NIDDK

Recent Advances & Emerging Opportunities

Diabetes, Endocrinology, and Metabolic Diseases

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This is a chapter from the NIDDK's Annual Report. The full Report includes highlights of research on these and many other areas across the NIDDK's mission and is available at: *www.niddk.nih.gov/about-niddk/strategic-plans-reports/niddk-recent-advances-emerging-opportunities*

U.S. Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes & Digestive & Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

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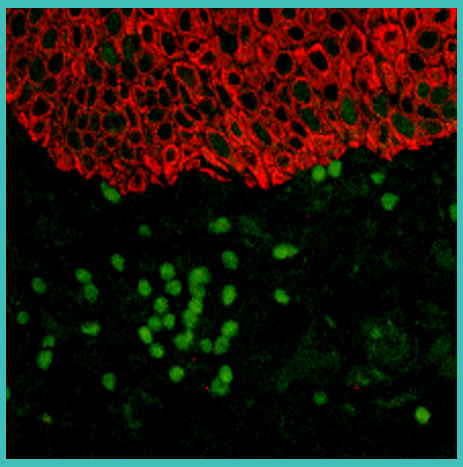

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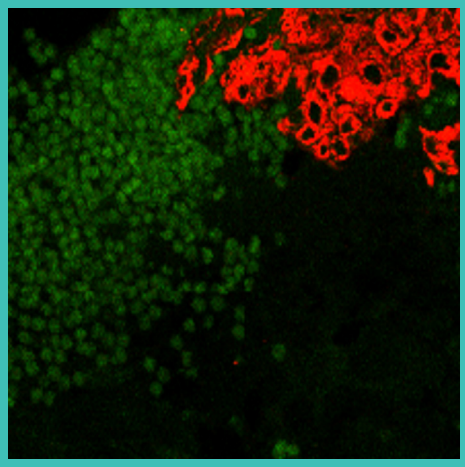

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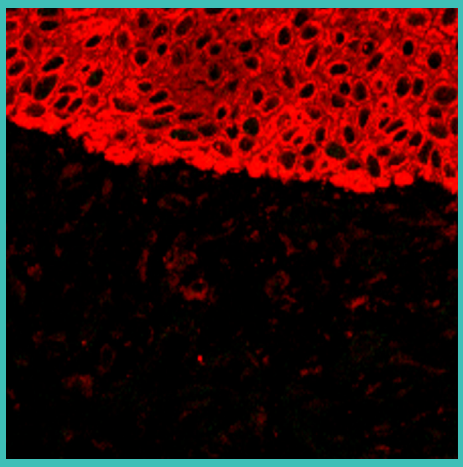

As described in this chapter, a recent study described how healing of diabetic foot ulcers (DFUs) may "stall" due to a blunted immune response at the wound. The protein FOXM1 was known to promote the replication and survival of key immune cells involved in wound healing. Researchers found that levels of FOXM1 were reduced in human DFUs compared to levels in 3-day old acute wounds, both oral or non-oral skin wounds. This difference can be seen in the above microscopy image, where FOXM1 protein is indicated in green and keratin (a protein marking epithelial cells in oral, non-oral, and DFU skin) is indicated in red. Additional experiments in mice (not shown) confirmed that inhibiting FOXM1 reduced the wound-healing immune response and delayed wound closure. These results suggest that slow or delayed healing of DFUs could be due to reduced FOXM1 activity, a finding which opens new avenues to diagnose and treat these wounds.

Images provided by Dr. Maria Morasso, NIAMS/NIH and Dr. Marjana Tomic-Canic, University of Miami Miller School of Medicine. Originally published in Sawaya AP, Stone RC, Brooks SR,...Morasso MI, and Tomic-Canic M. Deregulated immune cell recruitment orchestrated by FOXM1 impairs human diabetic wound healing. Nat Commun 11: 4678, 2020. DOI: 10.1038/s41467-020-18276-0 and reprinted under the terms of the Creative Commons CC-BY license.

Diabetes, Endocrinology, and Metabolic Diseases

NIDDK support of basic, translational, and clinical research in the areas of diabetes, endocrinology, and metabolic diseases spans a vast and diverse range of diseases and conditions, including diabetes, osteoporosis, cystic fibrosis, and obesity. Together, these diseases and conditions affect many millions of Americans and can profoundly decrease quality of life. Many of these diseases are complex—an interplay between genetic and environmental factors contributes to disease development.

Diabetes is a debilitating disease that affects an estimated 34.2 million people in the United States—or 10.5 percent of the total population—and is the seventh leading cause of death.[1] Although overall rates of diabetes-related complications have declined substantially in recent years, disease burden remains significant as the number of people with diabetes is still very high.[2] Diabetes can affect many parts of the body and is associated with serious complications, such as heart disease and stroke, blindness, kidney failure, and lower-limb amputation. In addition to these human costs, the estimated total financial cost for diagnosed diabetes in the United States in 2017—including costs of medical care, disability, and premature death—was $327 billion.[3] Effective therapy can prevent or delay diabetic complications, but more than one-fifth of U.S. adults with diabetes are undiagnosed and therefore not receiving therapy.[1]

Diabetes affects an estimated 34.2 million people in the United States—or just over 1 in every 10 people.[1] Another 88 million U.S. adults have "prediabetes," which puts them at elevated risk of developing type 2 diabetes.[1] The estimated total financial cost for diagnosed diabetes in the United States in 2017 was $327 billion.[3]

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone that is necessary for the body to absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of disease complications. The most common forms of diabetes are type 1 diabetes, in which the body loses its ability to produce insulin, and type 2 diabetes, in which the body becomes resistant to insulin, with subsequent impaired insulin production. In addition, a significant proportion of pregnant women each year are diagnosed with gestational diabetes, a form of diabetes that develops during pregnancy, but in many cases resolves after pregnancy. However, women who develop gestational diabetes are at greater risk of developing type 2 diabetes later in life. Untreated, any form of diabetes during pregnancy increases the risk of serious complications for the mother and baby before, during, and after delivery. There are also rarer forms of diabetes associated with specific genes such as those known as monogenic diabetes.

In addition to increasing the risk for complications of vision loss, kidney failure, and amputation, diabetes doubles the risk for heart disease, many forms of cancer, some forms of dementia, hearing loss, erectile dysfunction, urinary incontinence, and many other common diseases.[2]

[1] *Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2020.*

[2] *Diabetes in America, 3rd edition, Cowie CC, et al., Eds. Bethesda, MD, National Institutes of Health, NIH Pub No. 17-1468, 2018.*

[3] *American Diabetes Association. Diabetes Care 41: 917-928, 2018.*

Type 1 diabetes affects approximately 5 percent of adults diagnosed with diabetes and the majority of children and youth diagnosed with diabetes.[1] It most often develops during childhood but may appear at any age. Type 1 diabetes is an autoimmune disease in which the immune system launches a misguided attack and destroys the insulin-producing β (beta) cells of the pancreas. Thus, people with type 1 diabetes require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—to regulate their blood glucose levels.

The NIDDK's landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that keeping blood glucose levels as near to normal as safely possible reduced the risk of eye, kidney, nerve, and heart complications associated with type 1 diabetes. These results underscore the importance of pursuing research to develop novel technologies to help people with type 1 diabetes manage their blood glucose levels with less burden, including new methods to improve blood glucose monitoring and insulin delivery. In this regard, NIDDK-supported research has contributed to the development or testing of new U.S. Food and Drug Administration-approved diabetes management technologies, including artificial pancreas devices that automatically link glucose monitoring and insulin delivery. Researchers are also working to further develop and enhance β cell replacement therapies, such as islet transplantation, to cure type 1 diabetes.

NIDDK-supported research has contributed to the development and testing of new diabetes management technologies, including new artificial pancreas devices that automatically link glucose monitoring and insulin delivery.

Type 2 diabetes is the most common form of the disease, affecting about 90 to 95 percent of adults diagnosed with diabetes in the United States.[1] The risk for developing type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity. Type 2 diabetes occurs at higher rates among racial and ethnic minority populations in the United States, including African Americans, Hispanic and Latino Americans, American Indians, some Asian Americans, and Native Hawaiians and Pacific Islanders.[1] Gestational diabetes is also a risk factor: about half of women with gestational diabetes will develop type 2 diabetes within 5 to 10 years after giving birth.[4]

In people with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. As a result, the pancreas initially produces more insulin to compensate. Gradually, however, the pancreatic β cells lose their ability to secrete enough insulin to restore balance, and the reduction of insulin secretion, relative to the body's needs, results in elevated and abnormal blood glucose levels. Treatment approaches for managing glucose levels include lifestyle modification (*i.e.*, diet and exercise), and oral and injected medications, with insulin often required as the disease progresses. There are also an estimated 88 million U.S. adults who have "prediabetes," in which blood glucose levels are higher than normal but not as high as in diabetes.[1] This population is at elevated risk of developing type 2 diabetes. Fortunately, the NIDDK-supported Diabetes Prevention Program (DPP) clinical trial has shown that people with prediabetes who make lifestyle changes to lose weight by adopting a healthy diet and increasing physical activity can dramatically reduce their risk of developing type 2 diabetes. To a more limited degree, the safe and well-tolerated drug metformin can also help prevent or delay type 2 diabetes.

