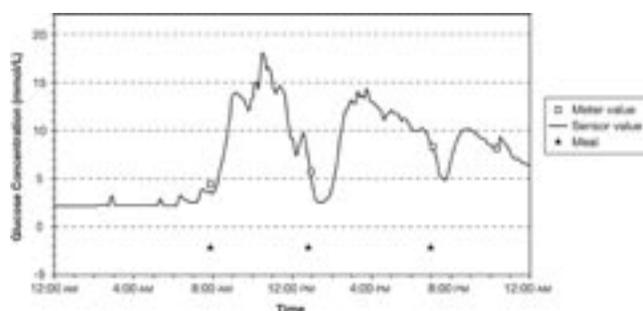
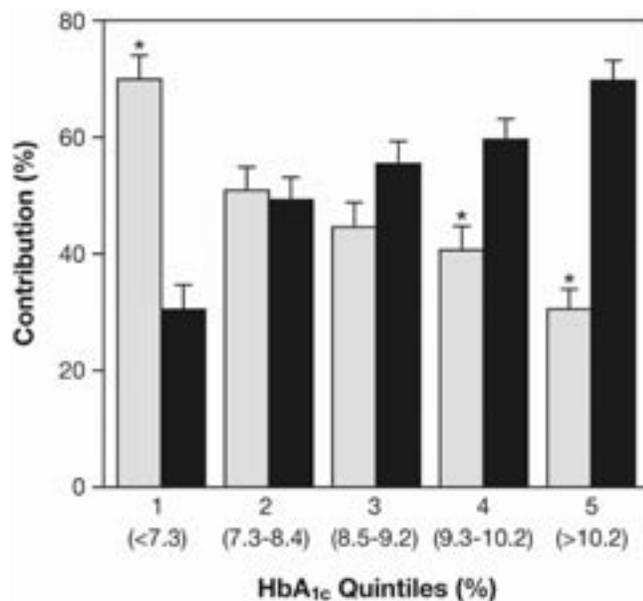


Fig. 2 : Glucose profile illustrating postprandial glucose (PPG) excursions. Representative 24-hour glucose profile generated by continuous glucose monitoring showing nocturnal hypoglycemia and significant daily PPG increases. Reprinted with permission from Hay LC et al. *Diabetes Technol Ther.* 2003;5:19-26.²⁴

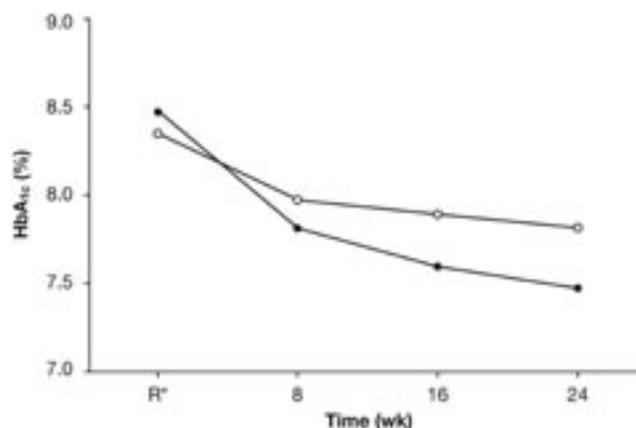


((Permission requested from Diabetes Care))

Fig. 3 : Influence of fasting and postprandial glucose by glycosylated hemoglobin (HbA_{1c}). Relative contributions of postprandial (open bars) and fasting (filled bars) hyperglycemia to overall hyperglycemia by HbA_{1c} quintiles. Asterisk denotes a significant difference between fasting and postprandial glucose levels according to paired t-test.

postprandial glycemic excursions or isolated PPHG, whereas appropriately timed SMBG is ideal for detecting and monitoring PPHG. Glucose profiles, in which patients monitor at different times throughout the day or over several days to determine representative diurnal glucose levels, can help detect PPHG. Paired-meal SMBG testing, or testing before and 1 to 2 hours after meals, can evaluate the amplitude of glycemic excursions and can educate patients and their healthcare professionals about dietary habits. Unlike FPG, meal-based SMBG may enable patients to see the effects of their meal choices and portion sizes.²⁶ Postprandial SMBG values are often the highest glucose readings of the day and may motivate patients to avoid problem foods, increase physical activity to manage hyperglycemic excursions, or evaluate and adjust insulin doses.^{26,27}

In addition to detecting postprandial excursions, SMBG may facilitate significant improvement in glycemic control.^{12,28-30} The quality of research performed on the efficacy of SMBG has been comprehensively reviewed elsewhere and concerns about the quality of the studies expressed³¹; nevertheless, some evidence does exist for efficacy. Schwedes et al investigated the effect on HbA_{1c} of meal-related SMBG compared to no SMBG in non-insulin-treated patients.²⁸ In the 6-month study, patients in the intervention group performed SMBG before and 1 hour after main meals on 2 days of the week, kept a blood glucose/eating diary, and received standardized counseling designed to promote self-reflection on the results of SMBG testing. Patients in the control group received nonstandardized counseling on diet and lifestyle. The intervention group achieved a significant reduction in HbA_{1c} values compared with controls (1.0% vs 0.54%, $P=.0086$) (Fig. 4). The authors noted that patients in the SMBG group performed twice as many SMBG measurements as requested because patients were experimenting with their favorite meals.²⁸ Similarly, a study by Muchmore et al showed that meal-



Adapted with permission from Schwedes U et al. *Diabetes Care.* 2002;25:1928-32²⁸

Fig. 4 : Effect of self-monitoring of blood glucose (SMBG) on changes in glycosylated hemoglobin (HbA_{1c}) over time. There was a statistically significant between-group difference at 24 weeks favoring SMBG (filled circles) versus controls (open circles) ($P=.0086$).

based SMBG (before and 2 hours after meals for the first month) combined with dietary carbohydrate counting led to a significant decrease in HbA_{1c} values (1.54%, $P < .05$) from baseline over the 44-week study.²⁹ This study of 23 overweight patients with type 2 diabetes compared SMBG and carbohydrate counting (n=12) to a behavioral weight control program with no SMBG (n=11). Patients in the control group did not achieve a significant decrease in HbA_{1c} values (0.84%, $P > .3$) from baseline; while patients in the intervention group improved by 1.54% the same interval ($p < 0.5$). The differences between the 2 groups was not significant at the study end. This study demonstrated the value of linking SMBG measurements directly to carbohydrate consumption.

