

# NIDDK

Recent Advances & Emerging Opportunities

## Diabetes, Endocrinology, and Metabolic Diseases

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National Institute of  
Diabetes and Digestive  
and Kidney Diseases

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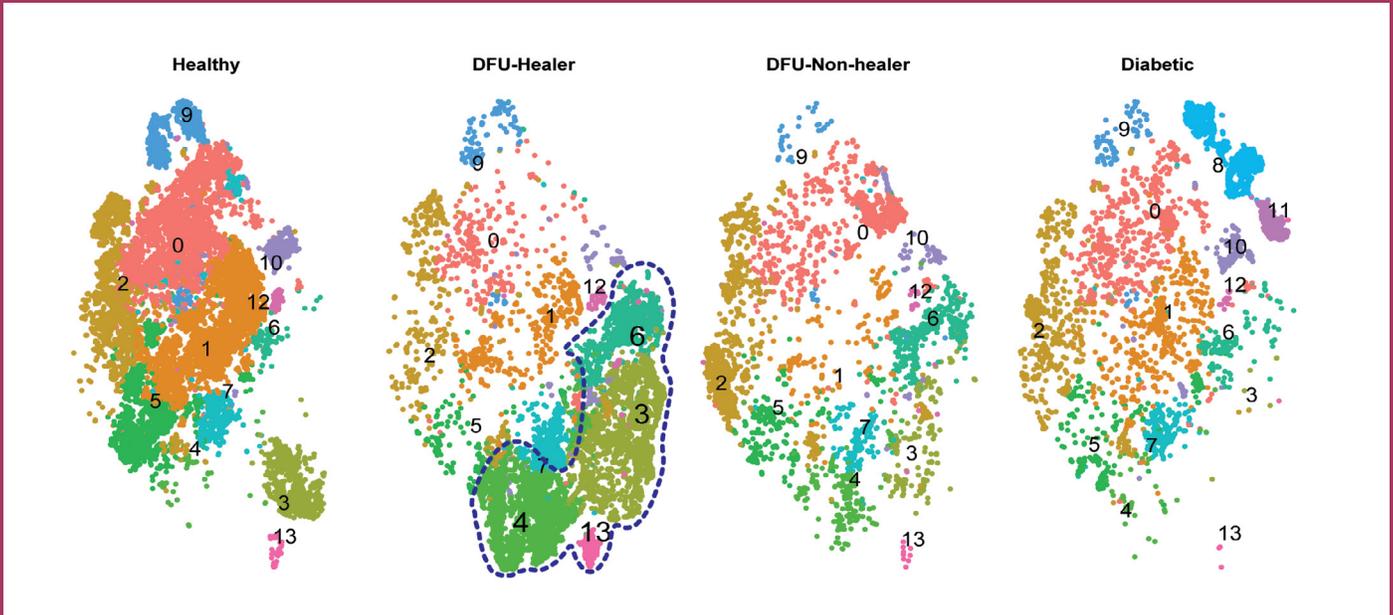
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As described in this chapter, scientists used cutting-edge technologies to perform a single-cell analysis of over 174,000 cells from the skin of four groups of people. The first group comprised individuals without diabetes (labeled “Healthy” in the figure above). The other three groups were people with diabetes who either had diabetic foot ulcers (DFUs) that healed within 12 weeks (“DFU-Healer”), had non-healing DFUs (“DFU-Non-healer”), or had no DFUs (“Diabetic”). This figure visualizes a map of the molecular characteristics of fibroblasts found in the skin of each group of individuals. Fibroblasts are a type of cell that play a major role in wound healing, and the scientists identified 14 distinct subsets of fibroblasts, represented by the different colors in the figure. Specifically, they discovered that “HE-Fibros,” a previously undescribed subset of fibroblasts, were abundant in wound beds of DFU-Healers, whereas the wound beds of DFU-Non-healers did not contain as many HE-Fibros. This finding is illustrated by the increased number of cells in the lassoed area under “DFU-Healer” and fewer cells in the equivalent position under “DFU-Non-healer.” Found only in the foot, these unique HE-Fibros promoted wound healing in DFUs by remodeling cellular structures and promoting inflammation associated with healing.