Type 2 diabetes is increasingly being diagnosed in children and adolescents, disproportionately affecting youth from racial and ethnic minority populations in the United States. NIDDK-supported research has shown that type 2 diabetes is more aggressive and difficult to treat in youth compared to adults.

Previously called "adult onset" diabetes because it is predominantly diagnosed in older individuals, type 2 diabetes is increasingly being diagnosed in children and adolescents, and disproportionately affects youth from racial and ethnic minority populations in the United States. Results from NIDDK-supported research has shown that the disease may be more aggressive and difficult to treat in youth compared to adults. This is worrisome because those with early disease onset are at especially high risk for developing complications. In

[4] *Kim C, et al. Diabetes Care 25: 1862-1868, 2002.*

addition, increasing rates of type 2 diabetes in girls may lead to more women who enter pregnancy with diabetes, and maternal diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or the development of gestational diabetes during pregnancy—confers an increased risk of type 2 diabetes in offspring. Thus, the rising rates of diabetes and prediabetes in young women could contribute to a cycle of ever-growing rates of diabetes, in addition to increasing risks for pregnancy complications. The advent of type 2 diabetes in youth has the potential to worsen the enormous health burden that diabetes already places on the United States.

The most common forms of diabetes, type 1 and type 2, are associated with variations in multiple genes. Some rare forms of diabetes, called monogenic diabetes, result from mutations in a single gene. Neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young (MODY) are the two main forms of monogenic diabetes. Many cases of monogenic diabetes may be incorrectly diagnosed, which may complicate management. For example, when high blood glucose is first detected, type 1 or type 2 diabetes may be considered the diagnosis instead of monogenic diabetes. A correct diagnosis allows for proper treatment and can lead to better glucose control and improved health. There are also unusual forms of diabetes that differ from known types, called "atypical diabetes." People with atypical diabetes may be diagnosed with and treated for type 1 or type 2 diabetes, but not have a history or signs consistent with their diagnosis. In addition, individuals may have a condition called latent autoimmune diabetes in adults (LADA). Finally, more recently, an additional type of diabetes, referred to as type 3c, has been described that is associated with disease or deficiency of the exocrine pancreas, as may occur with pancreatitis. It is critical to discover and define rare and atypical forms of diabetes, which could lead to better diagnoses, improved treatments, and potential prevention of these diseases.

The NIDDK is supporting research to better understand metabolism and the mechanisms that lead to the development and progression of diabetes and the many other endocrine and metabolic diseases within its mission; such research ultimately will spur the design of potential new intervention strategies. In parallel, based on knowledge from past scientific research investments, the NIDDK is vigorously pursuing studies of prevention and treatment approaches for these diseases.

Highlights of recent advances from NIDDK-supported research on diabetes, endocrinology, and metabolic diseases are provided in this chapter.

RESEARCH ON TYPE 1 DIABETES

Testing a Next-generation Artificial Pancreas Device for Managing Type 1 Diabetes: A clinical trial showed that a next-generation artificial pancreas device outperformed a commercially available first-generation device in adolescents and young adults with type 1 diabetes by increasing time that participants' blood glucose (sugar) levels were in a healthy range without increasing episodes of dangerously low blood glucose (hypoglycemia). These results are important because glucose management is extremely challenging during adolescence and young adulthood. Artificial pancreas technology, or a closed-loop system, aims to automate type 1 diabetes management by measuring blood glucose levels using a continuous glucose monitor and automatically delivering insulin when needed using an insulin pump. In 2016, the U.S. Food and Drug Administration approved Medtronic's MiniMed™ 670G as the first commercially available closed-loop system in the United States. However, research on real-world use of the 670G device shows a high discontinuation rate, especially in adolescents and young adults, suggesting that improvements are needed. In a recent clinical trial, researchers compared a next-generation, experimental closed-loop device from the same company with the 670G system. The experimental device had improvements such as advanced computer algorithms that control insulin delivery and easier operation.

The trial enrolled 113 female and male adolescents and young adults, ages 14 to 29 years, with type 1 diabetes. Participants were randomly assigned to use either the experimental device or the commercial 670G device for 12 weeks, and then were switched to the other device for 12 more weeks. The results showed that the experimental device improved the amount of time that participants' blood glucose levels were in a healthy target range, both during the daytime hours and during the entire 24-hour day and night period, without increased episodes of hypoglycemia. The improvements translated to about 1 hour more per day in the target glucose range than achieved when using the 670G device. Participants also reported greater user satisfaction with the experimental device compared to the commercial device.

These trial results showed that the next-generation device outperformed the 670G device and was also more user-friendly. Identifying new and improved type 1 diabetes management technologies—particularly for groups for whom glucose management is challenging—could help people achieve recommended

blood glucose levels with less burden, toward improving their short- and long-term health.

Bergenstal RM, Nimri R, Beck RW,...Phillip M; For the FLAIR Study Group. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): A multicentre, randomised, crossover trial. Lancet 397: 208-219, 2021.

Clinical trial results showed that a next-generation artificial pancreas device outperformed a commercially available device in helping adolescents and young adults with type 1 diabetes keep their blood glucose levels in a healthy range.

Large Study Sheds New Light on the Complex Type 1 Diabetes Genetics Landscape and Potential Drug Targets: Conducting the largest and most ancestrally diverse study of type 1 diabetes genetics thus far, researchers have identified new regions of the genome associated with the disease and potential drug targets. In recent years, there has been tremendous research progress in understanding genetic contributors to type 1 diabetes, an autoimmune disease in which the insulin-producing cells in the pancreas are destroyed by the immune system. However, most studies have only included people of European ancestry. Less is known about genetic risk for type 1 diabetes in people with other ancestries, who are experiencing increasing rates of the disease. Additionally, little is known about how genetic variants associated with type 1 diabetes cause disease. This information has implications for understanding the disease process and developing future strategies to prevent or treat type 1 diabetes.

In new research, scientists analyzed genetic contributors to type 1 diabetes by studying over 61,000 participants (with and without the disease), including individuals from diverse ancestries. This approach led to the identification of 36 new gene regions associated with type 1 diabetes, some of which are also associated with other autoimmune diseases. Additionally, the scientists did "fine mapping" studies to pinpoint the specific disease-causing variants in genetic regions previously associated with type 1 diabetes, toward elucidating the role these variants may play in the disease process. In another set of experiments, they used their genetic association results with data about other autoimmune diseases to identify 12 genes that could potentially be drug targets for type 1 diabetes. Drugs targeting these genes (by affecting the proteins the genes encode) have been studied in clinical trials for other autoimmune diseases, suggesting they could be repurposed for type 1 diabetes. Some of the targets are already being studied in type 1 diabetes clinical trials of various therapies, but others could potentially be explored in future trials to prevent type 1 diabetes.

This large research study with a diverse population has provided important knowledge about the complex type 1 diabetes genetics landscape, revealing new genetic regions associated with the disease, shedding light on how some genetic variants may influence disease, and identifying potential drug targets. Understanding what genes play a role in type 1 diabetes, and what role they play, paves the way to identify new targets to prevent or treat this autoimmune disease.

Robertson CC, Inshaw JRJ, Onengut-Gumuscu S,...Rich SS. Fine-mapping, trans-ancestral and genomic analyses identify causal variants, cells, genes and drug targets for type 1 diabetes. Nat Genet 53: 962-971, 2021.

RESEARCH ON TYPE 2 DIABETES

Determining What Prediabetes Means in Older Adults: Recent research suggests that we need better ways to assess the risk of future type 2 diabetes in older adults. People with blood glucose (sugar) levels higher than normal but lower than the levels used to define diabetes are said to have "prediabetes," because they are known to be at increased risk for the disease. Fortunately for those at high risk, the landmark, NIDDK-led Diabetes Prevention Program (DPP) clinical trial demonstrated that type 2 diabetes can often be prevented or delayed through diet and exercise changes designed to yield modest weight loss. This DPP lifestyle intervention was particularly effective in older DPP participants, and the infrastructure to provide a group-based adaptation of the approach has increased nationally in recent years. Targeting those programs to people most likely to benefit from them depends on knowing who has a high likelihood of developing diabetes. There are standard definitions for prediabetes using different measurements that work fairly well for individuals who are middle aged or younger, but less is known about how well they predict the development of type 2 diabetes among older individuals.

