

Understanding the Relationship Between Hyperglycemia and Microvascular Complications

Jointly sponsored by The Dulaney Foundation and *RETINA TODAY*

Release Date: August 2006. Expiration Date: August 31, 2007.

This continuing medical education activity is supported by an educational grant from Eli Lilly and Company.

BY BERNARD ZINMAN, MD

STATEMENT OF NEED

The epidemic of diabetes in the United States affects 7% of the population, most of these have type 2 diabetes. Currently, 20.8 million Americans have diabetes and 6.2 million more have unrecognized diabetes. Diabetic retinopathy is the most frequent late complication of type 1 diabetes. In fact, 100% of all patients with type 1 diabetes will develop diabetic retinopathy together with 60% of patients who have type 2 diabetes. Every incremental decrease in HbA1c significantly reduces the risk of microvascular complications.

TARGET AUDIENCE

This activity is designed for ophthalmologists, retinal specialists and other practitioners who treat patients with diabetic microvascular complications.

LEARNING OBJECTIVES

Upon successful completion of this learning program, the participant should be able to:

- Identify the major study questions from the DCCT trial.
- Discuss the findings from the DCCT and the EDIC trials.
- Describe what is meant by metabolic memory.
- Discuss the potential mechanisms by which hyperglycemia causes tissue damage.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (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 by visiting www.DiabeticMCToday.com; getting real-time results at www.CMEToday.net; or by using the print forms following this activity.

Upon completing the activity and achieving a passing score of $\geq 70\%$ on the self-assessment test, participants will receive a CME credit letter awarding *AMA/PRA Category 1 Credit™* 4 weeks after the registration and

evaluation materials are received. The estimated time to complete this activity is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and RETINA TODAY.

The Dulaney Foundation designates this educational activity for a maximum of 1 AMA/PRA Category 1 Credit.[™] Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

Dr. Zinman discloses receiving grants/research support from Eli Lilly and Company, Novartis, GlaxoSmithKline (GSK) and Novo Nordisk. He discloses that he is a consultant for Amylin, Lilly, GSK, Merck, Novartis, Pfizer and Sanofi-Aventis.

FACULTY CREDENTIALS

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INTRODUCTION

It is crucial that we as diabetologists and endocrinologists who are on the front lines treating patients at high risk for the microvascular complications of diabetes have a close, and functioning relationship with our ophthalmologist colleagues.¹

It is now clearly established that hyperglycemia is the initiating event responsible for the endothelial/metabolic dysfunction that leads to the development of neuropathy, retinopathy and nephropathy, as well as other vascular complications. Several glucose-mediated metabolic pathways have been postulated to be responsible for the intracellular events resulting in tissue damage.

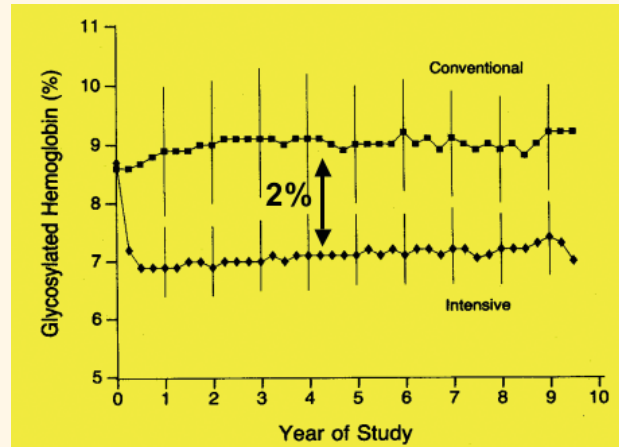


Figure 1. Metabolic results from the DCCT trial.

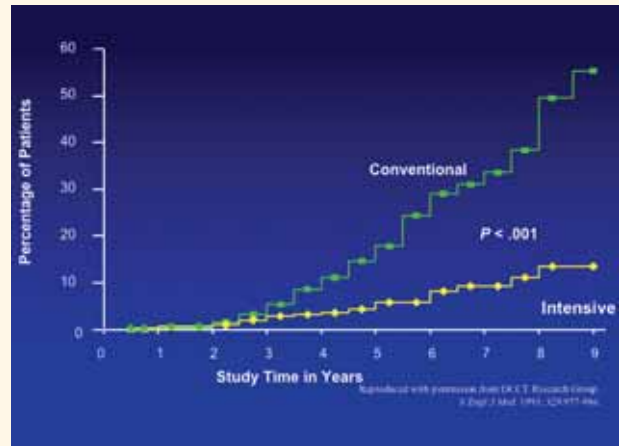


Figure 2. Cumulative incidence of retinopathy three-step progression in primary prevention cohort of DCCT.