*Image provided by Dr. Aristidis Veves, Harvard University, and Dr. Manoj Bhasin, Emory University. Originally published in Theocharidis G, Thomas BE, Sarkar D,...Bhasin M. Single cell transcriptomic landscape of diabetic foot ulcers. Nat Commun 13: 181, 2022. 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 37.3 million people in the United States—or 11.3 percent of the total population—and is the eighth leading cause of death.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> Effective therapy can prevent or delay diabetic complications, but 23 percent of U.S. adults with diabetes are undiagnosed and therefore not receiving therapy.<sup>1</sup>

*Diabetes affects an estimated 37.3 million people in the United States—or just over 1 in every 10 people.<sup>1</sup> Another 96 million U.S. adults have “prediabetes,” which puts them at elevated risk of developing type 2 diabetes.<sup>1</sup> The estimated total financial cost for diagnosed diabetes in the United States in 2017 was \$327 billion.<sup>3</sup>*

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, type 2 diabetes, and gestational diabetes, a form of diabetes that develops during pregnancy but in many cases resolves after pregnancy. There are also rare forms of diabetes, known as monogenic diabetes, which are associated with specific genes.

*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.<sup>2</sup>*

Type 1 diabetes affects approximately 5 percent of adults diagnosed with diabetes and the majority of children and youth diagnosed with diabetes.<sup>1</sup> 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  $\beta$  (beta) cells of the pancreas. Thus, people with type 1 diabetes require lifelong insulin administration to regulate their blood glucose levels.

<sup>1</sup> Centers for Disease Control and Prevention. National Diabetes Statistics Report website. <https://www.cdc.gov/diabetes/data/statistics-report/index.html>. Accessed October 12, 2022.

<sup>2</sup> Cowie CC, et al., Eds. Diabetes in America, 3rd edition. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, NIH Publication Number 17-1468, 2018.

<sup>3</sup> American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care* 41: 917-928, 2018.

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 (FDA)-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  $\beta$ -cell replacement therapies, such as islet transplantation, that potentially will eliminate the need for insulin injections, toward the ultimate goal of a cure for 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 people diagnosed with diabetes in the United States.<sup>4</sup> 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. The percentage of adults with diagnosed diabetes in the United States was highest among racial and ethnic minority populations, including American Indian and Alaska Native persons, non-Hispanic Black people, and people of Hispanic origin.<sup>1</sup> 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.<sup>5</sup>

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  $\beta$ -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 96 million U.S. adults who have "prediabetes," in which blood glucose levels are higher than normal but not as high as in diabetes.<sup>1</sup> 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 it disproportionately affects youth from racial and ethnic minority populations in the United States. Results from NIDDK-supported research have 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 addition, increasing rates of type 2 diabetes may lead to more people who enter pregnancy with diabetes, and diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or development of gestational diabetes during pregnancy—is associated with an increased risk of blood glucose abnormalities in offspring. Thus, the rising rates of diabetes and prediabetes could contribute to a

<sup>4</sup> Centers for Disease Control and Prevention. What is Diabetes? website. <https://www.cdc.gov/diabetes/basics/diabetes.html>. Accessed October 12, 2022.

<sup>5</sup> Kim C, et al. Gestational diabetes and the incidence of type 2 diabetes: A systematic review. *Diabetes Care* 25: 1862-1868, 2002.

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 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. 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, type 3c diabetes, a form of diabetes that may appear after pancreatitis, has been described. 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.

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, NIDDK is vigorously pursuing studies of prevention and treatment approaches for these diseases.

## TESTING NEW TYPE 1 DIABETES THERAPIES

**New Oral Therapy for Type 1 Diabetes Can Delay Disease Progression and Lower Insulin Requirements for at Least 2 Years:** A small clinical trial has highlighted a new possible oral therapy to delay type 1 diabetes progression, as well as a potential new biological marker to monitor disease progression. In type 1 diabetes, the immune system launches a misguided attack against the insulin-producing  $\beta$  (beta) cells in the pancreas. Novel therapies to protect  $\beta$ -cells from this attack are urgently needed. Similarly, easily monitored markers of  $\beta$ -cell health are needed to warn of the earliest stages of type 1 diabetes and to predict and track disease severity.

Previous NIDDK-supported research suggested that verapamil might slow diabetes progression. Verapamil is an oral medication approved by the U.S. Food and Drug Administration (FDA) over 30 years ago to treat high blood pressure. In a small clinical trial, 24 male and female volunteers recently diagnosed with type 1 diabetes were treated with insulin and either verapamil or an inactive placebo. In 2018, scientists reported that people taking verapamil for 1 year had better insulin responses, used less insulin, and had fewer incidents of low blood glucose (sugar) than did people taking a placebo, all with no adverse effects. These results suggested that verapamil could safely improve overall  $\beta$ -cell function and might prevent  $\beta$ -cell loss.