Researchers therefore studied a 3,412-person group of volunteers without diabetes (60 percent female; 17

percent Black; 83 percent White) who had an average age of about 75. The study tested different diagnostic criteria for prediabetes to compare how well they worked in older adults: using "HbA1c" levels; using fasting glucose levels; using either HbA1c or fasting glucose levels; or requiring the criteria for both measures to be met. The proportion of participants diagnosed with prediabetes differed greatly depending on which criteria were applied: 29 percent if using both HbA1c and fasting glucose, 44 percent based on HbA1c levels alone, 59 percent using fasting glucose levels alone, and 73 percent according to at least one of the two measures. As expected, a higher proportion of the individuals meeting one or more criteria for prediabetes developed type 2 diabetes than those who did not have prediabetes at the outset. However, for each of the individual prediabetes definitions, more of the volunteers saw their glucose or HbA1c levels improve to the normal range than progress to the diabetes range. Further, those considered to have prediabetes were also less likely to develop type 2 diabetes than they were to die of any cause. Taken together, these findings suggest the need for a better test to identify future diabetes risk in people over age 70.

Rooney MR, Rawlings AM, Pankow JS,...Selvin E. Risk of progression to diabetes among older adults with prediabetes. JAMA Intern Med 181: 511-519, 2021.

Young People with Type 2 Diabetes Are at High Risk for Having Complications in the Prime of Their Lives: People with type 2 diabetes diagnosed during youth have a high risk of developing complications at early ages and are more likely than adults with the disease to develop multiple complications within 15 years after diagnosis. These findings are from a follow-up study of the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial, which tested 3 therapeutic strategies in participants between 10 and 17 years old.

The original study produced sobering results, showing that type 2 diabetes is harder to treat and worsens more rapidly in young people than in adults. In view of these findings, researchers recognized that it was important to learn more about the clinical course of pediatric type 2 diabetes, so they invited the TODAY participants to continue in a follow-up study dubbed TODAY2. As in the original study, the more than 500 participants who agreed to continue were predominantly from minority groups disproportionately affected by type 2 diabetes: 38 percent were Hispanic, and 36 percent were non-Hispanic Black, while less than 20 percent were non-Hispanic White. TODAY2 revealed that serious complications of diabetes arose more quickly among the study participants than would be expected in adults with the disease or in young people with type 1 diabetes: within 15 years of their initial diagnosis, at least 60 percent of the participants in the original TODAY study had one or more serious diabetic complications, such as kidney disease, peripheral nerve damage, or eye disease, and at least 28 percent had two or more. Participants of minority racial and ethnic groups and those whose levels of HbA1c—a measure of blood glucose (sugar) levels over time—were comparatively high during the follow-up period were more likely than other participants to develop one or more complications. These results reveal that children and teens who develop type 2 diabetes may potentially face burdensome complications of the disease for the entirety of their adult lives. Because approved methods for treating pediatric type 2 diabetes are frequently ineffective, the results also underscore the critical need to identify better therapies for those who have the disease, as well as better prevention strategies for those at risk.

Bjornstad P, Drews KL, Caprio S,...Zeitler P. Long-term complications in youth-onset type 2 diabetes. N Engl J Med 385: 416-426, 2021.

Youth with type 2 diabetes are likely to experience serious complications of the disease by the time they are young adults.

Treatment for Teenagers with Type 2 Diabetes Can Help Keep the Disease from Getting Worse: Although a recent study did not identify a means to partially reverse pediatric type 2 diabetes and restore health, new results show that the interventions tested were helping to keep the disease from getting worse. Research in adults with recent-onset type 2 diabetes has shown that in some cases, early, aggressive treatment can partially restore the capacity of the pancreas to secrete insulin to control blood glucose (sugar) levels. Because type 2 diabetes tends to progress more rapidly when it occurs in young people, the Restoring Insulin Secretion (RISE) Pediatric Medication Study sought to determine whether early treatment similarly could improve natural blood glucose control in youth aged 10 to 19 years who either recently developed type 2 diabetes or who had elevated glucose levels close to that of diabetes. The original study tested whether treating youth with a long-acting form of insulin for 3 months followed by use

of the oral diabetes medication metformin for 9 months was more effective than simply using metformin for 12 months. Unfortunately, neither treatment approach succeeded in improving natural insulin secretion by the pancreas for blood glucose control: on average, the participants' blood glucose levels neither improved nor declined significantly during treatment. In follow-up, the researchers sought to determine whether the year of treatment was sufficient to stabilize blood glucose levels or whether longer-term medication may be needed. Thus, they continued measuring blood glucose levels for 9 months after the conclusion of the treatment phase. They found that type 2 diabetes progressed significantly more rapidly once the study participants stopped taking medication. These results suggest that it is valuable for young people with type 2 diabetes to use insulin or metformin to control their blood glucose levels until better, more durable means of treating pediatric diabetes are identified.

Hannon TS, Edelstein SL, Arslanian SA,...Nadeau KJ; for the RISE Consortium. Withdrawal of medications leads to worsening of OGTT parameters in youth with impaired glucose tolerance or recently-diagnosed type 2 diabetes. Pediatr Diabetes 21: 1437-1446, 2020.

Improving Type 2 Diabetes Self-care by Focusing on Friends and Family: Researchers have found that type 2 diabetes self-care may be improved by addressing the role of family and friends. Effective treatment of diabetes requires a long-term effort by the individual to take medications correctly and on time, and to manage diet and physical activity in a health-promoting way. Family and friends can be powerful allies in facing these challenges, but they can also have negative effects, such as by encouraging unhealthy meal choices or discouraging exercise. In a study of about 500 female and male adults with type 2 diabetes, researchers were investigating whether an intervention called REACH, which involves sending individualized text messages about type 2 diabetes self-care to participants' mobile phones, could improve diabetes self-care behaviors. A large percentage of the study participants were from racial and ethnic minority populations, and many had low income and were underserved. Half of the participants were assigned to the REACH group, and half received standard care (the control group). This study demonstrated that REACH resulted in short-term improvements to medication adherence and blood glucose control.

In an ancillary study, researchers further divided the REACH group into two groups, one of which continued in the original REACH program. The other, designated REACH+FAMS, received one-on-one coaching to help them set self-care goals along with suggestions for ways both to achieve more helpful support from friends and family and to reduce harmful interactions. This group also received individualized text messaging support related to the goals established in the coaching sessions, so their text messages were different from those sent to the REACH-only group. The REACH+FAMS participants also were invited to nominate a friend or family member to serve as an ally in their diabetes self-care; this part of the intervention was optional, and as such, only 42 percent of the REACH+FAMS group had allies involved in the study who received text messages designed to help the study participant achieve self-care goals. After 6 months, the REACH+FAMS participants had improved family/friend involvement in their self-care, did better in some measures of self-care, and had a better diet, on average, than participants in either the control or the REACH-only groups, although there were no statistically significant differences in exercise between the three groups. These results suggest that coaching and mobile technology might be valuable for helping people with type 2 diabetes take better care of themselves and adopt a better diet by improving interactions with family and friends.

Mayberry LS, Berg CA, Greevy RA,...Elasy TA. Mixed-methods randomized evaluation of FAMS: a mobile phone-delivered intervention to improve family/friend involvement in adults' type 2 diabetes self-care. Ann Behav Med 55: 165-178, 2021.

Multi-ethnic Genetic Study Greatly Expands Knowledge About Regulation of Glucose Levels: A new analysis of six genetic data sets from people in different parts of the world has yielded a wealth of discoveries about the wide array of genes affecting control of glucose (sugar) levels in human beings. The study of more than 280,000 people, 30 percent of whom had non-European heritage and none of whom had diabetes, looked at whether genetic variations across the genome were associated with 4 different measures of glucose control or insulin levels. In this way, the researchers identified 99 more regions of the genome affecting glucose levels than had been known previously, 24 of which could not have been identified by simply enlarging the European data set to match the size of the multi-ethnic collection. Data from other studies conducted about the same time show that 27 of the 99 regions are linked to type 2 diabetes risk in East Asian and trans-ancestry studies; it remains to be determined whether the remaining 72 gene regions affect the risk

of diabetes or simply contribute to normal variation in glucose levels among people without diabetes. Because these regions of the genome are large enough to contain multiple genes, the researchers sought to narrow these down to identify the most likely genes affecting glucose levels. Importantly, including genetic data from varied groups was instrumental in helping identify potential candidate genes within the genetic regions. Among the other key findings of the study, 80 percent of the glucose-level affecting genetic variations were found in most or all of the lineages, suggesting significant commonality in the genetics of blood glucose control. However, genetic risk scores for type 2 diabetes that had been previously developed based primarily on research with people of European descent proved significantly less predictive in other populations, demonstrating another key reason for studying the biology of glucose control in people with a wide array of differing ancestries, an approach that also may accelerate the search for new and better ways to treat or prevent the disease.

Chen J, Spracklen CN, Marenne G,...Barroso I for the Meta-analysis of Glucose and Insulin-related Traits Consortium. The trans-ancestral genomic architecture of glycemic traits. Nat Genet *53: 840-860, 2021.*

A large study of people with different ancestries has yielded a wealth of discoveries about the genes affecting blood glucose (sugar) levels.

