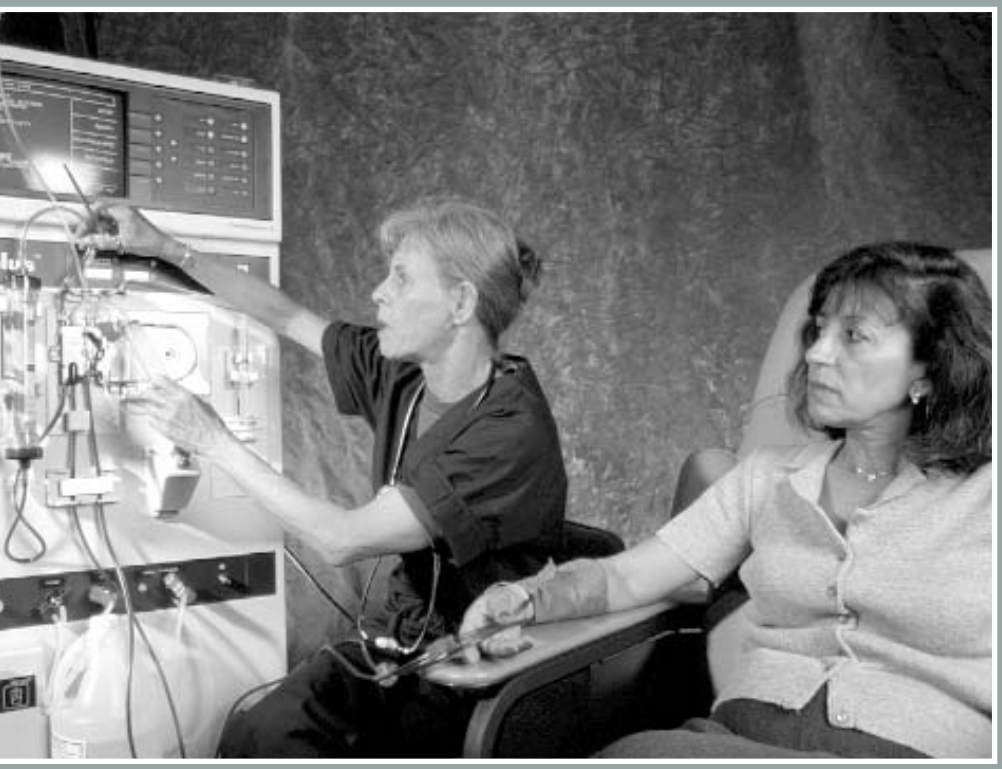
Special Needs for Special Problems



Diabetes is the leading cause of end-stage renal disease in the United States. This patient is receiving dialysis to remove wastes from the blood, a function that her failed kidneys can no longer perform. She requires dialysis or a kidney transplant to survive. Photo: Richard T. Nowitz for NIDDK.

Micro- and Macrovascular Complications

Diabetes can lead to widespread damage to blood vessels throughout the body. Small vessel (microvascular) damage results in debilitating diseases of the eye, kidney, and nervous system. Large vessel (macrovascular) damage results in premature cardiovascular disease that is the cause of death in two-thirds of patients with diabetes. Diabetes is a root cause of the following major health problems in the U.S.:

Blindness: Diabetic eye disease (retinopathy) is the leading cause of new blindness in U.S. adults, resulting in 12,000 to 24,000 new cases each year.

Irreversible Kidney Failure: Diabetic kidney disease (nephropathy) is the most common cause of end-stage kidney failure, accounting for 43 percent of new cases, and this proportion is projected to grow. In 1999, over 38,000 people with diabetes began treatment for end-stage renal disease and over 100,000 underwent dialysis or kidney transplantation.

Amputations: About 60 to 70 percent of people with diabetes have damage to the nervous system (neuropathy). Severe forms of diabetic nerve disease — coupled with circulatory failure in the foot and leg — lead to foot ulcers and about 82,000 amputations annually in the U.S. More than 60 percent of non-traumatic lower leg amputations in the U.S. occur in people with diabetes.

