

GOAL V:

PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES

Why It Is Important To Prevent or Reduce The Complications of Type 1 Diabetes

Destructive Complications of Type 1 Diabetes

Identifying Targets for New Diagnostics and Therapies—Learning How Diabetes Leads to Complications

- ▶ Insulin Deficiency
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- ▶ Additional Targets for Therapeutics Development—Blood Vessel Damage and Repair Pathways, Inflammation, and Abnormal Lipid Processing
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WHY IT IS IMPORTANT TO PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES

The constant companion of people with diabetes and their loved ones is fear of the complications of the disease. The newly diagnosed patient asks: “If my average blood glucose level is good, how dangerous is the occasional high? Will my vision be impaired? What about my kidneys? Can I be tested to find out my risk of developing complications?” Patients who already have one or more of the complications ask: “What, if anything, can I do to limit the damage that diabetes is causing to my body?”

Type 1 diabetes ravages nearly every part of the body: the heart, eyes, kidneys, nerves, lower limbs, mouth, and digestive and urologic systems. It can also ravage the emotional well-being of individuals with diabetes and their families and loved ones. Avoiding acute, life-threatening hypoglycemia and ketoacidosis is a daily concern for people with type 1 diabetes and their families. These daily worries are compounded by the fear of the tissue-damaging chronic complications that might strike in the future.

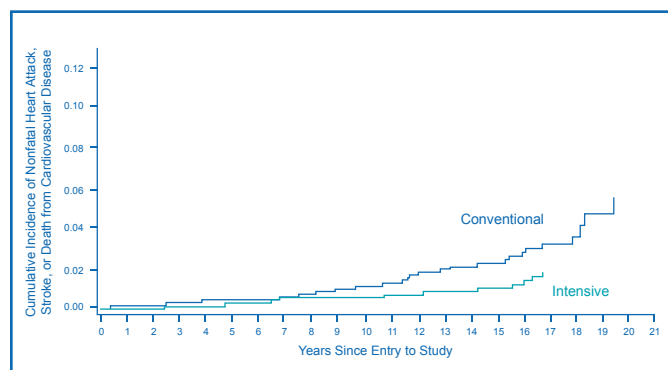
Destructive Complications of Type 1 Diabetes

Improved therapy has significantly increased life expectancy for people with type 1 diabetes in recent decades. Nonetheless, life expectancy may still be shortened by about 15 years (4), with heart attacks and strokes ranking as the primary cause of premature death (5). Cardiovascular disease strikes people with type 1 diabetes at 10-fold greater rates compared to people in the age-matched general population (2, 3); and treatment is particularly difficult because the effects of type 1 diabetes reduce the success of established cardiovascular therapies. The daily lives of many people with type 1 diabetes are made harder as a result of vision loss from diabetes. Patients with diabetes also face increased risk of irreversible kidney disease (end-stage renal disease), leading to the requirement for either dialysis for the remainder of their lives or a kidney transplant.

Amputation of the lower extremities is too frequently the end result of nonhealing foot ulcers. Patients with diabetes can lose sensation in the legs and feet because of diabetic nerve damage. The consequent inability to perceive pain allows the silent development of foot ulcers, which then fail to heal because of insufficient blood flow and other factors secondary to diabetes.

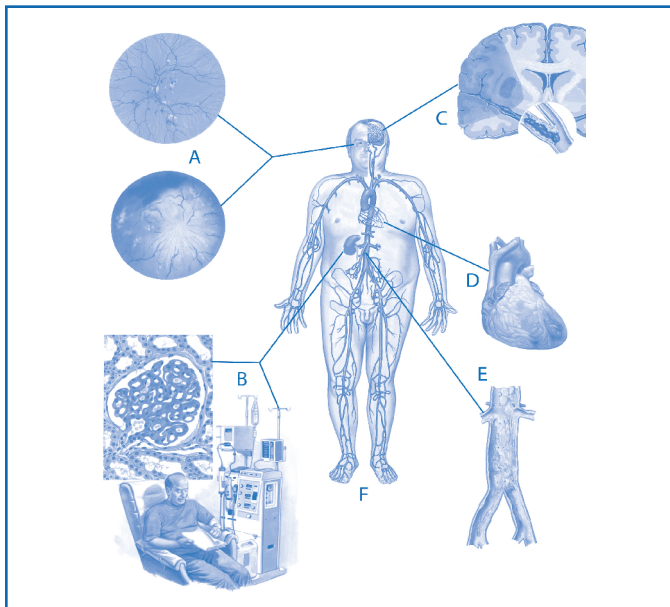
Among other complications of this disease are erectile dysfunction, urinary incontinence, nocturnal diarrhea, gum disease, and other oral health problems. Women with type 1 diabetes face additional health risks during pregnancy, and diabetes is associated with increased risk of birth defects in their children. Diabetes and its complications can lead to depression, poor quality of life, and family conflict. These difficulties can contribute to poor regimen adherence, accelerating the devastating complications of diabetes.

