Postprandial Glucose is Important in Attaining Total Glycemic Control

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BY STEVEN V. EDELMAN, MD

STATEMENT OF NEED

In the last 2 decades, type 2 diabetes has been reported among US children and adolescents with increasing frequency. If we do not aggressively treat their blood sugars, they will end up with severe microvascular complications. According to the Centers for Disease Control and Prevention, children and adolescents diagnosed with type 2 diabetes are generally obese, between 10 and 19 years old and have a strong family history for type 2 diabetes and have insulin resistance. Generally, children and adolescents with type 2 diabetes have poor glycemic control (HbA1c between 10% and 12%).

Those affected with type 2 diabetes belong to all ethnic groups, however the condition is more commonly seen in nonwhites. American Indian youths have the highest prevalence; with the current number for the 15- to 19-year-old age group being 50.9 per 1,000 Pima Indians in Arizona; 4.5 per 1,000 US American Indian populations.

TARGET AUDIENCE

This activity is designed for primary care physicians, endocrinologists and other clinicians who treat patients with and at risk for type 2 diabetes.

LEARNING OBJECTIVES

After successful completion of this program, the participant should be able to:
• discuss the physiology and natural history of postprandial hyperglycemia;
• cite observational data linking postprandial hyperglycemia and cardiovascular disease;
• review interventions targeting postprandial hyperglycemia;
• discuss the current guidelines for postprandial hyperglycemia; and
• review the role of postprandial hyperglycemia and the prevention of type 2 diabetes.

METHOD OF INSTRUCTION

Participants should read the learning objectives and CME program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions.

Participants have a choice of completing this activity online, either by visiting www.DiabeticMCToday.com or www.CMEToday.net to get real-time results, or by using the print forms following this activity. Mail the print form to The Dulaney Foundation, P.O. Box 44408, Phoenix, AZ 85064, or fax to 602-508-4893.

Upon completing this activity as designed and achieving a passing score of 70% or higher on the self-assessment test, participants will receive a CME credit letter awarding AMA/PRA category 1 credit after the registration and evaluation materials are received.

The estimated time to complete this activity as designed is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with the essentials and standards of the ACCME through the joint sponsorship of The Dulaney Foundation and *Diabetic Microvascular Complications Today.*

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services, that relate to the content of their presentation/material or the commercial contributors of this activity; and 2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE DECLARATIONS

Steven V. Edelman, MD, is engaged in research activities for Novo Nordisk, Amylin and Pfizer. He is a consultant for and a member of the speakers bureau for Eli Lilly and Company, Amylin, Novo Nordisk and Pfizer.

FACULTY CREDENTIALS

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INTRODUCTION

In a normal nondiabetic patient, you rarely see a blood sugar >140 mg/dL 1 to 2 hours after eating. I like to say that whether you believe in God or in Charles Darwin, it is not normal for diabetic patients to get >300 mg/dL 50% of the time. The loss of early insulin release is an important factor leading to postprandial hyperglycemia and type 2 diabetes. These patients experience a delayed and blunted release of insulin as well as an elevated fasting and postprandial glucose level.

In healthy patients, there is a postprandial suppression of glucagon and a reduction in hepatic glucose production. In type 2 diabetes patients we see no suppression of postprandial glucagon, which is very inappropriate, and endogenous glucose production stays much higher than in the nondiabetic state of postprandial.
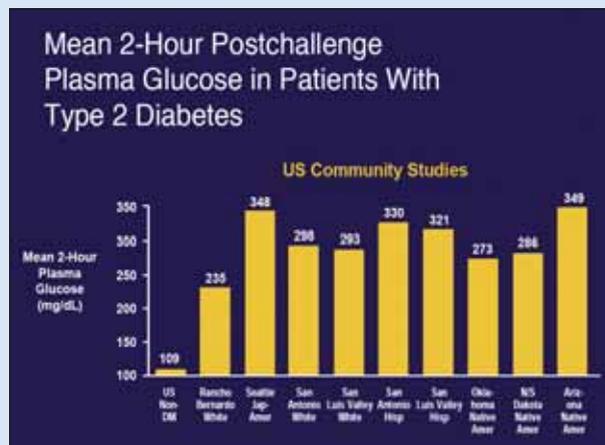

Figure 1. Mean 2-hour postchallenge plasma glucose in patients with type 2 diabetes.

