

Focus on Diabetes Management: Postprandial Glucose

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Diabetes is a worldwide health problem. Over 14 million people are currently diagnosed with type 2 diabetes, with another estimated 6.2 million undiagnosed.¹ The burden of diabetes and its complications on health care resources is increasing as the epidemic of diabetes spreads. Due to the severity of the complications, it is important to appropriately identify, educate, and treat individuals with diabetes.² This article will outline the evidence suggesting an association between postprandial hyperglycemia and cardiovascular risk and will summarize newer treatment options aimed at normalizing postprandial blood sugars.

Diabetes is relentlessly progressive. Increasingly aggressive treatment is often required as the disease progresses. Over time, treatment should reflect the progression of the disease state to optimally minimize and manage complications. Unfortunately, type 2 diabetes can often go undiagnosed until complications appear that reveal the disease. It is estimated that over one-third of persons with type 2 diabetes are undiagnosed. Intensive glucose control in patients with both type 1 and type 2 diabetes has been clearly shown by the DCCT³ and the UKPDS^{4,5} to reduce microvascular complications in diabetes, including retinopathy, neuropathy, and nephropathy.

It is well established that diabetes is an independent risk factor for macrovascular disease.² The DCCT and follow-up EDIC study showed that early intensive glucose control can prevent macrovascular disease.⁶ This problem is not insignificant, since it has been estimated that 65% of patients with diabetes die from cardiovascular events.¹ Additionally, it has been postulated that postprandial hyperglycemia in pre-diabetic individuals is linked to an increase in cardiovascular events.⁷ The question then becomes whether clinicians should be more proactive in monitoring and normalizing elevated postprandial blood glucose.

Table I outlines evidence favoring the routine monitoring and normalization of blood glucose in patients with postprandial hyperglycemia. The studies shown in Table I consist of three observational studies representing diverse geographical populations (Dutch, Polynesian, American),⁸⁻¹⁰ a meta-analysis,¹¹ and a prospective multicenter study of patients with diagnosed diabetes.¹² Overall, Table I suggests that elevated postprandial glucose independently increases cardiovascular risk among nondiabetic and diabetic populations. It is hoped that control of postprandial hyperglycemia will prove to reduce cardiovascular mortality in patients with 2-hour postprandial glucose >200mg/dL.

Currently there are several non-insulin options for the management of postprandial hyperglycemia. These newer options fall into three therapeutic drug classes: meglitinides, incretin mimetics, and dipeptidyl peptidase IV (DPP-4) inhibitors. The meglitinides (netaglinide [Starlix^R], repaglinide [Prandin^R]) are secretagogues that lower blood glucose levels by stimulating the release of insulin from the pancreas. The meglitinides have a similar mechanism of action as the sulfonylureas, but their quick onset of action and short half-life make them good options for postprandial glucose control. Repaglinide was compared to the sulfonylurea glyburide in previously untreated patients with type 2 diabetes.¹³ Both treatment groups had similar baseline postprandial glucose and

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Table I: Evidence Linking Postprandial Hyperglycemia to Cardiovascular Risk