Now, new research has detailed a year-long extension of this trial. In the trial’s second year, the verapamil-treated group was split into two subgroups: one continued taking verapamil, while the other stopped. Those who used verapamil for 2 years maintained their  $\beta$ -cell health and continued to need reduced levels of insulin compared to the group that never took verapamil. However, those who stopped the drug after 1 year saw their  $\beta$ -cell health decline and their insulin needs rise, demonstrating that verapamil’s benefits required continuous use. Researchers also found that levels of a protein called chromogranin A (CHGA) in the blood may be a promising biological marker for poor  $\beta$ -cell health. Specifically, they found that CHGA blood levels were elevated in people with type 1 diabetes compared to people without the disease. CHGA levels dropped substantially in people who took verapamil, but remained high in those who took the placebo, suggesting that CHGA levels reflect changes in  $\beta$ -cell health in response to verapamil treatment. Thus, CHGA levels might be a simple way to track type 1 diabetes initiation, progression, and/or response to treatment.

*A small clinical study has found that the oral medication verapamil may help preserve  $\beta$ -cell health in those newly diagnosed with type 1 diabetes.*

These findings may lead to new options to diagnose, treat, and monitor type 1 diabetes. Future studies will be needed to better characterize both verapamil’s safety and effectiveness, as well as CHGA’s usefulness as a marker of  $\beta$ -cell health.

*Xu G, Grimes TD, Grayson TB, ...Shalev A. Exploratory study reveals far reaching systemic and cellular effects of verapamil treatment in subjects with type 1 diabetes. Nat Commun 13: 1159, 2022.*

## RESEARCH TOWARD IMPROVING TREATMENT OF TYPE 2 DIABETES

### Study Demonstrated Two Diabetes Drugs Are More Effective Than Others in Long-term Treatment:

A large clinical trial comparing four commonly used blood glucose (sugar)-lowering medications found that glargine and liraglutide were more effective than sitagliptin or glimepiride at achieving and maintaining blood glucose levels within the recommended range when added to treatment with metformin. The study also examined each drug's side effects and impact on development of diabetes-related cardiovascular disease over an average of a 5-year period.

People with diabetes who keep their blood glucose levels in the near-normal range have a much lower risk of developing diabetes complications. Metformin is the first-line treatment, but, over time, people with type 2 diabetes may need another glucose-lowering drug, and there is no consensus on which drug to choose. Launched in 2013, NIDDK's Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) study was designed to directly compare four U.S. Food and Drug Administration (FDA)-approved, glucose-lowering drugs' long-term effectiveness. The study enrolled 5,047 participants from diverse racial and ethnic groups who had type 2 diabetes, were already taking metformin, and did not have established cardiovascular complications. Participants were randomly assigned to take one of four drugs: glargine, sitagliptin, liraglutide, or glimepiride.

After an average of 4 years, the researchers found that, in combination with metformin, all four drugs had a beneficial effect, but glargine and liraglutide were best at keeping blood glucose levels in the recommended range. However, they found that it was difficult to maintain the recommended glucose levels in nearly three-quarters of all participants over 4 years, showing type 2 diabetes' aggressive nature. In terms of side effects, severe hypoglycemia (dangerously low blood glucose) was uncommon but affected more participants receiving glimepiride, and gastrointestinal symptoms were more common in those receiving liraglutide. None of the drugs had robust effects on lowering the risk of cardiovascular disease over an average of 5 years, but the researchers found that participants taking liraglutide were least likely to experience any cardiovascular disease overall compared to the other groups.

*The GRADE study findings confirm the usefulness of glargine and liraglutide, in combination with metformin, in the treatment of people with type 2 diabetes and help health care providers make evidence-based recommendations when guiding long-term management of type 2 diabetes.*

The GRADE study closes important gaps in knowledge regarding the use of glucose-lowering drugs in people who are already taking metformin and confirms the usefulness of glargine and liraglutide in the treatment of people with type 2 diabetes. Unfortunately, a now-available class of diabetes drug called SGLT2 inhibitors was not FDA-approved at the launch of GRADE recruitment and was not included in the study, so questions remain as to how SGLT2 inhibitors would perform against the four drugs tested in the trial. The study also demonstrated a need for more effective treatments for long-term management of type 2 diabetes. NIDDK stands uniquely poised to support comparative effectiveness trials like GRADE to help people with type 2 diabetes and their providers make evidence-based treatment decisions that lead to better health.