LOSS OF FIRST-PHASE RELEASE

Patients with fasting blood sugar numbers that are not too high can show a loss of first-phase insulin release. So it is important not to be lulled into a false sense of security by the fasting blood sugar numbers.

In nine very well done studies from around the United States it was shown that in different ethnic populations the typical 2-hour blood sugar that is seen in type 2 patients is commonly in the upper 200- to 300-mg/dL range (Figure 1).

It is important to note that these patients are not just getting high blood sugars for a short period of time after each meal. People with type 2 diabetes most likely spend most of their waking hours in the postprandial state, not in the fasting state. So it's not just a quick rise and then back down to baseline. There is a lot of area under the curve, leading to glucose toxicity and hyperglycemia.

NATURAL HISTORY OF TYPE 2 DIABETES

Insulin resistance may begin to set in 10 or 15 years before a patient is actually diagnosed with type 2 diabetes. Endogenous hyperinsulinemia suppresses hepatic glucose production, with low fasting and postprandial blood sugars in these patients. The dangerous thing in the prediabetic state is that patients are asymptomatic, but associated macrovascular disease is a factor.

When the beta cells begin to fail, then the blood sugars rise and patients deteriorate more rapidly. The microvascular complications begin and hepatic glucose goes unchecked.

The Kuusisto study[1] was the first study to show the relationship between glycemic control and cardiovascular disease (CVD). While it was just an association study, the data in the literature has remained very consistent (Figure 2).
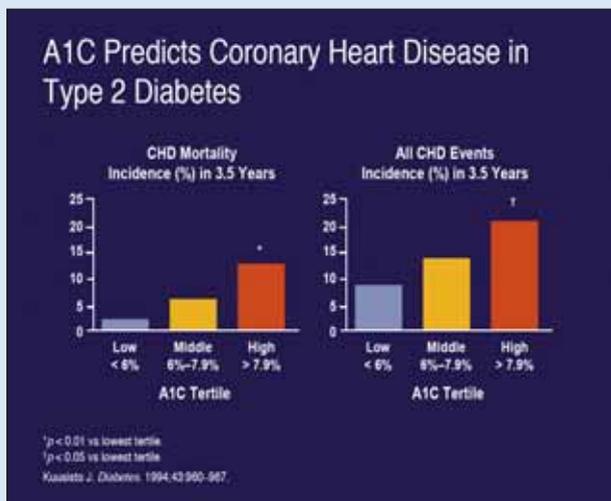
Figure 2. HbA1c predicts coronary heart disease in type 2 diabetes.

Figure 3. Hazard ratios (95% CI) for death according to fasting glucose.

The Honolulu Heart Program[2] looked at the incidence of heart disease based on 2-hour blood sugar. It found that the higher the post-challenge glucose the higher the incidence of coronary artery disease. The same results were seen in the Chicago Heart Association Detection Project in 1997,[3] even when multivariate analysis was performed and other cardiovascular risk factors were accounted for.

One of the best studies to show this correlation is the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study (Figure 3).[4] This study looked at the incidence of heart disease based on fasting blood sugar versus 2-hour blood sugar.

The major conclusions of DECODE were that fasting glucose concentration was not independently related to mortality after adjustment for the 2-hour concentration, and the 2-hour glucose concentration was independently related to mortality after adjustment for the fasting glucose level.

It is important to note that HbA1c is just an average. When caregivers see an HbA1c go down into the normal range, they assume there is good control. Many type 1 patients have a very good HbA1c but fluctuate quite erratically from >300 mg/dL to <40 mg/dL on a daily basis.

MEDICATIONS

Medications that target postprandial hyperglycemia do not traditionally lower the HbA1c as much as the drugs that target fasting glucose levels. The original FDA indication for lispro was for convenience because patients did not have to take it 30 minutes before a meal. Once further studies were done, p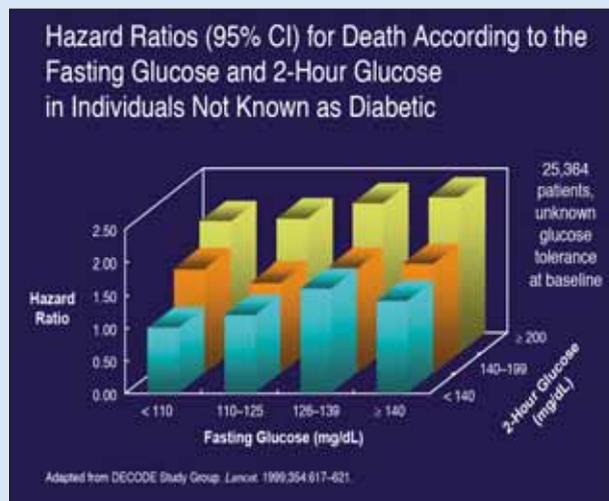hysicians learned how to use the fast-acting analog correctly in order to reduce glucose values as well as hypoglycemia. The alpha-glucosidase inhibitors acarbose and miglitol are not used very much in the United States because they do not lower HbA1c greatly. The fast-acting nonsulfonylurea insulin analogs repaglinide and nateglinide, target postprandial glucose more than fasting. They do not lower HbA1c as much as sulfonylureas. The not-yet-approved pramlinitide is also criticized because it is a postprandial hormone coming from the beta cell.