A REVIEW OF THE DCCT TRIAL

Testing the glucose hypothesis in the context of diabetic complications has been a major focus of research. Many studies have shown the association between hyperglycemia and retinopathy. In the Diabetes Control and Complications Trial (DCCT), however, we determined prospectively if intensive diabetes treatment with the goal of near-normal glucose control would prevent or delay long-term complications of diabetes.

The major questions in the DCCT were:²

- Primary prevention — Will intensive therapy prevent the development of neuropathy, retinopathy and nephropathy in those with no complications?
- Secondary intervention — Will intensive therapy affect the progression of complications in those who already have problems?

The DCCT showed conclusively that a 2% reduction in HbA1c in the intensive control patients³ (Figure 1) resulted in a dramatic reduction in the rate of the development of

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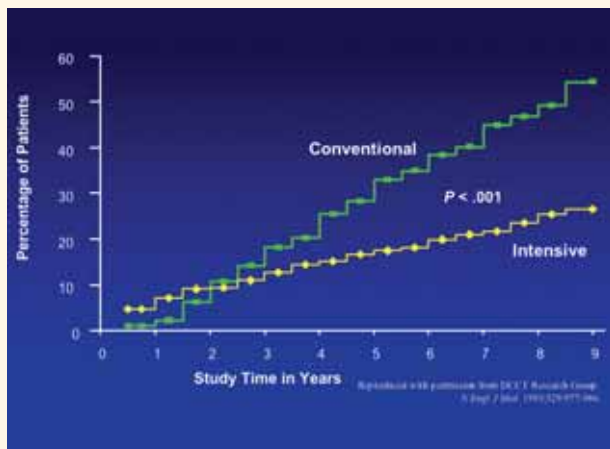


Figure 3. Cumulative incidence of retinopathy three-step progression in secondary intervention cohort in DCCT.

retinopathy when compared with conventional treatment (Figure 2).³ At the 3-year point, there was a very rapid separation between the rate of the development of retinal complications among the intensively treated group when compared with conventional therapy.

An often-overlooked fact is that when you implement intensive therapy there may be a period where you have some worsening of retinopathy. We saw this in the secondary intervention cohort in the DCCT trial,³ and this same phenomenon has been shown in other older studies as well. Introducing intensive glucose control can transiently result in some worsening of retinopathy. Over time, however, there is a dramatic improvement in outcome with intensive therapy (Figure 3).

EDIC FOLLOW-UP TO DCCT

The long-term follow-up of the DCCT study is called the Epidemiology of Diabetes Interventions and Complications trial (EDIC). When the DCCT results were known and announced to our patients, the patients were informed that intensive therapy clearly had major advantages with respect to nerve, eye and kidney complications, and all participants should initiate intensive therapy. The conventionally treated study participants were now given intensive diabetes management training, and were put on insulin pumps or multiple daily injections. These participants improved their HbA1c and were returned to their usual clinical care. As part of the EDIC protocol the investigators followed these patients on an annual basis. Given that the original intensively treated patients were now seen less frequently, their HbA1c rose to approximately 8% and was similar in both groups.^{3,4}

The DCCT/EDIC study provides us with the opportunity to determine the long-term impact of intensive therapy on both microvascular and macrovascular complications.

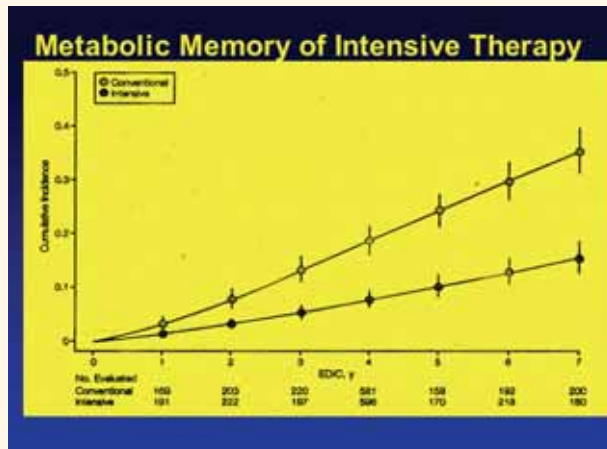


Figure 4. Metabolic memory of intensive therapy, cumulative incidence of three-step change from DCCT end of study, adjusted for EDIC baseline retinopathy.