Heart Attacks and Strokes: Macrovascular disease, including heart attacks and strokes, is the major cause of death among individuals with diabetes. Heart disease (atherosclerosis) is accelerated in individuals with diabetes, who have a two- to four-fold increased risk for developing macrovascular disease and suffer a two-fold excess in morbidity and mortality following a heart attack compared to individuals without diabetes.

The long-term vascular complications of diabetes impose a significant burden for the individual patient, as well as an economic burden for society. The DRWG highlighted the urgent need for multi-disciplinary basic and clinical research focused on understanding and developing new therapies for the micro- and macrovascular complications of diabetes. Many of the research initiatives that have been spurred by the DRWG's Strategic Plan reflect the collaboration of multiple Institutes and Centers within the NIH.

Understanding What Causes Complications: How Are Small and Large Blood Vessels Damaged by Diabetes?

Insights into the causes of diabetic complications at the molecular, genetic, and cellular level will provide new targets for pharmacologic or gene therapy approaches to their prevention and treatment. A number of new initiatives have solicited research focused on pathways that have been implicated in the onset of all diabetic complications.

Initiatives have emphasized mechanisms of damage or dysfunction of the endothelial cells lining the blood vessels as well as specific target cells in the eye, kidney, and other affected organs, the role of growth factors in the development of diabetic complications, and the potential value of antioxidants and growth factor inhibitors in their prevention.

While the various organ-specific complications share some similarities, many of the complications pose unique challenges. For example, the DRWG noted that diabetic neuropathy represented an area of special challenge and emphasized that research on diabetic nerve disease had been a "largely neglected area" and should become a focus of urgent, high priority research. Based on this DRWG recommendation, the NIH has since held a workshop and issued two research solicitations aimed at understanding the neurobiology of diabetic complications and at attracting basic neuroscientists to the study of diabetic nerve disease. Other organ-specific initiatives have focused on the cellular and molecular mechanisms of diabetic cardiomyopathy, the pathogenesis and therapy of diabetic foot ulcers, and the microbiology and immunology of oral complications of diabetes.

GENETICS OF COMPLICATIONS

Familial clustering of complications of diabetes suggests an important genetic component to their development. Finding susceptibility genes for complications has important implications for identifying and intervening in individuals at increased risk as well as for developing new therapeutic approaches. Several new initiatives are under way to identify genes that predispose individuals with diabetes to the development of complications. Some of these will use samples obtained from populations that have been well characterized through participation in epidemiologic studies or clinical trials. For example, the "Epidemiology of Diabetes Interventions and Complications (EDIC)" genetics study will investigate genetic susceptibility to complications of diabetes in a population for which up to twenty years of data will be available on glycemic control, blood pressure, lipids and other risk factors. Other studies such as "Family Investigation of Nephropathy and Diabetes (FIND)" will recruit and characterize appropriate populations. Conferences such as the "Genetics of Diabetic Retinopathy Workshop" have been particularly helpful in developing strategies to identify the genetic basis of diabetic complications. Additional discussion of this topic is located in the "Genetics of Diabetes" section of this report.