*Nathan DM, Lachin JM, Balasubramanyam A,...Younes N; for the GRADE Study Research Group. Glycemia reduction in type 2 diabetes—glycemic outcomes. [N Engl J Med](#) 387: 1063-1074, 2022.*

*Nathan DM, Lachin JM, Bebu I,...Younes N; for the GRADE Study Research Group. Glycemia reduction in type 2 diabetes—microvascular and cardiovascular outcomes. [N Engl J Med](#) 387: 1075-1088, 2022.*

### New Insights into Body Fat Tissue and Weight Gain Induced by Type 2 Diabetes Drugs:

Studying two forms of a master molecular regulator of body fat tissue, PPAR $\gamma$ , researchers discovered that, in mice, one form is associated with weight-gain side effects of a type 2 diabetes drug—a finding with implications for new treatment strategies. PPAR $\gamma$  is central to fat tissue development in mice and humans and is involved in other biological processes related to diabetes and metabolism. It is also the target of type 2 diabetes drugs called thiazolidinediones (TZDs), which activate PPAR $\gamma$  to improve blood glucose (sugar) levels but lead to unwanted weight gain. The two forms of PPAR $\gamma$  in mice and humans, PPAR $\gamma$ 1 and PPAR $\gamma$ 2, differ slightly in structure. While there were hints of other differences from earlier research, specific functional distinctions were not clear. Hoping for new insights that could lead to improved therapies, a team of researchers set out to study these two forms of PPAR $\gamma$  more closely.

For their research, the scientists designed a series of experiments and generated male mice that were deficient in one or the other form of PPAR $\gamma$  to identify any differences. Because PPAR $\gamma$  is known to control the activity of many genes, the researchers examined gene regulation in the mice and found that PPAR $\gamma$ 1 and PPAR $\gamma$ 2 regulate distinct sets of genes in various body fat tissues. They also identified other functional differences between PPAR $\gamma$ 1 and PPAR $\gamma$ 2. Most intriguingly, when the researchers gave a TZD drug to mice deficient in PPAR $\gamma$ 1, they discovered that the mice had improved blood glucose levels without the usual drug-induced weight gain. Although deficient in PPAR $\gamma$ 1, these mice still had PPAR $\gamma$ 2, so the researchers concluded that PPAR $\gamma$ 2 is sufficient for the drug's benefits, while PPAR $\gamma$ 1 must be responsible for the weight-gain side effect.

This research in mice brings to light previously unknown features of fat tissue and new understanding of weight gain caused by some type 2 diabetes drugs. If further studies show that PPAR $\gamma$ 1 and PPAR $\gamma$ 2 function similarly in humans, researchers may be able to develop drugs that specifically target one of PPAR $\gamma$ 's forms to treat diabetes with fewer side effects.

*Hu W, Jiang C, Kim M,...Lazar MA. Isoform-specific functions of PPAR $\gamma$  in gene regulation and metabolism. Genes Dev 36: 300-312, 2022.*

## RESEARCH ON DIABETES COMPLICATIONS

### **New Insights into Relationships Between Genetic Risk Factors for Type 2 Diabetes and Metabolic Conditions:**

A new study found that groups of genetic variations that increase the risk of type 2 diabetes may also influence the risk of developing associated metabolic conditions. Type 2 diabetes increases people's risk of developing serious and often life-threatening complications, such as cardiovascular disease and kidney failure. Because there is so much variability in whether or not individuals with type 2 diabetes develop these clinical outcomes, better understanding of genetic risk factors and the associated complications could help advance personalized patient care and improve prevention and treatment approaches.

In previous research, scientists used data from a large-scale cohort study to identify genetic variations that predispose an individual to type 2 diabetes and were able to group them into several subgroups based on the type of genetic mechanisms that led to the disease. For instance, within the group of genetic

variations that affect the body's glucose (sugar) uptake and increase insulin resistance, the scientists identified three subgroups, or "clusters," that also increase people's risk for obesity, lipodystrophy (a disorder that affects how the body accumulates and stores fat), and disrupted liver lipid metabolism. In this new study, the research team analyzed individual-level genetic data from a total of 454,193 participants, including 25,015 individuals with type 2 diabetes, in 13 cohort studies to determine whether these clusters were also associated with other clinical outcomes such as high blood pressure, coronary artery disease, and reduced kidney function. Even though all clusters included genetic variations that increase type 2 diabetes risk, there were differential associations with cardiovascular disease risk and kidney function. For example, coronary artery disease risk was decreased in the disrupted liver lipid metabolism cluster, whereas the risk was higher in the lipodystrophy cluster. Clusters for obesity and lipodystrophy were both associated with higher blood pressure, and the disrupted liver lipid metabolism cluster was associated with reduced kidney function.