Protein Identified That Governs Adaptive Increase in Beta Cell Production and Function in Obesity: Researchers studying insulin-producing β (beta) cells in a mouse model have identified a protein involved in increasing β cell numbers in mice with obesity. This finding, discovered by a team led by scientists in the NIDDK's Intramural Research Program, may open new avenues for treatment of type 2 diabetes, a disease associated with obesity. People with obesity and type 2 diabetes often have insulin resistance, a condition where tissues do not respond to insulin normally. To try to compensate for insulin resistance, the body often triggers an increase in β cell production that can delay or even prevent diabetes by increasing insulin levels. However, our understanding of the underlying cellular signals that trigger this adaptive increase in β cell numbers has been limited.

To further examine how β cells are regulated in obesity, researchers investigated the protein β-arrestin-1. β-arrestin-1 is part of the signaling machinery in many cells, including β cells, and was previously implicated in β cell activity. To explore the role of β-arrestin-1 in obesity, researchers generated male mice lacking β-arrestin-1 in their β cells. Both these mice and a group of normal mice were fed a high-fat diet so they would gain excess weight, and the mice's β cells were then compared. The scientists found that β-arrestin-1 was required for the increased β cell numbers seen in obesity. Mice without β-arrestin-1 in their β cells also had poorer metabolic health than normal mice of similar weight fed a similar diet. In comparison, obese mice with more β-arrestin-1 than usual in their β cells had better metabolic health than similar mice with normal levels of β-arrestin-1. Further investigations into how β-arrestin-1 was causing these differences revealed that a lack of β-arrestin-1 reduced production of the protein Pdx1, which regulates β cell function and overall β cell numbers. Similar poor outcomes on metabolic health and Pdx1 levels were also seen when β-arrestin-1 levels were reduced in human β cell lines in the laboratory.

Further research would be required to determine if β-arrestin-1 plays a similar adaptive role in people (both males and females) who have obesity and/or type 2 diabetes. If so, therapies to increase β-arrestin-1 activity might increase β cell numbers and thus might help treat or prevent diabetes.

Barella LF, Rossi M, Pydi SP,...Wess J. β-arrestin-1 is required for adaptive β-cell mass expansion during obesity. Nat Commun *12: 3385, 2021.*

RESEARCH ON DIABETES COMPLICATIONS

Alterations in Brain Structures in Type 1 Diabetes: In a study of people who have had type 1 diabetes for many years, researchers found structural alterations in regions of the brain involved in cognition and voluntary muscle movement—results that provide much-needed new insights into how the disease affects the brain. In type 1 diabetes, the complications to organs such as the heart, kidney, and central nervous system are associated with elevated blood glucose (sugar) levels and episodes of low blood glucose levels. Although the risk of impairment to the central nervous system in type 1 diabetes is not completely understood, several studies have reported subtle differences in cognitive ability between people with and without the disease.

To address the question of how type 1 diabetes may affect brain structure, the researchers analyzed magnetic

resonance imaging (MRI) brain scans of 61 women and men with long-duration (average of 21 years) disease compared to a control group of 54 women and men of similar ages who did not have type 1 diabetes. They found significant structural differences in several brain regions (*e.g.*, striatum, thalamus, and mesial temporal cortex) between those with the disease and the control group. These brain regions are largely associated with cognition and motor functions. The findings of this study identify structural brain alterations in people with long-duration type 1 diabetes. Future studies could assess whether such changes in the brain correlate with differences in cognition, or other functions, and pave the way toward a longer-term goal of identifying ways to intervene and protect the brain.

Filip P, Canna A, Moheet A,...Mangia S. Structural alterations in deep brain structures in type 1 diabetes. Diabetes 69: 2458-2466, 2020.

Risk Factors Associated with Cognitive Decline in Older People with Type 1 Diabetes: Researchers identified risk factors that contribute to cognitive decline in people with type 1 diabetes as they age—findings that could inform strategies to preserve cognitive function over the lifespan. Because multiple avenues of research have demonstrated the importance of controlling blood glucose (sugar) levels and led to the development of improved diabetes management technologies, people with type 1 diabetes are living healthier and longer lives. In further research to help people maintain good health as they age, scientists sought to determine whether type 1 diabetes affected the cognitive decline that is seen as people age, as well as to identify risk factors associated with cognitive decline. Understanding any loss of cognitive function is important to ensuring that high quality of life and diabetes self-management can be maintained as people with type 1 diabetes age.

The NIDDK's Epidemiology of Diabetes Interventions and Complications (EDIC) study has followed over 1,000 participants from the landmark Diabetes Control and Complications Trial (DCCT) for over 30 years from a median age of 27. As part of the follow up, participants completed cognitive assessments at the start of the DCCT and 2, 5, 18, and 32 years later (median age of 59), as well as other assessments. Overall, the researchers found that, as the group aged, they performed less well on assessments of memory and psychomotor and mental efficiency. These cognitive declines were associated with higher hemoglobin A1c (HbA1c) levels (a measure of blood glucose levels over time), more episodes of severe hypoglycemia (dangerously low blood glucose levels), and elevated systolic blood pressure levels. When combined, the presence of these three risk factors was associated with a cognitive decline equivalent to an additional 9 years of age, suggesting premature aging.

Participants who maintained better control of these risk factors, however, showed fewer changes in cognition. Lower average HbA1c, fewer episodes of severe hypoglycemia, and lower blood pressure were each associated with better performance on the cognitive assessments, suggesting that blood glucose control and blood pressure management could help to preserve cognitive function in people with type 1 diabetes as they age. These results add to the wealth of information that has come from the DCCT/EDIC demonstrating the long-term health benefits of maintaining blood glucose levels as close to those of a person without diabetes as safely possible.

> ***Research findings suggest that blood glucose (sugar) control and blood pressure management might preserve cognitive function in people with type 1 diabetes as they age.***

Jacobson AM, Ryan CM, Braffett BH,...Lachin M for the DCCT/EDIC Research Group. Cognitive performance declines in older adults with type 1 diabetes: Results from 32 years of follow-up in the DCCT and EDIC Study. Lancet Diabetes Endocrinol 9: 436-445, 2021.

New Analysis of Diabetic Foot Ulcers Reveals Reduced Activation of Wound-healing Immune Response: New research has revealed how diabetic foot ulcers (DFUs) may "stall" in their healing due to a blunted immune response at the wound. These findings may open new avenues for preventing or treating DFUs, a devastating complication of diabetes that can lead to lower limb amputation.

Little is known about how diabetes affects the skin or why some DFUs heal slowly or not at all. To better understand the various factors at work in DFUs, researchers compared the tissue samples collected from 21 individuals with diabetes, including DFUs, to wounded skin from people without diabetes. Scientists compared the genes active in these skin samples and identified several key differences between DFUs and wounded skin from people without diabetes. In general, they found that key molecular players in the immune response necessary for wound healing were dysregulated

in DFUs. In wounded skin from people without diabetes, there was increased activity of a network of genes responsible for recruitment, activation, replication, and survival of immune cells, but the same gene activity was markedly reduced in DFUs. This difference could be responsible for the decreased ability of certain immune cell types to replicate or survive at DFU wound sites, thus reducing their effectiveness during healing. In particular, the activity of the gene encoding the FOXM1 protein, which promotes the replication and survival of key immune cells involved in wound healing, was reduced in DFUs. Further experiments involving FOXM1 in male and female diabetic mouse models confirmed that inhibiting this protein reduced the immune response in wound healing and delayed wound closure, similar to what was found in patients with DFUs.

These results support the idea that DFUs are "stalled" wounds, where the immune system is not stimulated to the level needed to close the wound promptly. This study used samples from a limited number of participants, so further experiments will be needed to confirm that these findings are applicable to a larger number of DFUs. Nonetheless, this new knowledge about immune system activation in normal and chronically unhealing wounds has provided clues as to why some DFUs heal slowly or not at all. Because these findings also shed light on underlying pathways involved in this process, such as the identification of a key role for FOXM1, they also suggest possible new targets for ways to treat and predict healing in DFUs.

This study exemplifies a team science approach that was conducted as an ancillary study of the recently formed NIDDK Diabetic Foot Consortium (see feature later in this chapter) and funded, in part, by the NIH Bench-to-Bedside and Back Program. The goals of the NIH Bench-to-Bedside and Back Program are (1) to fund research teams seeking to translate basic scientific findings into therapeutic interventions for patients, and (2) to increase understanding of important disease processes by addressing barriers, such as the traditional silos between basic and clinical researchers in biomedical research, which can hinder progress toward finding new therapeutics for patients in need.

Sawaya AP, Stone RC, Brooks SR,..Morasso MI, and Tomic-Canic M. Deregulated immune cell recruitment orchestrated by FOXM1 impairs human diabetic wound healing. Nat Commun *11: 4678, 2020.*

New research reveals how healing of diabetic foot ulcers may be impaired by a reduced immune response at the wound.