GROWTH FACTORS EMERGE AS POTENTIAL THERAPEUTIC TARGETS IN DIABETES

Growth factors are emerging as important in the development, and potentially the therapy, of microvascular complications of diabetes. Two particular growth factors, vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-beta), have emerged as potential key players in these complications, by altering the permeability of small blood vessels. When small blood vessels leak, they attract damaging inflammatory cells, cause an excess accumulation of fibrous tissue (matrix) surrounding cells, and introduce into target tissues other factors that may promote further complications. Researchers now believe this is one of the key mechanisms underlying both small and large vessel disease in diabetes. While some of the effects of growth factors are seen in multiple organs, others appear to be limited to specific cells and tissues (for example, podocytes in the kidney and pericytes in the retina). Important new observations about the tissue specific effects of VEGF underscore the importance of understanding the pathologic processes operative in specific organs. Studies in animal models found inhibition of VEGF prevents diabetic eye disease, in part by decreasing abnormal formation of new vessels. However, other studies suggest that increasing VEGF to promote blood vessel formation may be an appropriate approach for microvascular complications in different organs. For example, VEGF treatment appears to be useful in treating diabetic nerve disease by promoting the formation of blood vessels and decreasing ischemia. Thus, it is of vital importance to delineate tissue-specific processes so that one complication can be successfully treated with growth factors such as VEGF without exacerbating another complication. Critical to this effort is the development of animal models that mimic human disease more accurately.

DEFINING THE ROLE OF OXIDATIVE STRESS IN DIABETIC COMPLICATIONS

Research has shown that high blood glucose levels are associated with the accumulation of toxic end products resulting from oxidation in cells and tissues. This process is known as oxidative stress. In recent years, studies have begun to reveal the mechanisms by which high glucose levels lead to oxidative stress and how the toxic products associated with oxidative stress lead to cell dysfunction and vascular disease. Further delineation and a more complete understanding of these oxidative stress pathways are needed in order to identify key steps that could be targeted to prevent or reverse activation of these damaging pathways. Developing better measures of oxidative stress is a related avenue of research opportunity.

ANIMAL MODELS

Research related to diabetes complications has been hampered by a lack of animal models that accurately recapitulate the disease seen in humans. Transgenic and knockout technologies will be very useful in the endeavor to create improved animal models. Initiatives are under way to develop mouse models of microvascular disease, as well as larger animal models of macrovascular disease, which more closely reflect human disease. The models developed under these initiatives will be useful for elucidating how complications begin and develop, as well as for studying prevention and treatment approaches, and will generate resources for the general research community.

UNDERSTANDING HOW HIGH GLUCOSE LEVELS ALTER THE STRUCTURE OF KEY PROTEINS

In addition to oxidative stress, diabetes has been associated with several other molecular, cellular, and biochemical abnormalities. For example, high levels of glucose can result in altered structures of key cellular proteins. These altered proteins have been termed "advanced glycation end products (AGEs)." Recent work has led to greater understanding of the exact biochemical rearrangements that take place under conditions of high blood glucose and how they lead to altered protein function. In addition, studies have begun to elucidate the mechanisms by which AGEs lead to vascular damage and tissue dysfunction in diabetes. A key advance has been the identification of a receptor for AGE (RAGE), providing a new target for preventing AGE-induced tissue damage. Several animal studies have demonstrated that RAGE blockade slows or prevents the development of accelerated heart disease or kidney disease in diabetic mice. These findings have opened up research opportunities to define more fully the AGE/RAGE pathway and to develop drugs that alter the clearance of AGEs or block their action. Improved assays are also needed to detect and quantitatively measure AGEs.

EPIDEMIOLOGIC STUDIES IDENTIFY FACTORS IMPORTANT FOR THE DEVELOPMENT OF DIABETES COMPLICATIONS

Numerous studies are under way that follow patients with or at high risk of diabetes to identify factors important for the development of complications. These include EDIC, which examines micro- and macrovascular complications in individuals with type 1 diabetes; the DPP Outcome Study, which will examine the development of complications in individuals with pre-diabetes to identify the threshold of glucose levels at which increased risk of complications occurs; important studies to identify risk factors for cardiovascular disease, which include substantial numbers of people with diabetes and will yield important insights into the mechanisms by which diabetes accelerates cardiovascular disease; and a study of individuals with early kidney disease to identify the determinants of progression. These studies are addressing key questions raised by the DRWG regarding the mechanisms by which diabetes and insulin resistance enhance the atherosclerotic process; the mechanisms responsible for the loss of the vascular protective effect in premenopausal women; the mechanisms that lead to increased mortality in people with diabetes immediately after a heart attack; and the identification and validation of markers that can identify the presence or predict the progression of complications. While minority populations are well represented in the ongoing studies, an important initiative encouraging additional research to investigate racial and ethnic disparities in the incidence of diabetes complications is described in more detail in the chapter of this report on "Special Needs for Special Problems: Diabetes in Women, Children, the Elderly and Minority Populations."