Although not yet ready for use in a clinical setting, knowing whether and how someone with type 2 diabetes genetic risk factors could be predisposed to cardiovascular diseases or metabolic conditions could one day be a useful tool for not only predicting disease risk and informing patient management, but also classifying participants for clinical studies. Further research to clarify relationships between type 2 diabetes genetic risk, cardiovascular risk, and metabolic function will also provide insight into complex biological mechanisms underlying type 2 diabetes and may even lead to new targets for drug development.

*DiCorpo D, LeClair J, Cole JB,...Udler MS. Type 2 diabetes partitioned polygenic scores associate with disease outcomes in 454,193 individuals across 13 cohorts. Diabetes Care 45: 674-683, 2022.*

### **Type 2 Diabetes Prevention Strategies May Not Provide Protection Against Cardiovascular Diseases in Adults:**

New findings from the Diabetes Prevention Program Outcomes Study (DPPOS) show that weight reduction through lifestyle changes or taking metformin, a medication that controls high blood glucose (sugar) levels to treat type 2 diabetes, may not provide additional protection against cardiovascular diseases in people with diabetes or at high risk of diabetes (prediabetes).

The Diabetes Prevention Program (DPP) was a landmark trial that transformed the way we approach type 2 diabetes prevention. Launched in 1996, the

randomized controlled clinical trial recruited a diverse cohort of people at high risk for type 2 diabetes and demonstrated that the disease can be effectively prevented or delayed through lifestyle interventions (moderate physical activity aimed at reducing weight) or with metformin. Even though the trial was completed in 2001, the ongoing DPPOS continues to follow most DPP participants, and the data show that lifestyle changes or metformin treatment continues to provide long-term benefits in preventing or delaying type 2 diabetes even after two decades. Because people with type 2 diabetes are at increased risk for cardiovascular events such as heart attacks and strokes, the DPPOS researchers sought to determine whether lifestyle changes or metformin can also prevent or delay cardiovascular episodes. In this new analysis, they found that, surprisingly, neither lifestyle interventions nor metformin had a significant impact, either beneficial or unfavorable, on the incidence of cardiovascular events despite the improvement of cardiovascular risk factors in the lifestyle intervention group. One of the reasons behind this result could be that more time is needed for these interventions to show a beneficial effect on cardiovascular health. Other potential explanations include the DPPOS participants receiving a less intensive lifestyle intervention than in DPP, as well as their extensively using out-of-study medications, including those that lower blood lipid (fat) levels and blood pressure. These medications may have diluted the differences between study groups. This suggests that even though metformin and lifestyle intervention reduce the risk of type 2 diabetes, they may not be effective against cardiovascular disease when blood glucose, lipids, and blood pressure are well controlled.

Continuing to investigate the effects of metformin and lifestyle interventions on cardiovascular health will help optimize diabetes prevention and care and may provide important clues to cardiovascular disease prevention. Further research is needed to better understand and clarify the long-term effects of these interventions.

Goldberg RB, Orchard TJ, Crandall JP, ...Temprosa M; on behalf of the Diabetes Prevention Program Research Group. *Effects of long-term metformin and lifestyle interventions on cardiovascular events in the Diabetes Prevention Program and its outcome study.* *Circulation* 145: 1632-1641, 2022.

**Early and Intensive Control of Blood Glucose Is Associated with Reduced Risk of Diabetic Foot Ulcers in People with Type 1 Diabetes:** New findings from a long-standing observational study show, for the first

time, that risk of diabetic foot ulcers (DFUs) is decreased by controlling blood glucose (sugar) levels early and intensively in individuals with type 1 diabetes. DFUs commonly occur in people with diabetes and can lead to lower extremity amputation, which is associated with high mortality. Prevention, if possible, is the best course of action, as current treatment options are limited. Identifying DFU prevention strategies is critical to improve the health and quality of life of people with type 1 diabetes.