Because sulfonylurea does not target postprandial hyperglycemia, you might get postprandial hyperglycemia and delayed hypoglycemia. A drug that targets postprandial glucose reduces that with less of or no chance of delayed hypoglycemia. If you wipe out the hypoglycemia, you will blunt the fall in glycohemoglobin (GHb). Drugs that target the postprandial blood sugar do not lower the HbA1c as much as drugs that focus on fasting blood sugar.

In a study by Bastyr et al,[5] a cohort of type 2 diabetic patients were randomized to three groups. They were given a combination regimen with glyburide that addressed postprandial blood glucose with insulin lispro, premeal blood glucose with metformin, or fasting blood glucose with bedtime NPH insulin. Researchers found that adding a second antihyperglycemic agent, regardless of its timing of action, lowered HbA1c and glucose values. However, when insulin lispro was used to focus on postprandial blood glucose, there was a greater impact on overall metabolic control. The authors reported in *Diabetes Care* that these data support the importance of lowering postprandial blood glucose to optimize overall glycemic control and thus improve long-term outcomes.

Several companies are working toward advances in inhaled insulin. In one study of patients who were doing poorly on their oral agents, within 12 weeks patients experienced a drop in glycosylated hemoglobin by >2%.

TARGET LEVELS

What should the target goal be? According to the National Health and Nutrition Examination Survey (NHANES) data, the prevalence of retinopathy does not start to go up until fasting blood sugar gets to about 109 mg/dL and a 2-hour value of 165 mg/dL and HbA1c of 5.9% (Figure 4). I think we should be normalizing the HbA1c by limiting hypoglycemia and excessive weight gain.
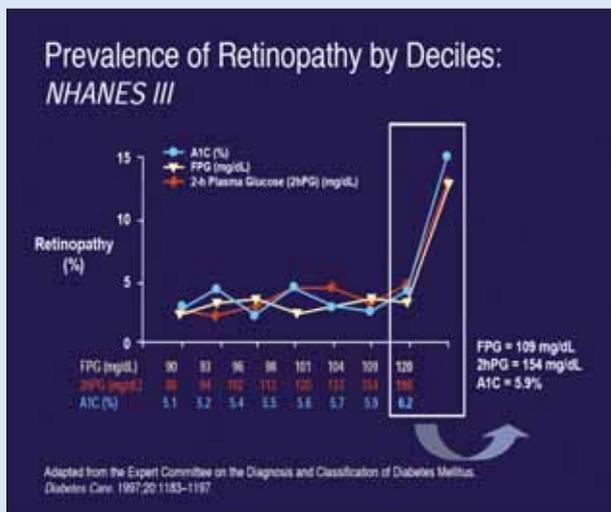
The Diabetes Control and Complications Trial (DCCT)[6] found that, even at the same HbA1c level, insulin therapy provided greater risk reduction for the development of retinopathy. While the reason for this is not completely known, it has been hypothesized that patients having this intensive control had multiple pump injections (as compared to the conventional therapy group) and therefore fewer fluctuations in their daily blood sugar. This may have played a role in the development of microvascular complications.