FOCUSING ON THE CRITICALLY IMPORTANT ROLE OF PRE-DIABETES IN THE DEVELOPMENT OF DIABETES COMPLICATIONS

Increasing attention is being focused on the risk of blood vessel disease in patients with pre-diabetes, whose glucose levels are higher than normal but not so high as to meet the criteria for full-fledged diabetes. Pre-diabetes is clearly associated with increased risk of heart disease even before the development of overt diabetes and recent data suggest that it may also be associated with nerve disease. Opportunities exist to elucidate the mechanisms by which pre-diabetes causes blood vessel disease. For example, it is not known whether damage to blood vessels is occurring because of the modestly elevated levels of blood glucose or because the body is resistant to the action of insulin, even in the presence of high levels of the hormone. Research opportunities exist to identify factors other than glucose as potential toxins to blood vessels in the diabetic or pre-diabetic state. Such factors include insulin and fatty acids. Furthermore, it is essential to capitalize on research opportunities to determine whether interventions that prevent progression from pre-diabetes to diabetes will also delay or prevent the development of vascular complications.

DEFINING INTERRELATIONSHIPS AMONG COMPLICATIONS

Poor control of blood glucose levels is the major predictor of the blood vessel damage at the core of the kidney, eye, nerve, and other complications of diabetes. However, researchers are beginning to perceive important interrelationships among the complications. For example, the presence in the urine of the protein albumin, an early marker for kidney damage, has been shown to be a powerful predictor of the development of heart disease independent of glucose levels. Albumin in the urine also predicts severity of diabetic nerve disease. Finding the reasons for these associations is a major area of research opportunity. For example, it is not known whether urine albumin is simply a measure of decreased integrity of the blood vessels—and therefore, a biomarker for all complications—or whether the leaking protein is itself a vascular toxin, which leads to inflammation and further vascular disease. Studies have also identified important risk factors common to multiple complications. For example, smoking—long recognized as a risk factor for heart disease—is also associated with diabetic kidney and nerve disease. In future studies, it will be important to characterize and establish more precisely the spectrum of blood vessel complications present in patients being studied for one complication. Additional studies are needed to understand the interaction between micro- and macrovascular disease. Critical to this effort is the opportunity to identify modifiable risk factors, such as smoking, high lipid levels, and high blood pressure, and to translate this information into improved clinical care of people with diabetes.

Developing New Treatment and Prevention Strategies for Diabetic Complications

Since the DRWG Strategic Plan, significant discoveries have emerged from several major clinical trials and the NIH has initiated important new clinical trials to treat or prevent diabetic complications.

These studies are described in more detail in the section of this report on "Clinical Trials and Clinical Research," including: ACCORD, Look AHEAD, and BARI 2D, major new multi-center trials that are testing approaches to reduce cardiovascular disease in individuals with type 2 diabetes; the Diabetic Macular Edema Clinical Research Network; and feasibility studies to assess potential new therapies for diabetic kidney disease.

DEVELOPING SURROGATE MARKERS FOR CLINICAL TRIALS

One problem in testing new therapies is the amount of time required to conduct clinical trials until patients reach long-term endpoints. This is particularly the case in chronic diseases such as diabetes in which disease progression may extend over many years, even decades. Therefore, clinical trials to prevent or treat complications are very costly, because either a very large number of patients or a very long time period is needed to accumulate enough "events" to determine differences between treatment groups. As previously discussed in "Autoimmunity and the Beta Cell," surrogate markers that could be used to assess the efficacy of new therapies at earlier time points could significantly reduce the time and expense of doing clinical trials and thus would greatly aid the development of useful interventions. In addition, surrogate markers for disease could identify patients at high risk who could benefit most from intensive interventions. The need for surrogate markers of disease is especially great for diabetic complications because patients often do not have signs or symptoms until significant tissue damage has already occurred. The search for biomarkers that could serve as surrogate markers of disease could be aided by the application of new technologies for studying how genes are expressed in tissues (genomic tools). In addition, opportunities exist to develop new imaging technologies and minimally invasive ways to obtain tissue samples.