Previous studies have suggested a link between high blood glucose levels and the risk of DFUs and lower extremity amputations in people with type 1 diabetes. However, questions remained as to whether intensive control of blood glucose could affect the risk of DFUs or amputations. Fortunately, NIDDK's Diabetes Control and Complications Trial (DCCT) and its ongoing observational follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, provided a rare and exciting opportunity to answer these questions. Completed in 1993, DCCT was the first randomized controlled trial to show that intensive treatment to keep blood glucose levels as near to normal as safely possible can reduce risk for several diabetic complications, including retinopathy (a form of eye disease), neuropathy (nerve damage), and kidney disease. The intensive treatment involved more frequent insulin administration and blood glucose monitoring than was conventional at the time. EDIC has continued to study the health of the majority of the DCCT participants for nearly 3 decades and has shown additional benefits of the intensive treatment. In this new analysis, researchers found that those whose blood glucose levels were intensively managed during the DCCT were less likely to develop DFUs starting at an average of 17 years from when the DCCT began. Additional analysis revealed several risk factors that put individuals at greater risk of DFUs: higher average glucose levels (as measured by hemoglobin A1c [HbA1c]), older age, albuminuria (having too much albumin in urine, which is a sign of kidney disease), cardiovascular autonomic neuropathy (damage to nerves in the heart and blood vessels), and retinopathy.

*Diabetic foot ulcers can now be added to the list of diabetic complications that may be preventable through early and intensive control of blood glucose levels in people with type 1 diabetes.*

This study suggests that controlling blood glucose levels intensively and early in the disease course is beneficial for people with type 1 diabetes to reduce long-term risk of DFUs, confirming the importance of early intervention to prevent diabetic complications. Further research on the risk factors identified may help predict who is at increased risk of DFUs and lower extremity amputations and guide appropriate prevention strategies in a timely manner.

Boyko EJ, Zelnick LR, Braffett BH,...de Boer IH; for the DCCT/EDIC Research Group. Risk of foot ulcer and lower-extremity amputation among participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. *Diabetes Care* 45: 357-364, 2022.

### **A Comprehensive Map of Cells from Diabetic Foot Ulcers Reveals Factors Critical for Successful Wound Healing:**

Researchers used state-of-the-art technologies to develop a detailed and comprehensive view of diabetic foot ulcers (DFUs) at the cellular and molecular level and revealed elements that promote successful wound healing. DFUs are a devastating complication of diabetes with limited treatment options. Even though most foot ulcers heal with appropriate management, recurrence is common after initial healing and, in worst cases, leads to lower extremity amputations, significantly affecting quality of life and putting a huge financial burden on the health care system. Improved knowledge about how wound healing occurs in DFUs is needed to identify novel treatment approaches that promote healing in a timely manner and prevent further complications.

*By studying differences between diabetic foot ulcers that heal and those that do not, researchers discovered a subset of cells that promote successful wound healing.*

In new research, scientists used cutting-edge technologies to perform a large-scale, single-cell analysis of over 174,000 cells from the foot, forearm, and blood to examine the cells from men and women with DFUs that healed within 12 weeks versus those with non-healing DFUs. They observed major differences in the types of cells found in different sites of the body and in different DFUs. Specifically, they discovered that a previously undescribed subset of fibroblast cells, which they called “HE-Fibros,” were abundant in wound beds of healing DFU samples. Found only in the foot, these unique cells promoted wound healing by firmly attaching to the structures between cells, remodeling

those structures, and communicating with immune cells to promote inflammation associated with healing. In contrast, non-healing DFUs did not contain as many HE-Fibros and instead showed signs of dysregulated chronic inflammation associated with impaired healing. Additionally, healing DFUs and non-healing DFUs showed types of inflammation and immune signatures that were significantly distinct from each other. For instance, immune cells called M1 macrophages, which promote inflammation and wound healing, were largely present in healing wounds, whereas the majority of the macrophages found in non-healing wounds were M2 macrophages, which suppress inflammation.

Exactly how DFUs form and heal is still not completely understood, but these new data identify specific cells that are important for wound healing in DFUs and provide insights into the roles they play in inflammation, as well as how they might interact with other cells to encourage an environment favorable to wound healing. Further studies of these cellular and molecular signatures will not only help identify the “foot at risk” of chronic ulcers or amputations, but also provide a recipe for successful wound healing in DFUs, which may lead to new treatment approaches.

Theocharidis G, Thomas BE, Sarkar D,...Bhasin M. Single cell transcriptomic landscape of diabetic foot ulcers. *Nat Commun* 13: 181, 2022.