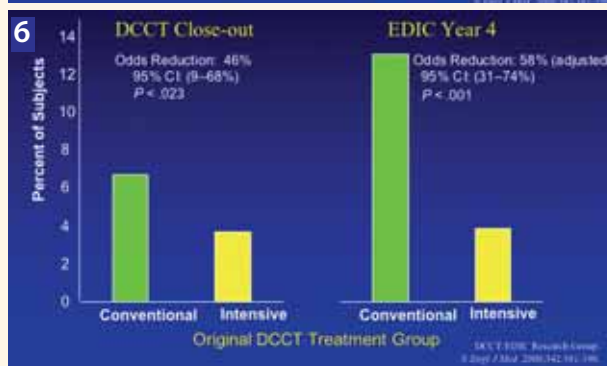
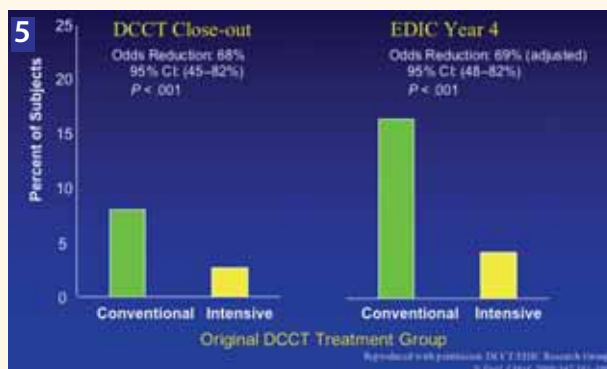


Figure 5 and 6. The prevalence of proliferative or severe non-proliferative diabetic retinopathy (5) and clinically significant macular edema (6) were also reduced.

Specifically, we can determine what will be the impact of 6.5 years of improved glycemic control on the subsequent development of complications.

METABOLIC MEMORY

The EDIC outcome data demonstrate that despite similar

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levels of control, the original intensive therapy group continued to have reduced rates of complication development. We called this phenomenon *metabolic memory* (Figure 4).⁵

This result applied to the outcomes of proliferative diabetic retinopathy as well as severe nonproliferative diabetic retinopathy (Figure 5) and clinically significant macular edema (Figure 6).⁴

Metabolic memory and diabetic complications appear to be an important phenomenon that applies generally to the complications of diabetes. Indeed, in late 2005 we described the same phenomenon in relationship to macrovascular disease.⁶ We documented a 58% reduction in clinically significant macrovascular disease outcomes in those individuals who were on originally intensive therapy.

The clinical message for patients with type 1 diabetes is that early intervention with intensive therapy should be the standard of care for preventing the long-term complications of diabetes. If intensive therapy is delayed, the momentum of complications is more difficult to slow.

Unfortunately, given our current tools for implementing intensive therapy, optimal glycemic control cannot be obtained in many patients with diabetes. In addition, the risk of increasing severe hypoglycemia remains as a significant barrier to intensifying diabetes control. In this context, there is a need for alternative therapies to reduce the impact of hyperglycemia on micro- and macrovascular complications.

ALTERNATIVE TREATMENTS

If we are going to consider alternate interventions for preventing or reducing diabetic microvascular complications, then we have to understand the underlying pathophysiology. We know that hyperglycemia is the initiating event that must be followed by other metabolic pathways. The potential pathways by which hyperglycemia-induced mitochondrial superoxide overproduction occurs include:⁷

- The polyol pathway, through increased sorbitol, fructose and its direct effect is hyperglycemia;
- The hexosamine pathway;
- The protein kinase C (PKC) pathway with an increase in diacylglycerol (DAG); and
- The advanced glycosylation endproduct (AGE) pathway.

Each of these pathways has been implicated as being key in the development of microvascular complications.

Recently there has been great interest in activation of PKC. Investigators have demonstrated that hyperglycemia increases the production of DAG and in turn, the beta and delta isoforms of PKC, resulting in a decrease in endothelial nitric oxide and an increase in endothelin 1. This then results in blood flow abnormalities — which can be visualized in the retina as an example — associated with an increase in vascular endothelial growth factor (VEGF) and changes in

vascular permeability. Transforming growth factor (TGF) beta increases along with collagen and fibronectin, resulting in capillary occlusion, increases in plasminogen activator inhibitor (PAI) 1 and fibrinolysis, and vascular occlusion. Additional changes include an increase in interferon (INF) kappa beta and proinflammatory gene expression, an increase in nicotinamide adenine dinucleotide phosphate (NADPH), and an increase in reactive oxygen species (ROS), which has multiple effects.

There appears to be a unifying hypothesis that relates to the mitochondria. Increased glucose in the extracellular space crosses the cell membrane in cells where glucose transport is not dependent on insulin. The mitochondria are the intracellular organelles that play the principal role of producing energy. The increased glucose flux results in an increase in ROS, which can lead to DNA damage.