To this end, the NIH has actively solicited studies to develop surrogate markers for diabetic microvascular complications. Particularly important are markers that will detect functional changes

that precede blood vessel damage. In addition, better staging methodologies are needed for diabetic nerve disease to predict its severity. Several surrogate markers for macrovascular complications—including carotid wall intimal media thickness and electron beam computed tomography scans to assess coronary artery disease—are being validated in clinical trials and epidemiologic studies.

GENE THERAPY HOLDS PROMISE FOR DIABETES COMPLICATIONS

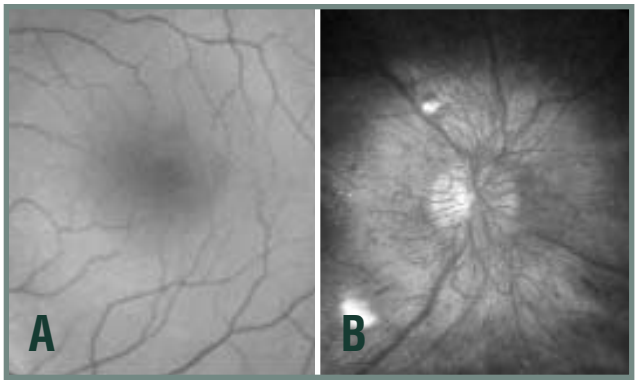
Gene therapy offers a potential means of selectively targeting particular tissues involved in diabetes complications. This may prove particularly useful for potential therapies with growth factors for which increased activity may be desirable in some tissues and decreased activity in others (see page 121). For example, it might be desirable to deliver a gene for making a growth factor stimulating new blood vessel formation to improve circulatory problems or nerve damage in the legs and feet and to use gene transfer techniques in the eye to block growth factors stimulating new vessel development. As recommended by the DRWG Strategic Plan, the NIH has solicited research proposals aimed at exploring the application of gene therapy techniques to the micro- and macrovascular complications of diabetes. In addition, the development of vectors with specificity for particular tissues, including those damaged by diabetes, has been a focus of research at NIH-supported gene therapy centers.

OPTIMIZING CONTROL OF BLOOD GLUCOSE LEVELS—A PROVEN WAY TO REDUCE THE COMPLICATIONS OF DIABETES

Major multi-center clinical trials supported by the NIH have clearly demonstrated that the microvascular complications of type 1 and type 2 diabetes can be prevented or delayed through control of blood glucose levels as close as possible to normal throughout the day. In addition, the EDIC study has already shown that the reduction in microvascular complications persists years after the intervention to improve glucose control has ended. Several large clinical trials now under way address strategies for optimizing glucose control as a means of preventing complications—a key recommendation of the DRWG. However, optimal glycemic control often cannot be attained with current therapies. The United Kingdom Prospective Diabetes Study (UKPDS) has shown that, in type 2 diabetes, glucose control often worsens over time. Moreover, in type 1 diabetes, it can be extremely difficult to achieve optimal control with current methods for monitoring glucose levels and delivering insulin when precisely needed. This problem must be addressed through expanded research on new approaches to control blood glucose as well as through the development of alternative therapies to reduce complications.