## **STUDYING LINKS BETWEEN STRUCTURAL RACISM AND DIABETES HEALTH DISPARITIES**

**Effects of Historic Redlining Persist To Elevate Risk of Death from Diabetes:** A recent study investigated the effects of historic residential redlining practices on current health outcomes, focusing on death rates from diabetes and premature death due to diabetes. The study showed significantly worse health outcomes in those who lived in “redlined” areas that were previously graded as less desirable, compared to those who did not, with this negative impact on health persisting for decades. Formalized in 1934 by the Federal Housing Administration and prohibited later in 1968, residential redlining was the systemic practice of denying various services, such as credit access and insurance, to residents of neighborhoods—populated primarily by racial and ethnic minority groups—that were graded as “declining” and “hazardous” in maps created by the Home Owners’ Loan Corporation (HOLC). Recent data show persistent effects of structural racism and inequities, such as

redlining, on various health outcomes, including mental health, preterm birth, and COVID-19 outcomes.

In new research, scientists sought to determine whether people with chronic medical needs and high medical cost burden, such as people with diabetes, are disproportionately and negatively impacted by historic redlining. Their analysis combined three sets of data—a digitized copy of the HOLC map of Seattle, Washington; census data; and data on mortality rate and years of life lost (an estimate of the average years a person would have lived if they had not died prematurely). They found that mortality rate and years of life lost in general were significantly higher in areas with exposure to worse HOLC grading, showing clinically meaningful differences in health outcomes. However, these differences were much bigger when they examined mortality and years of life lost specifically due to diabetes, showing an approximately 50 percent increase in the rate of diabetes mortality in areas with a 1-unit-higher HOLC grade (e.g., those with a “hazardous” rather than a “declining” grade); similar results were observed for years of life lost. Results also showed persistence of these differences over the course of 25 years from 1990 to 2014, even though redlining was formally prohibited in 1968.

*The historic and persistent effects of redlining may put individuals with diabetes at an elevated risk of early death and demonstrate the long-term negative impact of structural racism on health outcomes. This finding highlights the urgent need for targeted interventions that will stop perpetuating inequities in order to reduce diabetes health disparities.*

Current residents in areas with previous exposure to redlining are more likely to experience social risk factors such as poverty, discrimination, and poor educational attainment and employment opportunities. While this study does not establish redlining as a direct cause of increased diabetes mortality, it is the first study to show that redlining, as a surrogate for structural racism, can be a critical link between structural racism and diabetes disparities. It also highlights the important role that our living environment and social factors play in health and diabetes care, while underscoring the urgent need to identify and implement targeted interventions that will stop perpetuating inequities in order to close the gap on diabetes health disparities.

Linde S, Walker RJ, Campbell JA, and Egede LE. Historic residential redlining and present-day diabetes mortality and years of life lost: The persistence of structural racism. *Diabetes Care* 45: 1772-1778, 2022.

## UNDERSTANDING CELL SIGNALING AND COMMUNICATION

### **A Novel Protein Complex May Influence Diabetes**

**Development:** Scientists discovered a new complex of proteins that regulate the function of insulin-producing  $\beta$  (beta) cells and may influence the development of type 1 and type 2 diabetes. Hormones—signaling molecules that act on distant tissues and organs—regulate many physiological and behavioral processes, so elucidating their roles is critical to understanding health and disease. A previously identified hormone, fatty-acid-binding protein 4 (FABP4), has been shown to be released by fat cells (adipocytes) during times of starvation as these cells break down their stored fat for use as energy for the body, and FABP4 levels have been strongly associated with cardiometabolic disease. FABP4’s exact role, however, has been unclear.

In this new study, scientists discovered that FABP4 joins with two other proteins—adenosine kinase and nucleoside diphosphate kinase—to form a novel complex they named “Fabkin.” To determine the role of Fabkin, the scientists used two mouse models of diabetes. In a model of type 1 diabetes, they observed that Fabkin increased both shortly before and during disease development, suggesting that it may have a role in  $\beta$ -cell failure and disease pathogenesis. Interestingly, blocking Fabkin preserved  $\beta$ -cell mass and function, protecting against development of type 1 diabetes. In a mouse model of type 2 diabetes, blocking Fabkin improved control of blood glucose (sugar) and prevented the disease. To determine whether Fabkin had a role in diabetes in humans, the investigators looked at its levels and found that serum Fabkin was increased in individuals with new-onset type 1 diabetes compared to individuals without diabetes. In older people with type 1 diabetes with various durations of disease, serum Fabkin correlated with levels of hemoglobin A1c (HbA1c; a measure of blood glucose levels over time), suggesting that it is associated with control of blood glucose levels. Additional experiments to understand the underlying mechanisms of how Fabkin exerts its effects suggested that the hormone complex couples energy levels with a metabolic response to regulate the function of  $\beta$ -cells.