METABOLIC REGULATORS OF HEALTH AND DISEASE

Selective Fat-cell Elimination in Mice Leads to a Profound Increase in Bone Mass: By studying how fat cells in the bone marrow of mice affect bone growth, researchers have discovered potential therapeutic targets that may profoundly increase bone mass to prevent or restore bone loss. Osteoporosis, a bone disease that occurs when the body loses bone mass, is endemic in Western and Asian societies and predisposes older adults to weak bones, fractures, and premature mortality. Recent evidence that fat-cell depletion can trigger bone growth hints at the potential for new osteoporosis therapeutic strategies.

In the current study, researchers generated male and female mice in which administering a chemical could eliminate fat cells, including in bone marrow, which contains fat cells, and in other body fat tissue. They found that within 10 days of being given the chemical, bone growth increased 10-fold in mice without fat cells compared to mice with intact fat cells. New bone mass was markedly increased in older mice but to a lesser extent in young mice, and the new bone had enhanced strength and function compared to bones of mice with normal fat distribution. Moreover, researchers found that while removing the ovaries of normal female mice results in osteoporosis, those in the group that received the chemical and lacked fat cells were protected from bone loss. The researchers next investigated whether the bone growth was caused by depletion of fat cells in bone marrow or in other body fat tissues, in part by seeing whether the effects changed if they restored some fat tissue. When fat tissue from normal mice was transplanted under the skin of mice lacking fat, there was no effect on bone growth. This and other experiments suggested that bone formation is specifically inhibited by fat cells in the bone marrow, rather than by fat in other tissues. Further analysis indicated that marrow fat cells might be tamping down a signaling pathway previously associated with bone growth, providing potential therapeutic targets that may be considered to treat osteoporosis in humans. Because chronic activation of this pathway can lead to excessive growth of several other cell types, the use of

this strategy for treating bone disease may result in yet unknown effects that may present roadblocks.

Moreover, further research is needed to determine if bone growth in humans is similarly affected by marrow fat cells and, if so, to identify strategies for stimulating bone growth that may one day improve treatment or prevention of osteoporosis.

Zou W, Rohatgi N, Brestoff JR,...Teitelbaum SL. Ablation of fat cells in adult mice induces massive bone gain. Cell Metab 32: 801-813, 2020.

Individual Genetic Variations in Fat and Liver Cells Predict Adverse Drug Response: Researchers have uncovered cell-type specific and individual-specific genetic variations that predispose people to adverse metabolic side effects of commonly prescribed steroid hormones called glucocorticoids. Glucocorticoids are widely used as anti-inflammatory drugs to treat a variety of health problems including rheumatoid arthritis and inflammatory bowel disease. Moreover, the powerful glucocorticoid dexamethasone is now widely used to treat people with advanced COVID-19. However, the long-term use of glucocorticoids often can have severe side effects such as weight gain and elevated blood glucose (sugar) and lipid (fat) levels, since they play an important role in regulating metabolism. Thus, identifying ways to determine who is likely to experience adverse metabolic side effects could help guide and personalize therapy decisions.

In this study, researchers examined changes in gene activity, or gene "expression," after treating cells in the laboratory with dexamethasone. They studied fat cells and liver cells—two cell types responsible for many of the negative metabolic effects of glucocorticoids. The fat cells used in the experiments were generated from fat tissue samples from eight healthy females undergoing elective abdominal surgery. To generate liver cells, researchers first derived stem cells from blood donated by 11 healthy males and females, and then induced the stem cells to become liver cells. The researchers found a high degree of variation in the number of dexamethasone-regulated genes between fat cells and liver cells, as well as variation between different individuals. It is known that glucocorticoids regulate gene expression by binding to and activating the glucocorticoid "receptor"—a protein that binds to DNA and regulates the activity of genes. Thus, the researchers examined the individual-specific and cell-type-specific variation in glucocorticoid receptor binding sites on DNA to assess whether that could explain the observed variation in gene expression. Indeed, a high degree of variability was observed in the number and strength of receptor binding sites between individuals and between cell types in response to glucocorticoid treatment. This variation in receptor binding could be traced to single genetic mutations that alter receptor binding and regulation of genes by glucocorticoid drugs.

Remarkably, when they examined people undergoing glucocorticoid therapy for different conditions, they found that these genetic variants could predict a person's likelihood of adverse metabolic effects such as increases in blood glucose, lipids, and weight.

These findings provide new insight into the genetic variants that predispose people to metabolic side effects and pave the way for a future personalized-medicine approach to the clinical use of glucocorticoid therapeutics.

Hu W, Jiang C, Kim M,...Lazar MA. Individual-specific functional epigenomics reveals genetic determinants of adverse metabolic effects of glucocorticoids. Cell Metab 33: 1592-1609, 2021.

Researchers have uncovered genetic variations that predispose people to adverse metabolic side effects of commonly prescribed steroid hormones called glucocorticoids.

Toward Precision Medicine in Diabetes Treatment: Anniversary Symposium Brings Together Research Leaders to Propel Progress

The year 2021 marked the 100th anniversary of the discovery of the hormone insulin at the University of Toronto—a lifesaving discovery for people with type 1 diabetes. To commemorate this anniversary and global advances in diabetes research over the last 100 years, the NIDDK and the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism and Diabetes partnered to host a virtual symposium titled, "Heterogeneity of Diabetes: Beta Cells, Phenotypes, and Precision Medicine." The 2-day symposium brought together leaders in diabetes research for thought-provoking presentations and insightful discussions about opportunities and challenges in diabetes research.

Although diabetes has been traditionally classified as either type 1 or type 2, other subtypes of diabetes have been characterized and are now recognized. An even greater range of unrecognized subtypes likely exists, given the considerable variation in the development and clinical presentation of diabetes. Understanding this heterogeneity and providing a better understanding of the pathophysiology is the next frontier in diabetes research with the goal of tailoring prevention and treatment approaches and possibly offering a reclassification of the disease.

The symposium was organized around three major sessions. The first session on "Islet Biology in Health and Diabetes" highlighted research progress in understanding the biology of islets, the clusters of insulin-producing β (beta) cells and other cell types found in the pancreas. Scientists discussed research to elucidate how islet function is influenced by its neighboring cells in the pancreas; to engineer functional islets in the laboratory as a potential diabetes therapy or cure; and to understand how various types of stress influence the health and function of β cells.

A second session on "Heterogeneity of Diabetic Phenotypes Before and After Diagnosis—Impact on Management and Treatment" probed how diabetes varies in different individuals and the need to move away from a "one-size-fits-all" approach to management. Speakers presented research to characterize the heterogeneity in common and rare forms of diabetes; this led into discussions of efforts and ideas to bring precision medicine—designed to provide the most appropriate treatment to an individual based on genetic, metabolic, physiologic, and phenotypic factors—to diabetes in the third and final session "Precision Medicine in Diabetes."

Understanding the heterogeneity of diabetes paves the way for new approaches to prevention and treatment, helps fulfill the promise of precision medicine, and is a fitting extension of the research stemming from the seminal discovery of insulin. The NIDDK and the scientific community have made great progress in diabetes research, but the work is not done. As the century since the discovery of insulin comes to a close, the NIDDK will continue working toward finding prevention methods, better treatments and, one day, a cure for all types of diabetes.

RADIANT: The Rare and Atypical Diabetes Network

A nationwide, NIDDK-funded study will seek to discover the cause of several unusual forms of diabetes. For years, doctors and researchers have been stymied by cases of diabetes that differ from known types. Through research efforts at 20 U.S. research institutions, the Rare and Atypical Diabetes Network (RADIANT) aims to discover new forms of diabetes, understand what makes them different, and identify their causes.

A person with atypical diabetes may be diagnosed and treated for type 1 or type 2 diabetes, but not have a history or signs consistent with their diagnosis. For example, they may be diagnosed and treated for type 2 diabetes but may not have any of the typical risk factors for this diagnosis, such as being overweight, having a family history of diabetes, or being diagnosed as an adult. Alternately, a person with atypical diabetes may respond differently than expected to the standard diabetes treatments. For these reasons, diabetes management can be extremely frustrating for people with atypical forms of the disease.

RADIANT therefore provides these individuals hope for a treatment that better supports their health. Study scientists plan to screen about 2,000 people with such unknown or atypical forms of the disease. RADIANT researchers will collect detailed health information from participants using questionnaires, physical exams, genetic sequencing, and other tests. People found to have unknown forms of diabetes may receive additional testing. Some participant family members may also be invited to take part in the study. These efforts will help provide a comprehensive description of the genetic and clinical characteristics of rare forms of diabetes, and underscore diabetes as a disease with many forms. Ultimately, the data may provide a framework to establish new diagnostic criteria for diabetes, find new markers for screening, or identify drug targets for new therapies that could ultimately bring precision medicine to diabetes.