NEW APPROACHES TO THE PREVENTION OF MICROVASCULAR COMPLICATIONS OF DIABETES

Fundamental research on the mechanisms by which high blood glucose levels lead to damage of the small blood vessels of the nerves, eyes, and kidneys of diabetes patients has illuminated new biologic pathways that offer attractive, practical targets for successful drug therapy. One example is the use of a conveniently administered oral agent that selectively inhibits the enzyme known as protein kinase C or PKC, which basic research studies have implicated in the microvascular complications of diabetes. Published research findings of NIH-supported academic scientists, working in collaboration with industry, demonstrated that this PKC inhibitor can correct blood vessel abnormalities in both the retina and the kidneys of animals with diabetes. This inhibitor is now being tested in human trials.



These photos contrast a normal, healthy human retina (the inside back lining of the eyeball) **(A)** *with a retina damaged by proliferation of blood vessels—characteristic of diabetic eye disease (retinopathy)* **(B)**. *Photo: National Eye Institute.*

REDUCING HYPOGLYCEMIA—A MAJOR IMPEDIMENT TO ACHIEVING GOOD GLUCOSE CONTROL

A major risk of intensive diabetes management that can involve multiple administrations of insulin daily is dangerously low blood glucose levels, a condition known as hypoglycemia. As the DRWG pointed out, research to understand and prevent hypoglycemia is therefore critical to achieving optimal glycemic control and preventing eye, nerve, and kidney complications. New initiatives to address this problem have focused on developing improved methods of monitoring blood glucose and on understanding the effects of hypoglycemia on the brain and why repeated episodes of hypoglycemia lead to hypoglycemia unawareness. The ability to detect and prevent hypoglycemia in patients with diabetes has been enhanced by recent technological developments, including new continuous glucose monitoring devices. These new technologies have led to another initiative, which has established a cooperative multi-center research network to test the benefits of continuous glucose monitors in preventing hypoglycemia in children with type 1 diabetes.

INHIBITING THE RENIN-ANGIOTENSIN SYSTEM TO PREVENT PROGRESSION OF DIABETIC KIDNEY AND HEART DISEASE

Within the kidney, substances called renin and angiotensin play a key role in regulating salt and water balance. Blockade of the renin-angiotensin system is one therapeutic approach to the treatment of hypertension. Researchers previously demonstrated that angiotensin converting enzyme (ACE) inhibitors exert a protective effect on the kidneys of patients with type 1 diabetes; that is, these medicines slow the increase in levels of protein in the urine that are a marker of renal damage. This protective effect is independent of effects that ACE inhibitors have on blood pressure. Now, multiple studies have demonstrated that ACE inhibitors also slow the progression of renal disease in patients with type 2 diabetes, as do a related, newer class of drugs, the angiotensin receptor antagonists. In addition, one important study has demonstrated that an ACE inhibitor provides protection against cardiovascular events in individuals with type 2 diabetes. Additional studies are needed to determine if angiotensin receptor antagonists will also reduce cardiovascular events. Of particular importance is learning whether one of these classes of drugs — ACE inhibitors or angiotensin receptor antagonists — is superior to the other in protecting the heart or kidney, and whether there are differences in response in type 1 and type 2 diabetes.

PROMOTING AGGRESSIVE BLOOD PRESSURE AND LIPID CONTROL TO DECREASE CARDIOVASCULAR EVENTS

Clinical trials have demonstrated that lowering blood pressure to a target of less than 130 systolic and 80 diastolic, or "130 over 80," significantly decreases heart disease and kidney disease among patients with type 2 diabetes when compared with less stringent blood pressure control. Controversy still exists over the best choice of a blood pressure lowering drug in the diabetic population and answering this question provides an important research opportunity. Some important information on this topic is expected to emerge soon from the ALLHAT trial, which is comparing different classes of antihypertensive drugs. Another important question, which is being addressed in the ACCORD trial, is whether even further reduction of blood pressure will reduce heart disease in diabetes. While lowering of LDL cholesterol has been shown to prevent cardiovascular disease, type 2 diabetes is associated with a distinct lipid profile with low HDL cholesterol and increased triglycerides. The ACCORD trial is assessing the impact on cardiovascular disease of improving triglyceride and HDL cholesterol levels typical of type 2 diabetes. Additional opportunities exist to enhance translation efforts, so that the findings of clinical trials—such as those studying the relationship between blood pressure control and cardiovascular disease — can be broadly disseminated and adopted by clinical practitioners. Both patients and health care providers are the targets of such ongoing translation efforts.