The Kumamoto study was performed in insulin requiring type 2 diabetes patients using the same protocol as DCCT. Those investigators looked at the rate of microvascular complications as the postprandial glucose went
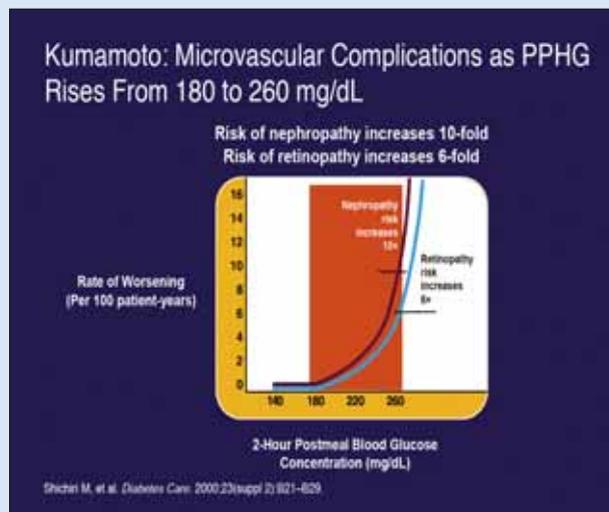

Figure 4. Prevalence of retinopathy by deciles.

Figure 5. Kumamoto: Microvascular complications as postprandial glucose rises from 180 mg/dL to 260 mg/dL.
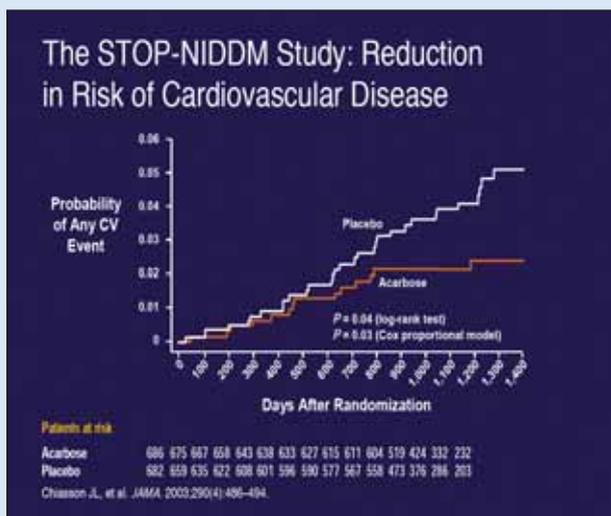

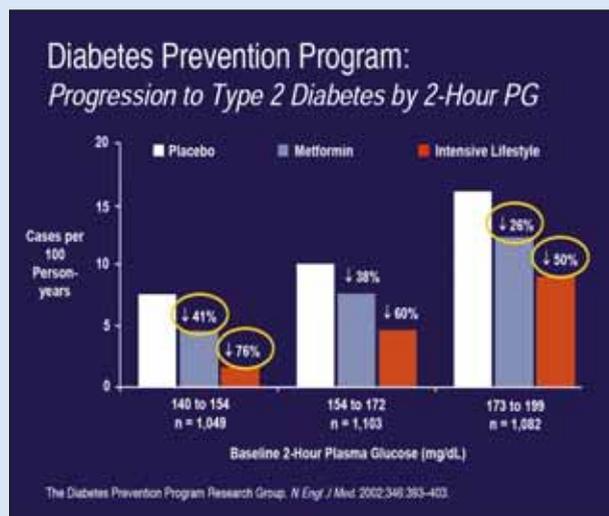Figure 6. STOP-NIDDM: Reduction in the risk of CVD

Figure 7. Progression to Type 2 diabetes in DPP.

from 180 mg/dL to 260 mg/dL (Figure 5). The risk of nephropathy increased tenfold as the postprandial went up and the risk of retinopathy went up sixfold.

What is the contribution to the HbA1c, fasting or postprandial? Postprandial may be a better indicator of HbA1c in type 2 diabetes. The closer the HbA1c gets to normal, the higher the percent contribution to that HbA1c is from the postprandial glucose. When you use combination therapy in type 2 diabetes, you can get the HbA1c down but it's difficult to normalize postprandially in certain patients.

According to the American Diabetes Association, HbA1c should be normalized to <6% and the peak value for postprandial glucose should be <180 mg/dL. The American College of Endocrinology has termed the 2-hour value <140 mg/dL because that's what it should be in normal individuals.

PREVENTION OF DIABETES

The Study to Prevent Noninsulin Dependent Diabetes (STOP-NIDDM) looked at the use of acarbose 100 mg/three times a day in patients with prediabetes. In 3.5 years, there was a reduction in the conversion from pre-diabetes to type 2 diabetes by 25%. That's almost as effective as metformin in the Diabetes Prevention Program (DPP). The drug also prevented CVD (Figure 6).