Until the prevention or cure of type 1 diabetes becomes possible, intensified research toward preventing and treating the complications of the disease is critically important. In addition to providing overwhelming benefits for people



Intensive treatment of type 1 diabetes, which includes four or more glucose measurements and three or more insulin injections daily, has been shown to reduce the onset and progression of complications. Results from the DCCT/EDIC research study have recently demonstrated that intensive treatment can reduce the risk of heart attack, stroke, or death from cardiovascular disease by 57 percent compared to conventional treatment.

(Image courtesy of Dr. David Nathan and adapted with permission from Nathan DM, et al. *Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. N. Engl. J. Med. 353: 2643-2653. Copyright © 2005 Massachusetts Medical Society. All rights reserved.*)



Type 1 diabetes is associated with serious medical complications. These complications can negatively affect the body in a variety of ways and include: (A) blindness; (B) kidney disease; (C) stroke; (D) heart disease; (E) atherosclerosis (clogged arteries); and (F) nerve damage leading to foot ulcers and amputation.

(Illustration credit: F. Netter, MD, C. Machado, MD, and ICON Learning Systems. Netter medical illustration adapted with permission of Elsevier. All rights reserved.)

with type 1 diabetes, this research would improve the lives of the millions of Americans with type 2 diabetes, who suffer many of the same complications.

Identifying Targets for New Diagnostics and Therapies—Learning How Diabetes Leads to Complications

Insulin Deficiency: The path from the onset of type 1 diabetes to the development of severe complications begins with insulin deficiency. Researchers are vigorously working to devise ways of replenishing the insulin-producing cells that are destroyed by type 1 diabetes, as described in Goal III. However, because of the extraordinary complexity of replacing or regenerating these cells, scientists are also accelerating research to target other points along the path from diabetes to its complications.

Elevated Blood Glucose: One immediate result of insulin deficiency is high blood glucose levels, termed “hyperglycemia,” a hallmark of type 1 diabetes. Scientists have demonstrated that intensive control of blood glucose levels can have long-lasting effects toward reducing the onset and progression of complications. Such intensive glucose control was achieved by type 1 diabetes patients in the landmark Diabetes Control and Complications Trial (DCCT), through more frequent monitoring of blood glucose levels than was

conventional, along with more frequent insulin injections or use of a pump. The intensively treated group had dramatic drops in eye, kidney, and nerve disease. In an ongoing follow-up effort, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, researchers are continuing to evaluate the health of the DCCT participants, both those who had been assigned to intensive treatment and those in the conventional treatment control group. After the DCCT ended, those in the conventional group improved their glucose control, but the individuals who had been in the intensive treatment group were unable to maintain such strict control of their blood glucose levels. During the decade following the trial, glucose control was similar in both groups. Surprisingly and provocatively, however, the effects of a finite time of intensive control have persisted for years. In fact, the difference in rates of development of complications between DCCT participants in the intensive and conventional groups has continued to widen. Compared to the DCCT participants from the conventional treatment group, those who were in the original intensive treatment group continue to have a lower incidence of complications—eye and kidney disease, heart attacks, and stroke—even 10 years later, despite similar levels of glucose during this period. In contrast, the effects of higher glucose exposure for a finite time in the DCCT participants from the conventional group have also persisted, causing increased complication rates, despite long-term improvement of hyperglycemia. The phenomenon of long-lasting effects of a period of intensive or nonintensive glucose control is termed “metabolic memory.” The discovery of the molecular and cellular basis of metabolic memory is urgently needed so that therapies can be designed to mimic or induce the body’s protective “memory” of good control of blood glucose levels and to counteract the harmful “memory” of higher glucose levels.