A recent example of a pharmacologic agent to block the effects of hyperglycemia on microvascular complication is the investigational PKC inhibitor ruboxistaurin. This agent has shown promise in early clinical trials. Ruboxistaurin limits PKC-beta overactivation and has been reported to have an impact on clinically significant retinal outcomes.⁸

Other pharmacologic approaches to improving microvascular outcomes by blocking other metabolic pathways — aldose reductase inhibitors, AGE inhibitors and reduction of increased oxidative stress — have been studied and to date have not been successful.

CONCLUSION

Hyperglycemia is the principal cause of microvascular complications. Glycemic normalization is frequently difficult to achieve with current therapies and may also be associated with increased rates of severe hypoglycemia. We need to do everything we can to get the best possible control in our patients. Pharmacologic therapy to prevent the impact of hyperglycemia on target organs, however, still represents an important strategy for complications prevention. ■

1. The Eyes Have It: Preserving Vision in Patients with Diabetes. Presented as a live CME activity. June 12, 2006. Washington DC.

2. The DCCT Research Group. The Diabetes Control and Complications Trial (DCCT). Design and methodologic considerations for the feasibility phase. *Diabetes*. 1986;35:530-545.

3. The DCCT 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;329:977-986.

4. The DCCT/EDIC Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med*. 2000;342:381-390.

5. The Writing Team for the DCCT/EDIC Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA*. 2002;287:2563-2569.

6. The DCCT/EDIC Study Research Group. Intensive diabetes treatment and cardiovascular Disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653.

7. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001;414:813-20.

8. Aiello LP. Effects of orally administered PKC-beta inhibitor ruboxistaurin on visual acuity in the PKC-DRS2 study. Presented at the Association for Research in Vision and Ophthalmology 2006 Annual Meeting. April 29 to May 4, 2006. Fort Lauderdale, Fla.

CME QUESTIONS

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

1. What was the MAJOR question in the DCCT with regard to primary prevention?
 - a. Will intensive therapy prevent the development of microvascular complications in those with no existing complications?
 - b. Will intensive therapy prevent macrovascular complications in those with no complications?
 - c. Will intensive therapy be costly to implement in a large cohort?
 - d. Will intensive therapy result in an increase of serious hypoglycemic events?

2. Which of the following is a finding from the DCCT trial?
 - a. Both intensive therapy and conventional treatment resulted in a 2% reduction in HbA1c.
 - b. Intensive therapy resulted in a 2% reduction in HbA1c when compared to conventional treatment.
 - c. There were no significant differences in HbA1c between the two groups, as compared with baseline.
 - d. While intensive therapy patients enjoyed a 2% reduction in HbA1c compared with conventional treatment, this had no effect on microvascular complications.

3. Which of the following statements is true with regard to the EDIC trial?
 - a. EDIC confirmed the concept of metabolic memory.
 - b. EDIC showed that the prevalence of proliferative or nonsevere proliferative diabetic retinopathy was reduced in the former intensive control patients from DCCT.
 - c. EDIC showed that clinically significant macular edema was reduced among former intensive control DCCT patients.
 - d. all of the above.

4. Episodes of severe hypoglycemia remain a barrier to intensifying diabetes control.
 - a. True
 - b. False.

5. Which of the following is NOT a potential pathway discussed in this activity, by which hyperglycemia-induced mitochondrial superoxide overproduction occurs:
 - a. The advanced glycosylation endproduct (AGE) pathway
 - b. The hexosamine pathway
 - c. The protein kinase C (PKC) pathway with an increase in diacylglycerol
 - d. The pentose-phosphate pathway

6. Pharmacologic approaches to improving microvascular outcomes by blocking which of the following pathways has shown success to date, according to the activity:
 - a. aldose reductase inhibitors
 - b. PKC
 - c. AGE inhibitors
 - d. reduction of oxidative stress

REGISTRATION/EVALUATION FORM: HYPERGLYCEMIA AND MICROVASCULAR COMPLICATIONS

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, PO 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 46.

1. A B C D 2. A B C D 3. A B C D 4. A B
5. A B C D 6. A B C D

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 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 August 31, 2007.

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:

- | | | | | | |
|---|---|---|---|---|---|
| • Identify the study questions from the DCCT trial. | 5 | 4 | 3 | 2 | 1 |
| • Discuss the findings from the DCCT and the EDIC trials. | 5 | 4 | 3 | 2 | 1 |
| • Describe what is meant by metabolic memory. | 5 | 4 | 3 | 2 | 1 |
| • Discuss the potential mechanisms by which hyperglycemia causes tissue damage. | 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: _____