Patients in the DPP with impaired fasting glucose were randomized to either metformin, intensive lifestyle intervention or placebo. Patients in the metformin group had a 31% reduction in the conversion to diabetes in about 3.5 years, intensive lifestyle patients had a 58% reduction. Metformin also seems to work only in younger, heavier patients where intensive lifestyle modification worked in all age groups, no matter their weight. While metformin is an excellent drug, it is not really a prevention drug.

A subanalysis of patients in DPP looked at how effective each therapy was based on patients' 2-hour glucose test a randomization (Figure 7).

LESSONS FROM GESTATIONAL DIABETES

Gestational diabetes is a great way to study diabetes, because you have outcomes data for 9 months. Pre-DCCT era, physicians knew that tight glycemic control reduced perinatal morbidity and mortality. The gold standard now is to focus therapy on the postprandial glucose value.

A rather famous study was published in *The New England Journal of Medicine* in 1995 where the investigators monitored patients with gestational diabetes. They adjusted their insulin based on either fasting blood sugar or only postprandial glucose. For the fasting group, they
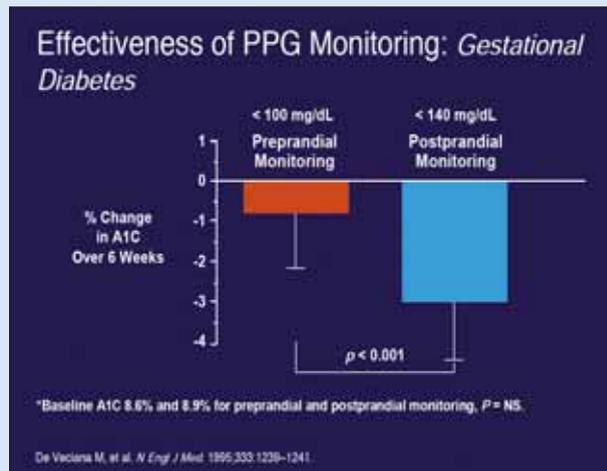

Figure 8. Effectiveness of postprandial monitoring in gestational diabetes.

tried to keep levels <100 mg/dL; they adjusted insulin to maintain those levels. They kept postprandial glucose <140 mg/dL and they did not even measure premeal glucose. They used more insulin to achieve that goal but the difference in HbA1c was 3% versus 1% (Figure 8).

The outcome data showed that 42 patients were large for gestational age versus 12; 36 C-sections versus 12 and 21 neonatal hypoglycemics versus seven.

A normal individual rarely gets >140 mg/dL – if you have diabetes it is not physiologically impossible to get >300 mg/dL three times a day for 3 hours after each meal. When we treat patients with diabetes, we have to do much more than treat the fasting blood sugar. We have to treat the postprandial. Postprandial hyperglycemia is pathologic, postprandial glucose levels positively correlate with CVD and microvascular disease. All major diabetes organizations have guidelines for postprandial glucose, it is not a matter of debate anymore.

Early intervention to reduce the postprandial glucose may prevent or delay the onset of type 2 diabetes. Pregnancy is the best model, and we should learn from it. ■

1. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes.* 1994;43:960-967.
2. Donahue RP, Abbott RD, Reed DM, Yano K. Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu Heart Program. *Diabetes.* 1987;36:689-692.
3. Lowe LP, Liu K, Greenland P, et al. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. The Chicago Heart Association Detection Project in Industry Study. *Diabetes Care*. 1997;20:163-169.
4. The DECODE study group. Glucose tolerance and mortality: comparison of WHO and American Diabetic Association diagnostic criteria. *Lancet.* 1999;354:617-621.
5. Bastyr EJ, Stuart CA, Brodows RG, et al. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. IOEZ Study Group. *Diabetes Care.* 2000;23:1236-1241.
6. The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N Engl J Med* 1993;329:977-86.

CME QUESTIONS

Circle the most appropriate answer in the "ANSWER SECTION" on the following page.

1. Which statement is untrue? Type 2 diabetes:
a. Is increasing in children and adolescents.
b. Can result in microvascular complications if not treated.
c. Is uncommon in American Indians.
d. Corresponds with poor glycemic control in children.

2. Which statement is true? Postprandially, healthy patients:
a. have a suppression of glucagon and a reduction of hepatic glucose production.
b. no suppression of glucagon.
c. delayed blunted release of insulin.
d. endogenous glucose production stays high.