Study	Population	Observation	Follow-up	Findings	
Observational Trials	Hoom Study ⁸ (de Vegt)	3,553 men & women (without diagnosed diabetes)	<ul style="list-style-type: none"> Fasting glucose 2-hour glucose after a 75g load 	8 years	<ul style="list-style-type: none"> High fasting glucose (>126mg/dL) did not correlate with increased risk of all-cause or cardiovascular mortality. After adjustments for age, sex, hypertension, waist-to-hip ratio, triglycerides, LDL cholesterol, and cigarette smoking, 2-hour post-load glucose >200mg/dL was associated with a 2-fold increase in relative risk for all-cause mortality [RR 2.03 (95% CI: 1.10 - 3.75)].
	Shaw ⁹	9,297 men & women (18% diabetic)	<ul style="list-style-type: none"> Fasting glucose 2-hour glucose after a 75g load 	5 years	<ul style="list-style-type: none"> High fasting glucose (>126mg/dL) did not correlate with increased risk of all-cause or cardiovascular mortality. Hazard ratios for all-cause & cardiovascular mortality in men & women were significantly increased in subjects with 2-h post-load glucose >200mg/dL [men: all-cause HR 2.7 (95% CI: 1.8 - 3.9), cardiovascular HR 2.3 (95% CI: 1.2 - 4.2); women: all-cause HR 2.0 (95% CI: 1.3 - 3.3), cardiovascular HR 2.6 (95% CI: 1.3 - 5.1)].
	Framingham Offspring Study ¹⁰ (Meigs)	3,370 men & women without diabetes	<ul style="list-style-type: none"> Fasting glucose 2-hour glucose after a 75g load HbA1c 	4 years	<ul style="list-style-type: none"> When compared to elevated fasting glucose or elevated HbA1c, relative risk for cardiovascular events increased 26% for each 37.8mg/dL increase in 2-hour post load glucose >200mg/dL (RR 1.26 [95% CI: 1.17 - 1.34]).
Meta-Analysis	DECODE ¹¹	22,514 men & women, (majority without prior diabetes history)	<ul style="list-style-type: none"> Fasting glucose 2-hour glucose after a 75g load 	8.8 years (median)	<ul style="list-style-type: none"> Impaired fasting glucose (110 - 124mg/dL) did not correlate with increased risk of all-cause mortality or cardiovascular disease. 2-hour post-load glucose >200mg/dL was associated with increased risk of all-cause and cardiovascular mortality [all-cause HR 1.37 (95% CI: 1.25 - 1.51); cardiovascular mortality HR 1.32 (95% CI: 1.12 - 1.56)].
Prospective Study	Diabetes Intervention Trial ¹² (Hanefeld)	1,139 men and women with newly diagnosed diabetes	<ul style="list-style-type: none"> Fasting glucose 1-hour postprandial glucose 	11 years	<ul style="list-style-type: none"> High fasting glucose (>126mg/dL) did not correlate with increased risk of coronary heart disease or all-cause mortality. Statistically significant higher incidence of all-cause mortality and MI with 1-h postprandial glucose >180mg/dL. At 1-h postprandial blood glucose <144mg/dL and >180mg/dL absolute risk for MI and all-cause mortality increased 9% and 9.5%, respectively.

A fasting plasma glucose of >126mg/dL, symptoms of diabetes and a random plasma glucose >200mg/dL, or a 2-h plasma glucose >200mg/dL during an oral glucose tolerance test (OGTT) is diagnostic of diabetes.

Currently, the ADA recommends treatment of postprandial hyperglycemia (2-h plasma glucose >180mg/dL).

HbA1c values. The meglitinide resulted in a greater reduction of postprandial blood glucose (70mg/dL vs. 51mg/dL, respectively; $p < 0.001$). In addition, 52% of the patients in the repaglinide group showed a statistically significant reduction in carotid intima-media thickening (IMT) (>0.02mm) compared to 18% of the glyburide group patients. Since the mean HbA1c lowering was not different between the two groups, this suggests that elevated postprandial blood glucose may contribute to carotid IMT, a surrogate marker for cardiovascular complications. These results suggest that the sulfonylureas are less suitable agents for reducing the cardiovascular complications of diabetes.

In 2005, exenatide (Byetta[®]), the first incretin mimetic entered the market. Exenatide is the first analog of glucagon-like peptide-1 (GLP-1), which is one of the endogenous incretin hormones. Incretin hormones are released from the gastrointestinal tract when food is ingested and work to lower postprandial glucose by several mechanisms. Persons with type 2 diabetes have a decreased level of GLP-1.¹⁴ GLP-1 increases secretion of insulin when the body detects rising glucose levels, decreases inappropriate postprandial glucagon release, and slows gastric emptying, potentially increasing prandial satiety and thereby suppressing food intake. It has also been shown that GLP-1 may preserve pancreatic beta-cells in animal models by proliferation and inhibition of apoptosis.¹⁴ Exenatide, an injectable agent, has been previously reviewed in *Drug Therapy Topics* (see http://depts.washington.edu/druginfo/DTT/2005_Vol34_Files/V34N11.pdf).

Due to their pharmacokinetics and pharmacodynamics, sulfonylureas are not optimal for postprandial glucose lowering.

Evolving knowledge of diabetes has resulted in the emergence of new medications that target physiologic insulin release and resemble other hormones or proteins in the body.

Endogenous GLP-1 has a half-life <2 minutes. Sitagliptin inhibits DPP-4 enzyme activity resulting in a 2–3 fold increase in circulating levels of GLP-1.

The half-life of sitagliptin is ~12h in patients with normal renal function.

While the body of literature is limited, to date sitagliptin appears to be a “weight neutral” drug.

With evidence to show there is an association between postprandial hyperglycemia and cardiovascular risk, a reduction in the complications of diabetes may be attained through heightened awareness and postprandial glycemic control.