The study opened recruitment on September 30, 2020, for people with atypical diabetes or a form of diabetes that seems different from known types of diabetes. RADIANT may one day provide critical understanding of the spectrum of diabetes and improve lives of people with rare forms of the disease and of everyone who cares for them.

Visit *www.atypicaldiabetesnetwork.org* for more information on the study and how to join.

The Diabetic Foot Consortium

Funded by the NIDDK, leading U.S. research institutions have launched the first-ever multi-center network to study diabetic foot ulcers, a common and burdensome complication of diabetes and the leading cause of lower limb amputations in the United States. Up to 34 percent of people with diabetes will develop a foot ulcer in their lifetime, and half of foot ulcers become infected. Each year, about 100,000 Americans with diabetes will lose part of a lower limb because a foot ulcer becomes infected or does not heal. People with diabetic foot ulcers must manage careful at-home foot care over a long time to avoid infection until the wound heals. The Diabetic Foot Consortium (DFC) aims to lay the foundation for a clinical trial network that will address a major research gap to find ways to treat diabetic foot ulcers effectively and to prevent the risk of complicated infections and potential amputation among the more than 34 million American adults with diabetes. The DFC consists of clinical research sites that recruit patients who are undergoing foot ulcer treatment or follow-up care.

The first studies are focusing on finding biological clues, called biomarkers, that can guide treatment in people with diabetic foot ulcers and predict how the ulcer will heal or the likelihood of it returning. For example, a study led by the Indiana University School of Medicine is testing whether body fluid leaking through the skin on a newly healed ulcer can predict the likelihood of its recurrence. The DFC is also photographing the ulcers, collecting wound fluid, blood, urine, and the medical histories of patients with diabetic foot ulcers when they first come to the clinic and during their treatment. These biological samples and information will be available for future research studies to understand diabetic wound healing. An advantage of a consortium such as the DFC is the collaboration among leading investigators in the field of diabetic wound healing and clinical research, working together to participate in the same clinical study. In addition, the DFC will build a roadmap and framework that will provide an opportunity for researchers to follow up on interesting leads or pursue new studies.

For people with diabetes, foot ulcers can be complex and difficult to manage and can lead to devastating amputations. They affect quality of life and cost the United States up to $13 billion a year in care. Major obstacles to progress in the field are the diversity of wounds and complexity of causes. Finding biological clues from these ulcers to help tailor treatment to the individual will provide much-needed relief and could prevent future diabetic foot injuries.

Making Extraordinary Contributions to Type 1 Diabetes Prevention Research

To achieve the goals of preventing, treating, and curing type 1 diabetes, it is imperative to understand the causes of this autoimmune disease. There has been tremendous research progress in understanding genetic contributors to type 1 diabetes. However, genes do not tell the whole story. Intriguingly, not everyone with high-risk genes develops type 1 diabetes, and most people with type 1 diabetes do not have a family history of the disease. Thus, it is believed that environmental factors represent another important piece of the complex type 1 diabetes puzzle. In some people genetically predisposed to the disease, a "triggering" environmental agent may prompt the body's immune system to destroy the insulin-producing cells in the pancreas, leading to type 1 diabetes. Research to uncover possible environmental triggers of type 1 diabetes and other autoimmune diseases is underway in the NIDDK's long-standing The Environmental Determinants of Diabetes in the Young (TEDDY) study. The dedicated contributions of over 6,000 families who enrolled their newborns in TEDDY have made the study possible. (See inset for the story of a family participating in TEDDY.)

STUDYING ENVIRONMENTAL FACTORS INVOLVED IN TYPE 1 DIABETES

Environmental factors that may trigger type 1 diabetes in those at genetic risk include dietary components, environmental toxins, infectious agents, stress, or other factors. Finding these factors is like looking for a needle in a haystack, as people are exposed to large numbers of environmental influences each day. However, identifying these factors is critical to designing new prevention approaches. For example, if a dietary factor is found to play a role in type 1 diabetes onset, or shown to decrease the risk for the disease, then modifying one's diet could be recommended.

Recognizing the importance of investigating environmental factors that trigger or protect against type 1 diabetes in genetically susceptible children, the NIDDK—with support from the Special Statutory Funding Program for Type 1 Diabetes Research—began the TEDDY study in 2002. Since then, TEDDY has been providing a coordinated and multidisciplinary approach to investigating the possible environmental causes of type 1 diabetes.

TEDDY—AN EXTRAORDINARY COMMITMENT FROM CHILDREN AND FAMILIES

The ongoing TEDDY study is an international, long-term, ambitious effort involving many investigators and other study personnel at six research centers and a data coordinating center. During enrollment, researchers needed to screen about 425,000 newborns to find infants with genes that predicted an increased risk of type 1 diabetes. The researchers screened newborns who had a parent or sibling with type 1 diabetes (for the "first-degree relative" group), as well as newborns who did not (for the "general population" group). Since then, the scientists have been following over 6,000 of those high-risk children from birth until age 15. These "TEDDY children" are routinely monitored for the development of autoantibodies (proteins in the blood that are early markers of the autoimmune attack in type 1 diabetes) and type 1 diabetes.

The TEDDY study requires an extraordinary commitment from the participating children and their families, and provides for a comprehensive assessment over many years. As such, for 15 years, families are asked to provide regular information on their child's diet, illnesses, vaccinations, and psychosocial stresses.

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They are also asked to visit the TEDDY clinic at regular intervals—every 3 or 6 months depending on the child's age and autoantibody status—where the scientists draw the child's blood, collect urine, take other measurements (*e.g.*, weight and height), and interview parents about the child's life events. The parents also collect other biological samples at home, such as regular stool samples. Over the course of the study, the families have contributed over 3 million samples. The hope is that this treasure trove of information will enable scientists to find that needle in a haystack—environmental factors that could trigger or protect against type 1 diabetes.

TEDDY is also studying environmental triggers of other autoimmune diseases in addition to type 1 diabetes. For example, type 1 diabetes shares many risk genes with celiac disease—an autoimmune disease where the immune system responds abnormally to dietary gluten. TEDDY begins testing children for blood markers of celiac disease at age 2 and annually thereafter, so the TEDDY children are regularly monitored for both celiac disease and type 1 diabetes while researchers look for environmental triggers of both diseases.

NEW INSIGHTS EMERGING FROM TEDDY

The TEDDY study is still ongoing, but important data has already been obtained and participating children have already benefitted. For example, undiagnosed type 1 diabetes can result in a condition called diabetic ketoacidosis, a potentially fatal acute complication. TEDDY researchers demonstrated that children who develop type 1 diabetes while in TEDDY are diagnosed earlier and have lower rates of diabetic ketoacidosis compared to children diagnosed with type 1 diabetes outside of TEDDY. This earlier diagnosis is due to TEDDY's close follow-up of children, the heightened awareness of onset of diabetes, and the education the study provides to families about diabetes risk.

Additionally, TEDDY scientists have already started analyzing the precious samples provided by TEDDY families, using sophisticated "-omics" technologies to examine the gene activity, proteins, and metabolites in cells. They are also analyzing the microbes in the children's gut (*i.e.*, the gut microbiome), which have been shown to be associated with metabolism, and have reported some intriguing results about how environmental factors affect the gut microbiome as children age. For example, they identified three distinct phases of gut microbiome development: a developmental phase (3 to 14 months of age), a transitional phase (15 to 30 months of age) when the microbiome diversifies, and a stable phase (31 to 46 months of age) when the microbiome's composition is largely established. Through these and other analyses, TEDDY is expanding our understanding of child development and the human microbiome.

Knowledge already gained from TEDDY—and new findings expected in the future—would not be possible without the unwavering and long-term dedication of the TEDDY children and their families, as well as TEDDY researchers. With continued research, TEDDY's goal is to revolutionize our ability to prevent type 1 diabetes and potentially other autoimmune diseases.

JENAE'S AND KATELYN'S STORY

Katelyn (front right) pictured with her father Rod, mother Jenae, and sister Madison

Jenae and her husband, Rod, first heard of The Environmental Determinants of Diabetes in the Young (TEDDY) study when their second-born daughter, Katelyn, was only a few hours old. They were unfamiliar with type 1 diabetes when they agreed to have their newborn's blood tested in the hospital as part of TEDDY and found out that she had genes that increased her risk for developing the disease. TEDDY is examining environmental factors that trigger or protect against type 1 diabetes in genetically susceptible children—those with a family history and those without—so the TEDDY researchers invited the family to join the study. Katelyn was eligible to enroll as part of the "general population" group because she had high-risk genes but did not have a family history of type 1 diabetes.

The invitation to join TEDDY was a big ask: requesting that a family without a personal connection to type 1 diabetes enroll their newborn in a 15-year study that would require a lot of work but could help identify ways to prevent this disease. Because most people with type 1 diabetes do not have a family history of the disease, it was critical to include children like Katelyn in TEDDY. Even though it was a huge commitment, Jenae says, "It really didn't take us long to make the decision [to enroll]. We just felt like … we can be helpful, and if she ever gets diabetes, they're going to find it faster. We felt, actually, almost more safe about being involved." They did not know that their decision would have a profound impact on the health of Katelyn, now 12 years old, and on the family's lives.