3. Which study was the first to show the relationship between glycemic control and CVD?
a. Kuusisto
b. The Honolulu Heart Study
c. DECODE
d. DCCT

4. Which of the following statements is untrue regarding the DECODE study?
a. This study looked at the incidence of heart disease based on fasting blood sugar versus 2-hour blood sugar.
b. A major conclusion of DECODE was that fasting glucose concentration was not independently related to mortality after adjustment for the 2-hour concentration.
c. The 2-hour glucose concentration was independently related to mortality after adjustment for the fasting glucose level.
d. The 2-hour glucose concentration was had no relationship to mortality after adjustment for the fasting glucose level.

5. Which statement is untrue?
a. Acarbose is an alpha-glucosidase inhibitors.
b. Nateglinide is a fast-acting non-sulfonylurea insulin analogs.
c. Sulfonylureas target postprandial hyperglycemia.
d. Lispro does not have to be given 30 minutes before a meal.

6. What is the ADA goal target for HbA1c and postprandial glucose?
a. <6% and <180 mg/dL
b. <7% and a 2-hour value of <140 mg/dL
c. <6% and a 2-hour value of <140 mg/dL
d. <7% and <180 mg/dL

7. In STOP-NIDDM, patients assigned acarbose were less likely to develop type 2 diabetes.
a. true
b. false

8. Which statement is untrue regarding the DPP?
a. Patients in the trial had impaired fasting glucose.
b. The drug studied was metformin.
c. Metformin worked equally well in younger, heavier patients as it did in older, lighter patients.
d. Intensive lifestyle modification worked in all age groups, no matter their weight.

9. Gestational diabetes is an excellent model for studying diabetes in general.
a. true
b. false

10. Early intervention to reduce the postprandial glucose may prevent or delay the onset of type 2 diabetes.
a. true
b. false

REGISTRATION/EVALUATION FORM: TOTAL GLYCEMIC CONTROL

To obtain AMA/PRA category 1 credit, you must:
• Read the learning objectives and the CME article and complete the self-assessment test.
• Photocopy and complete this registration/evaluation form and record your test answers in the Answer Section below.
• Send the Registration/Evaluation form to **The Dulaney Foundation, P.O. Box 44408, Phoenix, AZ 85064, or fax to 602-508-4893.**
• Retain a copy of your test answers. Your answer sheet will be graded, and if you achieve a passing score of 70% or better, you will receive a CME credit letter awarding AMA/PRA category 1 credit within 4 weeks. If you do not achieve a passing score, you will be notified and offered the opportunity to complete the activity again.

ANSWER SECTION

Circle the best answer for each question on page 44.

1. A B C D	2. A B C D	3. A B C D	4. A B C D	5. A B C D
6. A B C D	7. A B	8. A B C D	9. A B	10. A B

REGISTRATION FORM

First name _____ Last name _____ Degree (MD, PhD) _____

Specialty _____

Institution or practice name _____

Address _____

City _____ State _____ Zip Code _____ Country _____

Telephone _____ Fax _____ E-mail address _____

The processing fee has been underwritten by an unrestricted educational grant from Eli Lilly and Company.

I attest that I have completed this activity as designed and I am claiming _____ (up to 1 credit) AMA/PRA category 1 credit.

Signature _____ Date _____

Credit for this activity is available until May 31, 2006.

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. Please assist us in evaluating the effectiveness of this activity and make recommendations for future educational offerings by completing this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters and long-term credit retention information will only be issued upon receipt of this completed evaluation. Thank you for your cooperation.

OBJECTIVES

After successful completion of this program, you should be able to:

• discuss the physiology and natural history of postprandil hyperglycemia.	5	4	3	2	1
• cite observational data linking postprandial hyperglycemia and cardiovascular disease.	5	4	3	2	1
• review interventions targeting postprandial hyperglycemia.	5	4	3	2	1
• discuss the current guidelines for postprandial hyperglycemia.	5	4	3	2	1
• review the role of postprandial hyperglycemia and the prevention of type 2 diabetes.	5	4	3	2	1

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

OVERALL EVALUATION

• The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
• The information presented will influence how I practice.	5	4	3	2	1
• The information presented will help me improve patient care.	5	4	3	2	1
• The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
• The program was educationally sound and scientifically balanced.	5	4	3	2	1
• The program avoided commercial bias or influence.	5	4	3	2	1
• Overall, the program met my expectations.	5	4	3	2	1
• I would recommend this program to my colleagues.	5	4	3	2	1

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

• If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so: _____

• Please provide any additional comments pertaining to this activity (positive and negative) and suggestions for improvements: _____
_____

• Please list any topics you would like to see addressed in future educational activities: _____
_____