OPTIONS FOR MANAGING PPHG

The Role of Diet and Exercise

Dietary counseling, regular physical exercise, and weight loss have been recommended for all patients with diabetes.³²⁻³⁴ SMBG may help patients understand how food choices and exercise affect their blood glucose levels.³⁵ The total amount and nature (composition, portion size, preparation method, consumption, and digestion rate) of the carbohydrates consumed are all important determinants of PPG levels, and low carbohydrate/low glycemic index diets can reduce PPHG, at least in the short-term.³⁵⁻³⁸ SMBG testing around meals or following exercise may be the best way to determine how certain foods or habits affect blood glucose levels.²⁶

Newer Pharmacotherapeutic Strategies to Lower FBG and PPG

Many oral agents successfully lower both FPG and PPG levels but may lose their effectiveness over time.³⁹ Thus, combinations of agents with complementary

mechanisms of action may provide better control of FPG and PPG levels.⁴⁰ These combinations include agents that specifically target PPHG (Table 3), including α -glucosidase inhibitors, short-acting insulinotropic agents, amylin analogues, glucagon-like peptide-1 (GLP-1) analogues, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and rapid-acting insulin analogues.

α -Glucosidase inhibitors such as acarbose and miglitol inhibit intestinal tract α -glucosidases and pancreatic α -amylase.³⁹ Although monotherapy with these agents reduces overall HbA_{1c} values less than do sulfonylureas or metformin, the former are useful when PPHG is the primary problem.³⁹ Short-acting insulinotropic agents, including repaglinide and nateglinide, dissociate faster from their receptors than do the sulfonylureas, mitigating the potential for delayed hypoglycemia although having a similar overall incidence of hypoglycemia.³⁹ Rapid-acting insulin analogues such as insulin lispro are absorbed quickly but have a shorter duration of action than that of regular human insulin.³⁹ When taken just prior to meals, they target PPHG. Pramlintide, an analogue of the glucoregulatory peptide amylin, which is deficient or suppressed in patients with diabetes, lowers postprandial glucose excursions and HbA_{1c} values.⁴¹ The GLP-1 analogue exenatide, which has a longer duration of action than that of naturally occurring GLP-1, reduces FPG and PPG values, decreases appetite, and delays gastric emptying.⁴² The DPP-IV inhibitor sitagliptin and vildagliptin delay the degradation of endogenous GLP-1, lower HbA_{1c} values, and help improve glycemic control.^{43,44}

SUMMARY

Traditionally, diabetes management has focused on HbA_{1c} for long-term glycemic control and FPG for day-

Table 3 : Classification and mode of action of antidiabetic agents with potential use in combination therapy ^{39,40,42-44}

Mode of Action	Class	Examples	Primary Target
Augment insulin concentration	Sulfonylureas	Glyburide	FPG
	Benzoic acid derivatives	Repaglinide	PPG
	Amino acid derivatives	Nateglinide	PPG
Increase insulin sensitivity	Biguanides	Metformin	FPG
	Thiazolidinediones	Rosiglitazone	FPG
Reduce intestinal breakdown of complex carbohydrates	α -Glucosidase inhibitors	Acarbose	PPG
Decrease gastric emptying rates; reduce postprandial glucagon secretion; promote hepatic glycogen storage	Amylin analogues	Pramlintide	PPG
Enhance glucose-dependent insulin secretion; increase glucose disposal, lipogenesis, and glycogen synthesis; decrease gastric motility and delay gastric emptying	GLP-1 analogues	Exenatide	PPG
	DPP-IV inhibitors	Vildagliptin	PPG
		Sitagliptin	PPG
Insulin-like actions	Rapid-acting insulin analogues	Insulin lispro	PPG

FPG, fasting plasma glucose; PPG, postprandial glucose; GLP-1, glucagon-like peptide-1; DPP-IV, dipeptidyl peptidase-IV.

Adapted with permission from Van Gaal LF, De Leeuw IH. *Diabetologia*. 2003;46(suppl 1):M44-M50.⁴⁰

to-day monitoring. PPHG is now increasingly recognized as an important risk factor for CVD in patients with diabetes or prediabetes. PPG concentrations may be elevated in patients who are seemingly well controlled with diet, exercise, and medical therapy, even those with normal FPG and HbA_{1c} values. SMBG may complement information provided by HbA_{1c} as it provides information on glucose excursions in response to daily events, meals, medications, exercise, and illness. To realize the full potential of SMBG, patients must be educated on how and when to monitor and what steps to take in response to high or low blood sugar levels. New and emerging medications specifically target PPHG in patients experiencing postprandial glycaemic excursions. The combination of improved detection and monitoring of PPHG and effective medications to address it may help establish optimal glycaemic control and reduce the microvascular and macrovascular complications of diabetes. There is a need for high-quality studies looking at the impact of reduction in PPHG on the incidence of CVD.

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Announcement

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