KATELYN'S EARLY YEARS IN TEDDY

With Katelyn enrolled in TEDDY, the family started following the demanding protocol. "The first few years of her life, all I remember is poop," Jenae says with a laugh, referring to the fact that they had to collect monthly stool samples until Katelyn was 4 years old and then every 3 months until she was 10 years old as part of the study. They also visited the TEDDY clinic in Seattle, Washington, every 3 months until Katelyn was 4 years old and then every 6 months thereafter. Jenae shares that it was difficult watching Katelyn have her blood drawn at these visits, but they knew that the blood samples enabled the scientists to test if Katelyn had early markers (autoantibodies) of the autoimmune attack in type 1 diabetes.

Regarding participating in a clinical study, Jenae's advice to others is: "Do not be afraid to take on things like this. The work is worth it…. It's empowering."

Another challenging part of the protocol was when Katelyn started eating solid food and Jenae and Rod had to track everything that Katelyn ate and drank over a 3-day period before study visits. "The first 3 years weren't that bad because as a toddler and baby, you control all of that [food] environment…. It got a little bit trickier as she got older and was in school," Jenae

explains, discussing how they had to adjust the food log if Katelyn did not eat all her packed school lunch.

"We just felt like … we can be helpful, and if she ever gets diabetes, they're going to find it faster," says Jenae, talking about why she and her husband enrolled their daughter, Katelyn, in the TEDDY study.

Even during those busy early years, the family took everything in stride. "It really has not been a difficult thing," Jenae shares. "[TEDDY] has been brilliant this whole time. They make it very easy…. They are very friendly and engaging." Jenae also got personal satisfaction out of their hard work: "I felt scientific, like I was part of research. There was something fulfilling in that."

A DIAGNOSIS OF CELIAC DISEASE

Things drastically changed for the family when Katelyn was 3 years old. In addition to screening for type 1 diabetes, TEDDY also screens children for celiac disease—an autoimmune disease that is triggered by eating foods containing gluten and that shares the same risk genes as type 1 diabetes. Although Katelyn tested negative at her 2-year-old screening, Jenae reports that, "She scored off the chart" for celiac disease autoantibodies at her 3-year-old screening. Their personal doctor then diagnosed Katelyn with celiac disease after a blood test and a biopsy of her small intestine—the organ that is damaged by gluten consumption in people with celiac disease.

Looking back, Jenae recognizes that Katelyn was having some symptoms of celiac disease at the time of her diagnosis, but the symptoms were indistinguishable from common toddler behaviors and thus did not raise a red flag. For example, like many young children, Katelyn would say she was hungry but then not eat. Jenae says that it was only because of TEDDY that Katelyn's celiac disease was promptly diagnosed. "Every day, I am unbelievably grateful for TEDDY … and that we knew [about the celiac disease] and we were immediately able to change course."

However, changing course to implement a gluten-free diet was extremely difficult. "It was really life-altering," Jenae recalls, "I remember standing in my kitchen and crying. I didn't know what was going to poison her," referring to the small intestine damage that results when people with celiac disease eat gluten. A particular challenge came shortly after Katelyn was diagnosed and the family had to live in a hotel for 6 weeks after a kitchen fire in their home. Jenae and Rod quickly had to learn how to advocate for their daughter at restaurants to ensure that the food was gluten-free. Even with such challenges and the incredible amount of work that Jenae and her husband have had to do to navigate the complexities of celiac disease, she focuses on the positives: "That Katelyn was healthy and that TEDDY had caught [celiac disease] so early so that we would be able to keep her safe." Her advice to other parents of children with celiac disease is not to be afraid to advocate for your child and to ask for help, such as through support groups that Jenae says have been very helpful to her.

For Katelyn, the hardest part of having celiac disease is feeling left out—like when kids are eating food that she cannot eat. This was especially striking to Jenae after one of Katelyn's basketball games about 5 years ago—Katelyn was hiding her gluten-free snacks from her teammates. "My heart sank, and I thought: 'This is ridiculous. People should be able to have … amazing gluten-free food that everybody could eat.'" That was a major reason why, in 2016, Jenae decided to quit her job in banking and open a gluten-free bakery out of her home. Because she has worked so hard to make her gluten-free baked goods taste like gluten-containing foods, her bakery has been a huge success. She is thrilled to see people's joy when they have delicious birthday and wedding cakes that look and taste just like cakes they may have had before their celiac diagnosis. She loves that adults and children alike do not feel left out because of their

celiac disease. Jenae adds that providing gluten-free wedding cakes brings her much happiness by greatly reducing her clients' stress on their wedding day and, importantly, improving the lives of people with celiac disease—the reason she started the bakery in the first place. Not only is Jenae bringing joy to her clients, she is also serving as a great entrepreneurial role model for Katelyn and her older sister, Madison.

TEDDY TODAY—AND IN THE FUTURE

Today, Katelyn remains an active TEDDY participant, with the family's contributions mostly involving study visits twice a year. Jenae happily reports: "She's still negative for [type 1 diabetes] antibodies—yay!" Katelyn says that her favorite part of TEDDY is getting prizes at study visits, while the "pokes" (blood draws) are the hardest part. For the pokes, TEDDY staff give her things like a lollipop to distract her from the needle stick pain. "They do such a fabulous job of making it a kid-friendly experience," says Jenae. Katelyn also loves the TEDDY staff, many of whom have been working with them from day 1. "It feels like we're part of a big community," Jenae states. When asked if she would enroll in TEDDY again, Jenae enthusiastically says: "Yes!" Her advice to others is: "Do not be afraid to take on things like this. The work is worth it.... It's empowering."

"Every day, I am unbelievably grateful for TEDDY," says Jenae, talking about how TEDDY facilitated her daughter's diagnosis of celiac disease.

Katelyn, who loves camping, video games, playing guitar, hanging out with friends, and cheering on her beloved Seattle sports teams, will age out of TEDDY at 15 years old and will no longer be monitored for type 1 diabetes autoantibodies. Jenae admits that she is a little worried about the coming transition, as the regular monitoring has been a great comfort to the family, but she also adds: "It is fascinating to see how much is being discovered, and to be a tiny little piece of sand in that feels great."

When asked how she would feel if TEDDY found ways to prevent type 1 diabetes and celiac disease because of her participation, Katelyn's response is, "Cool."

Very few people could say that they have been active participants in a research study since birth—what an incredible legacy for Katelyn, her proud parents, and the other TEDDY participants.

PERSONAL PERSPECTIVE

Contributing to Research on Type 2 Diabetes in Youth

Once considered an adult-onset disease, type 2 diabetes is increasingly diagnosed in children and adolescents—especially in racial and ethnic minority populations—largely as a consequence of the increase in childhood obesity. To address the rising trend of type 2 diabetes in young people and develop better treatment strategies, the NIDDK launched the multi-center trial Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) in 2004. It was the first NIDDK-sponsored trial to focus on this challenging problem. The TODAY trial compared 3 treatment options for type 2 diabetes in children and teens in 15 medical centers and their affiliated sites across the United States to identify the best therapeutic strategies to combat this disease in young people. At the conclusion of the TODAY clinical research trial in 2012, participants were transitioned to an observational follow-up study, TODAY2, to assess diabetes complications. Through the TODAY and TODAY2 studies, NIDDK-supported scientists, together with hundreds of research participants, aimed to change the health trajectory of at-risk youth and positively impact the course of young people's lives. (See inset for the story of a TODAY participant.)

A RISING TREND: TYPE 2 DIABETES IN YOUTH

More than 34 million Americans—just over 1 in 10—have diabetes. It is the main cause of kidney failure, lower limb amputations, and new-onset blindness in adults, and is a major cause of heart disease and stroke. In diabetes, the body cannot keep blood sugar (glucose) levels from getting too high. Normally, the hormone insulin, which is made by the pancreas, acts in the tissues of the body (*e.g.*, muscle) to promote absorption of sugar from the blood for use as fuel. In some people, their bodies become resistant to insulin, requiring the pancreas to produce more of the hormone to keep blood sugar at a healthy level. Type 2 diabetes develops when the pancreas loses its capacity to produce enough insulin to compensate for insulin resistance.

The number of people with diabetes has risen dramatically during the last 30 years. Importantly, type 2 diabetes, which previously only affected older adults, has been rising in youth 10 to 19 years of age. The most recent data show that the growing number of young people with type 2 diabetes stems from rising incidence among racial and ethnic minority groups. Type 2 diabetes in both adults and youth is closely linked to having overweight/obesity, being inactive, and having a family history of diabetes.