PATIENT PROFILE: Aylin Riedel

FOR AYLIN RIEDEL, MANAGEMENT OF DIABETES AND KIDNEY DISEASE IS A DAILY BALANCING ACT

Most of us seek balance in our lives. But for 30-year-old Aylin Riedel, a person with type 1 diabetes whose condition has led to kidney disease, medically referred to as nephropathy, the pursuit of balance takes on a whole new meaning. Starting at age four and one-half, when she was diagnosed with diabetes, Aylin has worked hard to balance her glucose levels on a daily basis to keep her diabetes under control. Despite her best efforts, about eight years ago she began experiencing higher blood pressure and kidney problems related to her diabetes, so now she also struggles to keep her blood pressure in check. Her situation is compounded by the fact that her body responds poorly to the angiotensin-converting enzyme (ACE) inhibitor she needs to control her blood pressure and retard her kidney disease. This has exacerbated a condition called orthostatic hypotension that makes Aylin dizzy and literally lose balance frequently when she stands up from a sitting or lying position. Without the ACE inhibitor, however, she faces the real possibility of having to go on dialysis or receive a kidney transplant within a couple of years.

Impact on Life Decisions

Aylin's need to achieve balance in her life doesn't stop with her blood sugar, blood pressure, or medications. Nearly every decision she makes needs to be weighed against her diabetic condition and subsequent kidney disease. "For example, I could never be self-employed or work for a company that didn't provide adequate health insurance as a benefit to its employees," says Aylin, who holds a Ph.D. in health care economics and works for a large managed care organization.

Pictured are Aylin (right) and her husband, Eric (left). Nearly every decision that Aylin makes needs to be weighed against her diabetic condition and subsequent kidney disease. Since she began using an insulin pump two years ago, she enjoys more freedom.

Conservative estimates place the total cost of diabetes in the U.S. at $98 billion annually, including direct medical costs and costs associated with disability, work loss, and premature mortality.

Aylin's health also has implications for people she loves dearly. One of the most difficult decisions Aylin and her husband, Eric, recently have had to make was to weigh the trade-off between having their own biological child and the fact that pregnancy could possibly hasten the deterioration of Aylin's kidneys. Women who manifest nephropathy before pregnancy run as high as a 90 percent risk of developing hypertension and pre-eclampsia,

a condition that can cause dangerously high blood pressure in the mother and force an early delivery of the baby. After consulting with two physicians, Aylin and Eric decided against pregnancy. "It was a shock to us... we had always expected that we would have biologic children," Aylin says. "Now we are exploring other ways to build our family." She and Eric are pursuing the possibility of adopting a child from overseas, which unfortunately comes with its own set of issues for the couple. "We've learned that overseas adoption agencies take into consideration the health of the prospective adoptive parents, including life expectancy," says Aylin, almost matter-of-factly. The fact is that kidney disease is a major cause of excess illness and premature death in people with type 1 diabetes.

The Impact of Research

Aylin uses an insulin pump to provide her daily insulin requirements. "I've been using the pump for two years, and I think it's the greatest invention for diabetes," she says. "It gives me so much more freedom than having to take insulin shots."

The good news is that an extensive body of research aimed at understanding the underlying mechanisms of both diabetes and kidney disease is well under way, much of it funded by the NIH. The goal is to develop effective treatments and possible methods of prevention.

Prior to taking an ACE inhibitor, Aylin's blood pressure at times would spike to 220 over 140. The ACE inhibitor Aylin now takes, however, induces serious side effects that affect her balance. It is hoped that one or more of the medications currently being developed to enhance blood pressure control, used in combination with an ACE inhibitor, may reduce the side effects in patients like Aylin.