Mechanisms by Which Hyperglycemia Causes Damage: In addition to lowering blood glucose, another strategy for blocking the path from type 1 diabetes to its complications is to impede the processes by which high glucose levels cause cell and tissue damage. Pursuing this approach, scientists have recently suggested that a variety of deleterious molecular effects of diabetes may all arise from a single, hyperglycemia-induced process: the overproduction of a molecule called superoxide. Several novel agents based on this pathway have shown promise in pre-clinical experiments and should be evaluated in clinical studies in type 1 diabetes patients.

Additional Targets for Therapeutics Development—Blood Vessel Damage and Repair Pathways, Inflammation, and Abnormal Lipid Processing: Other advances in understanding the molecular events leading to diabetic complications will spur the design

of potential new therapies. For example, a key aspect of diabetic complications is the underlying damage to blood vessels throughout the body. Scientists recently found that diabetes not only leads to blood vessel damage, but also may impair the regeneration of healthy new blood vessels. Novel drug- or cell-based therapies to induce new blood vessel growth (angiogenesis) in type 1 diabetes patients may help promote wound healing and assist with repair of diabetes-induced damage to the heart and nerves. In contrast, excessive angiogenesis contributes to diabetic eye disease; thus, limiting new blood vessel growth in the eye may be beneficial. Cancer researchers have developed effective new cancer drugs targeted at angiogenesis. The role of such new therapeutics in slowing or reversing diabetes complications is under active investigation. Other researchers are focusing on the abnormal metabolism of fats in type 1 diabetes, including the toxic accumulation of fatty acid molecules in heart cells and the activation of molecular pathways related to inflammation, which also provides opportunities for intervention.

Finding New Therapeutics: An approach pioneered in the NIH Roadmap for Medical Research provides a new strategy to accelerate the discovery of therapeutics for diabetes complications. “High-throughput screening” refers to the testing of large numbers of compounds (i.e., a library) to see whether any show promise as potential drugs. Screening for therapeutic drugs requires biological assays that can be performed rapidly in the laboratory and reflect what is happening in the body as complications develop. Compounds identified as potentially useful by a high-throughput screen for diabetic complications can then be more intensively investigated to choose the most promising candidates for clinical trials. A crucial step in this selection process is testing compounds in animal models for diabetic complications. Suitable animal models that mimic the human condition are critical for the success of drug development. Efforts are under way to create such models by drawing upon new understanding of the molecular pathways underlying development of complications.

Facilitating Clinical Trials Using “Biomarkers” as Early Molecular Signs of Diabetic Complications:

The multi-organ damage caused by type 1 diabetes progresses silently for many years before signs or symptoms become apparent. Even more years may elapse before complications reach the severity of a heart attack, kidney failure, or other devastating event. Very early detection of the development of complications could permit early, successful intervention and reduced suffering for type 1 diabetes patients. Thus, a critical area for research is the discovery and evaluation of “biomarkers” for early detection of damage to cells and tissues. For example, the abnormal excretion of small amounts of protein in urine is currently used as a biomarker for early diabetic kidney disease, before organ deterioration to kidney failure.

Early intervention based on this biomarker has been credited with the recent slowing in rates of kidney failure in the United States. The molecular processes along the path from insulin deficiency to development of complications, discussed earlier, present rich opportunities for the discovery of new biomarkers. Scientists are also exploring noninvasive imaging techniques as a means of detecting disease progression.

Biomarkers research will also facilitate and expedite clinical trials. The development of therapeutics for diabetic complications is severely constrained because of the relatively slow progression rate of these complications. Therefore, clinical trials must extend for long durations for researchers to detect the effect of a candidate drug. “Surrogate endpoints” are biomarkers that are strongly associated with and predictive of disease outcomes. Valid surrogate endpoints can be used in shorter clinical trials to choose the most promising drug and trial conditions, prior to longer clinical trials assessing the definitive clinical endpoint. However, the standards for acceptance of new biomarkers and surrogate endpoints are extremely high, adding to the challenges of this area of research.