The most recent development to reduce postprandial hyperglycemia is the use of dipeptidyl peptidase IV (DPP-4) inhibitors. DPP-4 is the enzyme that breaks down endogenous GLP-1. DPP-4 inhibition, therefore, enhances the action of native GLP-1. The first drug in the DPP-4 inhibitor class to receive FDA approval is sitagliptin (Januvia[®]) which was licensed in October 2006. Other drugs in development in this class are vildagliptin (Galvus[®]) and saxagliptin (tradename has yet to be determined).

Sitagliptin is indicated for patients with type 2 diabetes as adjunctive therapy with thiazolidinediones (e.g., pioglitazone) or metformin or as monotherapy with diet and exercise to improve glycemic control. It is available in 25mg, 50mg, and 100mg tablets. In patients with normal renal function, sitagliptin is administered orally at a dose of 100mg once daily. The dose must be reduced in patients with renal dysfunction. While drug interaction studies with prototype drugs (warfarin, oral contraceptives, cyclosporine, etc.) have not revealed clinically significant drug interactions, it is important for prescribers to be aware of the following characteristics of sitagliptin:

- Approximately 79% of sitagliptin is excreted unchanged in the urine by a process that involves active tubular secretion.
- Sitagliptin is a substrate for human organic anion transporter-3 and p-glycoprotein.
- Metabolism by CYP3A4 and CYP2C8 is a minor pathway of elimination for sitagliptin; however, it is neither an inhibitor or inducer of these isozymes.

FDA approval of sitagliptin was based on data from 2316 patients with type 2 diabetes randomized in four double-blind, placebo-controlled clinical safety and efficacy studies. Two were monotherapy studies and two were studies of sitagliptin combined with either metformin or pioglitazone. One of these, a double-blind, placebo-controlled study of patients with type 2 diabetes and average baseline HbA1c of 8.1%, measured overall glycemic control and change in 2-hour postprandial glucose.¹⁵ Patients were randomized to placebo or sitagliptin at a dose of 100mg or 200mg daily for 18 weeks. Patients were given metformin if they failed to reach glycemic goals: fasting glucose <270mg/dL at week 6, <240mg/dL at week 12, and <200mg/dL at week 18. All patients went through a 7-week washout period prior to randomization. Statistically significant but modest glycemic control was achieved with the 100mg regimen as demonstrated by change in HbA1c (-0.48% [95% CI: -0.61 to -0.35] vs. +0.12% [95% CI: -0.05 to 0.30] for placebo). In addition, at both doses of sitagliptin, there was a statistically significant decrease in 2-hour postprandial glucose levels relative to placebo at study end (mean -41.4mg/dL, -48.6mg/dL, and +5.4mg/dL in the 100mg, 200mg, and placebo groups, respectively). While this is statistically significant, it is also clinically meaningful, as a drop of this magnitude could reduce postprandial hyperglycemia to a normal postprandial glucose level.

Historically, fasting blood glucose has been the most commonly used measure to diagnose and manage diabetes. As evidence of an association between cardiovascular risk and postprandial hyperglycemia evolves, it may become more valuable to look at and treat, postprandial blood sugars earlier in the course of the disease. Unfortunately, at the point in the disease when patients might benefit most from treatments targeting postprandial hyperglycemia, many remain undiagnosed. A more proactive approach to identifying postprandial hyperglycemia and aggressive management with newer antidiabetic agents may prove to reduce cardiovascular mortality in the future.

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(References listed on page 54)

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Darunavir (Prezista)	Tablet: 300mg	Protease inhibitor	HIV infection	600mg po with ritonavir BID
Human papillomavirus vaccine (Gardasil)	Injection: 20µg HPV 6 & 18 L1 protein + 40µg HPV 11 & 16 L1 protein/0.5mL	Vaccine	Immunization against diseases caused by HPV types 6, 11, 16, and 18	Series consists of 0.5mL IM x 3 doses
Mycophenolate sodium (Myfortic)	Tablet, delayed-release: 180mg,360mg	Immunosuppressive	Prophylaxis against rejection	720mg po BID
	Myfortic was added to formulary on the basis of the results of a competitive bid against the therapeutically equivalent mycophenolate mofetil (Cellcept).			
Rotavirus vaccine (RotaTeq)	Oral liquid: containing rotavirus outer capsid protein G1, G2, G3, G4, and attachment protein P1A	Vaccine, Live	Prevention of rotavirus gastroenteritis in infants and children	Series consists of 3 2mL po doses
Other Actions				
Dexmedetomidine (Precedex)	Formulary restriction extended to include use by the OR and Anesthesiology services.			

* Refer to product labeling for full prescribing information. ‡ Contact pharmacy for information on drug costs.

Focus on Diabetes Management: Postprandial Glucose (continued)

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