Low-Protein Diets — Researchers are finding that a diet containing reduced amounts of protein may benefit people with kidney disease. Therefore, experts are recommending that most patients with advanced nephropathy consume limited amounts of protein.

Intensive Management of Blood Glucose — Major NIH-supported studies in type 1 and type 2 diabetes provide compelling evidence that keeping blood glucose as close to normal as possible dramatically reduces onset and progression of diabetic kidney disease. The regimen includes frequently testing blood glucose, administering insulin frequently throughout the day on the basis of food intake and exercise, following a diet and exercise plan, and frequently consulting a health care team.

New Blood Pressure Medications — NIH-supported research has established the value of a specific type of drug, ACE inhibitors, and specific blood pressure targets in slowing progress of kidney disease. These measures are helping patients preserve kidney function while controlling their blood pressure.

Genetic Research — In addition to new medications, diet, and intensive glucose management, researchers also are investigating the genetic links to diabetes and kidney disease. For example, recent research sponsored by the NIH has identified a "variation" in the apolipoprotein E gene that, in type 1 diabetics, is associated with a three-fold greater risk of developing kidney disease. NIH-supported researchers are hoping to find more genetic relationships like this one through an ongoing large-scale study of families with diabetic kidney disease.

PATIENT PROFILE: Aylin Riedel

Much remains unknown when it comes to diabetes and its impact on major organs. Although we can slow development of diabetic kidney disease, we cannot prevent it. Also, it is still unknown why some people are more genetically predisposed to diabetes and kidney disease than others.

Living with the Disease

In many respects, Aylin is very fortunate. "Without ACE-inhibitor treatment, Aylin would very likely have experienced renal failure at this point," says her personal physician, Betsy Seaquist, M.D., who conducts diabetes research at the University of Minnesota. "However," she adds, "complications never exist in a vacuum, and treatment for the nephropathy has caused Aylin serious side effects. In addition to the orthostatic hypotension, which causes Aylin to lose her balance, she suffers from cardiac problems and damage to her eyes," says Dr. Seaquist.

"Although my vision is now stable," says Aylin, "I've undergone lots of laser surgeries." Nonetheless, her diabetic condition has left her with less than acute vision in one of her eyes. Consequently, Aylin, whose work as an economist entails lots of reading and writing, is forced to use large fonts on her computer. "I'm very up-front with my employers about my diabetes and how it intersects with my work life," says Aylin. "Before I am even hired, I tell them that I need special accommodations, including more time off for doctors' appointments. I get away with it because I'm very good at what I do," she adds.

It's not unusual for people with diabetes to see a number of medical specialists, including ophthalmologists for eye examinations, podiatrists for routine foot care, dieticians for help in planning meals, and diabetic educators for instruction in day-to-day care.

Aylin would like nothing more than to do away with her daily balancing act. "I'd like to think that a pancreatic/kidney transplant would cure me of my diabetes," she says. The irony is that, given her intolerance to the ACE inhibitor she now takes, she still would need to weigh the transplant against the impact that the immunosuppressant drugs, required to avert rejection of the transplanted organ, would have on her body for the rest of her life.

Although current therapies have done much to delay the need for dialysis or organ transplants in people with diabetes who suffer from nephropathy, much more still needs to be done. The lives of Aylin Riedel and millions of others hang in the balance.

The prevention and treatment of the long-term micro- and macrovascular complications of diabetes—kidney, eye, nerve, and cardiovascular disease—remain critical problems in diabetes care. Because the blood vessel damage leading to these complications can begin as soon as a person becomes diabetic, early intervention is key. The NIH is currently supporting studies to identify "surrogate markers," for the micro- and macrovascular complications of diabetes. These surrogate markers would indicate disease progression before it is clinically apparent. The hope is that such surrogate markers will assist researchers in identifying individuals at risk for developing diabetes-related complications, and also enable them to evaluate the benefits of current and evolving therapies.