Predicting Risk of Complications

The occurrence and progression of diabetic complications vary markedly among patients. Many factors contribute to the risk for complications, including genetic variation. Several research consortia are conducting studies to identify genetic factors that confer susceptibility or resistance to diabetic complications, including the Genetics of Kidneys in Diabetes Study (GoKinD) and the Family Investigation of Nephropathy and Diabetes Study (FIND), as well as a component of the EDIC study. Results of this research may help to inform patient care, advance the discovery of new mechanisms of disease progression, and aid the development of potential new therapeutics. In addition, research on the behavioral, emotional, and family systems processes by which people with type 1 diabetes experience barriers to self-care may help to identify patients at high risk of developing complications and to test interventions that can improve their adherence to treatment regimens.

A Brighter Future

The prognosis for people with type 1 diabetes is steadily improving, yet the disease continues to exact a devastating toll. By elucidating the cellular and molecular processes by which type 1 diabetes progresses to complications, and by propelling research on detection methods and advanced techniques for drug development, scientists will greatly improve the lives of people with this disease. These efforts will further reduce the heightened risk for heart disease, kidney failure, blindness, and other debilitating, costly, and deadly complications of diabetes. A great hope of this research is that children and adults with type 1 diabetes today will have a much brighter future.



Dana Lewis:

Teen on a Mission To Help People with Type 1 Diabetes

Dana Lewis, of Huntsville, Alabama, is on a mission.

A self-proclaimed “good talker,” Dana began speaking at American Diabetes Association (ADA) events on behalf of people with type 1 diabetes shortly after she was diagnosed with the disease at age 14. Two years later, she was ADA’s Alabama Ambassador.

Dana’s message is simple and clear to people with type 1 diabetes: “The number one priority is to take good care of yourself and to maintain good blood sugar levels... and don’t let diabetes get you down,” she exclaims, “it’s a disease we can control.”

Today, 17-year-old Dana crisscrosses the United States as ADA’s 2005-2006 National Youth Advocate. She meets with policy makers to increase awareness of type 1 diabetes, and reaches out to her peers, as well as adults, to encourage them to become involved in the fight against diabetes.

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Dana is also a strong advocate for helping others

through volunteerism. “No matter what you do,” she says, “doing something for someone else is better for you than anything else. Volunteering is what puts diabetes in perspective for me.”

But getting to this point wasn’t easy, even for this dynamic teen.

A Teenager with Type 1 Diabetes

Dana was a high school freshman when she was diagnosed with type 1 diabetes. She says she was “scared” of diabetes because her grandmother had been diagnosed with the type 2 form of the disease when Dana was 9 or 10 years old. Dana knew that type 1 and type 2 diabetes are not the same. It took her a while to get used to being “different” from everyone else. “Diabetes was a curse word to me,” she says, “and I didn’t want to tell anyone that I had it.”

Except for sharing with a few very close friends, Dana kept the fact that she had type 1 diabetes a secret from others for 4 or 5 months after her diagnosis. Then one day, when she was in her advanced geometry class, Dana suddenly made a complete turnaround. “I just all of a sudden said to myself that I want to get an insulin pump; I want to find a cure for this disease, possibly as a doctor or a researcher; I want to do whatever I can.” Dana is currently considering majoring in biomedical engineering when she enters college.

In the meantime, she stays focused on her mission of keeping herself healthy, helping others, and advocating for a cure for type 1 diabetes.

PATIENT PROFILE

Taking Care of Herself

As captain of her high school's color guard, Dana leads the group in its four to five practices a week. She says she loves being part of the color guard because, "It's a fun way to exercise." She also likes to take walks around her neighborhood with her family, ride bikes with her friends, and play percussion instruments in her school band, which, she says, is also very physical. "Exercise may seem like work, but it can also be fun," says the vivacious, articulate Dana.

Dana is acutely aware that exercising, eating the right foods, and testing her blood sugar levels numerous times a day help to keep her blood sugar level in the normal range. Tight regulation of blood sugar levels helps to prevent or delay the development of life-threatening disease complications, such as diabetic eye, kidney, nerve, and heart disease.

Diabetes has put Dana very much in touch with her body and herself. "I find that when I get stressed, my blood sugar goes up." To help prevent this problem, she spends part of every day by herself, just relaxing, perhaps reading or writing, which are two of her favorite things. To control her blood sugar levels, Dana also uses an insulin pump and is meticulous about checking her blood sugar levels. "I test (my blood sugar), on average, 10 to 12 times a day, and I'm careful about counting my carbs (carbohydrates)," she says.