IMPLICATIONS OF EARLY ONSET TYPE 2 DIABETES

The longer a person has diabetes, the greater the chances of serious damage to the eyes, nerves, heart, kidneys, and blood vessels. This aspect of diabetes makes the growing burden of type 2 diabetes in children particularly alarming, as children with this diagnosis have a greater chance of developing medical complications during their lifetimes. Prevention of type 2 diabetes in youth is therefore a key public health goal. However, optimizing type 2 diabetes treatment options is equally critical to stall the onset of complications in children who already have the disease. Given the physiological changes that occur during adolescence, it is unclear whether treatments found to be effective for controlling diabetes in adults will work as well in youth.

THE TODAY TRIAL

The TODAY trial tested how well 3 treatment approaches controlled blood sugar levels in ethnically

and racially diverse youth who were 10 to 17 years of age, had overweight or obesity, and had been diagnosed with type 2 diabetes no more than 2 years before enrollment in the study. All participants received metformin, the first-line drug of choice among adults with type 2 diabetes and the only oral diabetes medication approved for use in children. Participants were randomly assigned to receive metformin alone; metformin plus another diabetes drug, rosiglitazone; or metformin plus a program of intensive lifestyle changes aimed at helping participants lose weight and increase physical activity.

Results showed that metformin alone failed to control blood sugar in 51.7 percent of participants, and metformin plus the lifestyle intervention failed 46.6 percent of the time. Although blood sugar levels remained healthier, on average, in participants who received both metformin and rosiglitazone than in the other groups, the two-drug combination still failed an alarmingly high 38.6 percent of the time over the course of the study.

To better understand the way the disease progressed in youth in the three TODAY treatment groups, study scientists analyzed changes in participants' insulin resistance and capacity for pancreatic insulin production over the course of the trial. They found that average insulin sensitivity gradually worsened for the metformin and metformin plus lifestyle groups, while for the metformin plus rosiglitazone group it improved significantly in the first 6 months of the trial, but later gradually fell back to initial levels. Thus, at the end of the trial, average insulin sensitivity among those youth getting both medicines was about where it began, but it had worsened among those receiving just metformin or metformin plus lifestyle.

In contrast, insulin-production capacity fell similarly in all three groups. Importantly, TODAY scientists found that in all the treatment groups, the participants with the poorest blood sugar regulation and insulin production at the beginning of the trial were the ones most likely to have higher than recommended blood sugar levels when the study ended. This points to the importance of beginning treatment for pediatric type 2 diabetes before significant loss of insulin production capacity occurs and the body can no longer control blood sugar levels sufficiently. TODAY demonstrated that the development of insulin resistance and the deterioration of insulin-producing beta cell function progress more rapidly in youth-onset type 2 diabetes than in adult-onset diabetes.

THE TODAY2 FOLLOW-UP STUDY

After completion of the TODAY study, participants were transitioned to treatment with metformin and/or insulin and enrolled in TODAY2, an observational follow-up. (In 2010, the U.S. Food and Drug Administration significantly restricted use of rosiglitazone for the treatment of type 2 diabetes due to increased risk of cardiovascular events.) Study scientists assessed participants for high blood pressure, elevated blood lipid levels, and early signs of diabetic kidney disease or nerve disease annually; eye (retina) health was assessed twice. In 2020, the 500 TODAY participants who enrolled in TODAY2 were on average 27 years old with diabetes duration of 13 years. Over the course of the studies, about 67.5 percent of participants developed high blood pressure and 51.6 percent developed elevated blood lipids. Diabetic kidney disease occurred in 54.8 percent and nerve disease in 32.4 percent of participants. The prevalence of retinal disease increased from 13.7 percent to 51.0 percent over 7 years, including more advanced stages. Sixty percent had at least one complication. Although these are staggering statistics, these studies have been instrumental in furthering our understanding of type 2 diabetes in children and adolescents.

THE PROMISE OF FUTURE RESEARCH

The TODAY and TODAY2 studies had several strengths, including a large cohort of youth-onset type 2 diabetes participants and up to 15 years of prospective, comprehensive, and rigorous assessment. In addition, the cohort's diversity is representative of the general U.S. population with youth-onset type 2

diabetes. The studies indicate that more research is needed to develop effective strategies to prevent and treat this disease in vulnerable young people. Understanding what makes type 2 diabetes more difficult to treat in youth is critical to combatting the disease when it occurs in young people and preventing them from developing complications that often exact a heavy burden.

KATHRINE'S STORY

Thirty-year-old Kathrine works for a non-profit organization whose mission is to create opportunities for people to live in affordable homes, improve lives, and strengthen communities. She grew up in Cleveland under the guardianship of her grandparents. Kathrine's grandparents both have type 2 diabetes, and as a child she was used to seeing them treat themselves with medication. She describes herself as having been an overweight child, but nonetheless very active. "I never felt limited by my physical health," she says.

"These medical problems happen more often in marginalized communities because we experience the health care system differently. If my grandparents hadn't been paying attention, I could have become another statistic," says Kathrine, explaining how her grandparents noticed she was having diabetes symptoms at age 11.

However, her grandmother noticed that Kathrine appeared thirstier and more tired than normal and recognized there might be a problem. So, she took Kathrine to the hospital to have her tested—she was diagnosed with type 2 diabetes at age 11. Shortly thereafter, Kathrine and her family were informed of a new clinical trial that was about to begin that would test treatment approaches for type 2 diabetes in youth—the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study. As it turned out, a study site was located at Rainbow Babies & Children's Hospital right there in Cleveland. "These medical problems happen more often in marginalized communities because we experience the health care system differently. If my grandparents hadn't been paying attention, I could have become another statistic. But they jumped into action to make the conversation easier. It became a no-brainer for me to participate in the study," remembers Kathrine. And so, her journey began.

Kathrine became the first participant to be placed in the TODAY study's metformin and intensive lifestyle group. (Each of the participants was randomly assigned to receive either metformin alone or metformin in combination with another treatment strategy.)

The doctors and nurses involved in the study explained to Kathrine that she could make lifestyle changes such as incorporating healthy eating habits and increasing her physical activity to help control her blood sugar. This was appealing to her because she knew she did not want the burden of being dependent upon injected insulin to control her blood sugar. She thought the lifestyle changes would be helpful to achieving her many goals in life, including attending a prestigious private high school and going to college.

Kathrine was determined to take these measures to regain control of her own health, a resolution strengthened by meeting her TODAY lifestyle coach—a Black woman who happened to be from the same neighborhood in Cleveland. "I knew this was going to change my life because I have this Black woman I can relate to, looking out for me." Her coach turned her on to cooking; Kathrine had never cooked healthy foods before, and she grew to enjoy

PERSONAL PERSPECTIVE

it. Learning new skills in the kitchen, Kathrine was well on her way to improving her health. She lost 15 pounds and saw her blood sugar levels improve. "So much of the education I got from TODAY was about nutrition and that I can make the choice to eat well."

"I knew this was going to change my life," says Kathrine about meeting her TODAY lifestyle coach—a Black woman from her local Cleveland neighborhood.

After graduating from an elite private high school in Cleveland, Kathrine was accepted into and attended a university in Atlanta. The TODAY study team ensured she would have continuity of care in the trial and arranged for quarterly visits in Cleveland. As for many college students, Kathrine faced challenges during this time. She was no longer able to cook for herself in this setting—grabbing a bag of chips on the go was cheap and easy. There were also the additional stressors of college studies. Her weight fluctuated and her blood sugar spiked. Kathrine realized that she was neglecting her health during this time and needed to regain control. "Twenty-year-old me didn't realize that this is a journey, not a destination," she recalls.

Kathrine graduated with degrees in psychology and sociology and continued in the TODAY2 follow-up study. She returned for a time to Cleveland to work in grassroots community development, establishing farmers' markets and community gardens in the neighborhood where she grew up, before ultimately returning to Atlanta for work and to pursue graduate studies. Through the years, Kathrine has relied upon the lifestyle education she received in the TODAY study to help guide her choices. She joined a running club, runs several miles per day now, and cooks healthful meals for herself daily. Today, Kathrine maintains a healthy weight and, quite impressively, her blood sugar levels are below that of even being considered to have prediabetes. This, along with the fact that she no longer requires diabetes medication, is a testament to her incredible determination and dedication. This past August, Kathrine received her master's degree in communications and public policy, and she's excited to continue her career in community development and confident her future is bright and healthy.

Reflecting upon her experience in the TODAY study, Kathrine expresses extreme gratitude. She says the study team watched her grow up, tracked her progress, and provided continuity of care. "TODAY didn't complete me. It complemented me. It gave me the tools to be a better me."

Reflecting upon her experience in the TODAY trial, Kathrine expresses extreme gratitude: "TODAY didn't complete me. It complemented me. It gave me the tools to be a better me."

Diabetes does not define Kathrine. She knows now that she is in control of her own health. She's not Kathrine, the person with diabetes. She is Kathrine, the student, the professional, the runner, the home cook, the community activist—who happens to be managing risk for type 2 diabetes. She exclaims proudly: "I am not one thing. I am everything!"