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"It's *really* important for me to take good care of myself." Yet, part of Dana's mission is to take good care of others, as well.

Taking Care of Others

To help teens like herself, Dana created a support group, called "Teen Team," which serves as a venue for members to share their experiences. "Support groups provide an opportunity to meet other teens who have diabetes and to learn how they are managing and juggling the disease with everything else that's going on in their busy lives," she says. She encourages young people to contact a local diabetes education center or doctor's office to help get a support group up and running in their school or community.

In addition to leading her support group, Dana gives presentations on diabetes in her human anatomy and physiology classes. "It gives me a platform to inform my peers about my disease. All my friends know exactly what to do to help me if my blood sugar suddenly gets too high or too low."

This past summer, Dana traveled to more than 10 states and met "so many kids" with diabetes to whom she always brings her important messages of: (1) keep your blood sugar levels in normal range; and (2) never give up on yourself because you have diabetes. The best thing about these encounters is that Dana gets as much out of them as the young people with whom she interacts. "It's truly inspirational for me when I meet these kids. Being an ADA youth advocate has been an incredible experience," says Dana.

Trying To Take Care of the Future

Although she has two older brothers, Dana is the only member of her family diagnosed with type 1 diabetes. "My mom keeps a close watch on my brothers for any symptoms, but so far they are diabetes-free," says Dana.

Even at such a young age, Dana knows that little will change for type 1 diabetes patients unless more research is done. Dana is doing everything she can to get the word out.

She already has met with several congressional leaders and has written a number of articles that have been published in her hometown newspaper—all to bring attention to type 1 diabetes. She continues to speak at ADA events, and encourages people to participate in America’s Walk for Diabetes and the Tour de Cure to help find a cure for the disease.

Despite all of her self-help and advocacy work, Dana harbors a great personal fear.

“I’m working very hard and trying to get a lot of things done, and if something should happen to me, I’m worried that things may fall through the cracks. That’s why I’m encouraging as many young people as I can to get involved in the fight against diabetes.”

Thankfully, Dana is healthy and active right now. “Even though I have diabetes, I am still Dana, a senior captain of my high school’s color guard. I live my life the way I do in spite of having diabetes, not because of it! I plan to make a difference in the fight against diabetes.” And she would like nothing more than for others to join her.

How Research Helps Patients

Patients with type 1 diabetes, such as Dana, have benefited from the results of a landmark NIH-supported research study, the Diabetes Control and Complications Trial (DCCT). Completed in 1993, the trial compared the relationship between intensive versus conventional treatment of blood sugar levels and the development of disease complications in adults with type 1 diabetes. The DCCT proved conclusively that intensive therapy reduces the risk of microvascular (small blood vessel) complications, such as diabetic eye, kidney, and nerve disease. Nearly all patients who participated in the DCCT volunteered to continue to be followed in the

Epidemiology of Diabetes Interventions and Complications Study (EDIC), which began in 1994. The DCCT/EDIC researchers continue to report remarkable long-term benefits of intensive blood sugar control in preventing or delaying complications of the eyes, kidneys, and nerves. Important recent findings have demonstrated the value of intensive therapy in preventing damage to large blood vessels in diabetes patients—damage that can lead to heart attacks and strokes. These findings are significant because two-thirds of patients with diabetes die of cardiovascular disease. The dramatic, positive results of DCCT/EDIC have had a profound impact on clinical practice for the management of type 1 diabetes: they led to the development of clinical guidelines by the ADA and other groups; spurred the creation of the National Diabetes Education Program (NDEP) to disseminate the findings to the public (www.ndep.nih.gov); and stimulated multifaceted research efforts to develop tools and therapies that enable patients to achieve tight control of blood sugar levels.

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Because of the limitations and difficulties of current therapies and technologies for achieving good blood sugar control, the NIH is also vigorously pursuing research to increase understanding of the underlying molecular mechanisms of diabetes complications and potential behavioral interventions to develop new therapeutic approaches. The identification of new prevention and treatment strategies for diabetes complications has the potential to not only dramatically improve quality of life for Dana and other type 1 diabetes patients, but also for patients with type 2 diabetes, who suffer from similar disease complications.