This important discovery of Fabkin and its novel mechanism to integrate energy status with regulation of metabolism has revealed a promising new therapeutic target to combat metabolic diseases, including type 1 and type 2 diabetes. Further research on Fabkin and its impacts on human health and disease will be required to capitalize on these exciting results.

Prentice KJ, Saksi J, Robertson LT,...Hotamisligil GS. A hormone complex of FABP4 and nucleoside kinases regulates islet function. *Nature* 600: 720-726, 2021.

**New Insights on Cell-to-cell Communication—miRNA “Zip Codes”:** Researchers have identified short genetic sequences on microRNAs (miRNAs) that help determine which miRNAs are retained by the cell that produced them and which are released to affect other cells. This knowledge provides important new insights into cell-to-cell communication and could inform the development of therapies for diseases associated with miRNA dysfunction. miRNAs are very short RNA molecules involved in regulating gene activity and play a role in both health and disease; miRNA dysfunction has been linked to type 2 diabetes, obesity, and other diseases. miRNAs may be retained by their parent cell or released in exosomes—small cellular delivery packages that transfer miRNAs and proteins from one cell to another. However, the mechanisms by which cells determine which miRNAs go where are not understood.

To address this gap in knowledge, scientists examined miRNAs in exosomes secreted by different types of mouse cells grown in the laboratory, including fat cells (adipocytes), liver cells, and other cells, finding that each cell type secreted different miRNAs in their exosomes. Additionally, some miRNAs were more likely to be found in exosomes, while others were mostly retained by the cell that produced them, suggesting a mechanism of miRNA sorting. To understand how the sorting occurred, the scientists studied whether specific genetic sequences in miRNAs determined whether they were packaged into exosomes or retained by cells—was there a “zip code” telling the cell where miRNAs should go? Indeed, experiments identified several short sequence motifs associated with miRNAs either being released in exosomes (called EXOmotifs) or retained by cells (called CELLmotifs); interestingly, each of the cell types studied used different sequence motifs, suggesting that there is no one universal exosome “addressing” system. The scientists next confirmed the importance of these motifs by showing that genetically modifying an miRNA’s sequence motif “zip code” changed its location.

For example, adding an EXOmotif to one of the cellular miRNAs promoted its release into exosomes. This redirection of miRNAs led to changes in gene activity in the recipient cells, suggesting that altering these sequence motifs to change the location of miRNAs could be used to affect downstream cellular activity.

These results provide new understanding about how cells sort miRNAs and communicate with one another. Further understanding of the mechanisms underlying miRNA sorting could facilitate new approaches for miRNA-based therapies for a variety of diseases.

Garcia-Martin R, Wang G, Brandão BB,...Kahn CR. MicroRNA sequence codes for small extracellular vesicle release and cellular retention. *Nature* 601: 446-451, 2022.

**Cellular Aberrations Associated with Insulin Resistance in People Without Diabetes:** Researchers have discovered a large network of cellular alterations in people with insulin resistance but without diabetes. Insulin resistance is a major risk factor for the development of metabolic syndrome and type 2 diabetes, and the impact of insulin resistance on metabolic syndrome is well studied. However, many people without diabetes have insulin resistance, and the molecular determinants underlying this remain elusive.

In this study, researchers generated myocytes—a type of muscle cell that absorbs glucose (sugar) in response to insulin—from blood samples of 20 individuals without diabetes but with a range of insulin sensitivities. Ten individuals had insulin resistance (I-res), while the others had insulin sensitivity (I-sen), and both groups were equally divided between men and women. Individuals with I-res had elevated blood glucose levels compared to their I-sen counterparts, and an assessment of insulin-stimulated glucose uptake by the laboratory-grown myocytes showed this was significantly impaired in I-res cells compared to I-sen cells. Next, the team analyzed the spectrum of cellular signaling changes among these samples. The results indicated large differences in molecular signatures in cells based on I-res status and that many of the alterations in these I-res cells overlapped with alterations observed in cells from individuals with type 2 diabetes in a previous study by the same group. Many of these alterations were found in biological pathways not previously known to be involved in insulin signaling. Moreover, the researchers found striking molecular differences between cells from men and women, many of which occur in diabetes and could contribute to sex-specific differences in physiology and disease.

These findings indicate critical points of regulation of cellular processes in insulin resistance that can potentially serve as novel sites for future therapeutic development. Further research is needed to clarify how sex-specific differences in molecular signatures affect normal physiology and the risk of metabolic disease between men and women.

Haider N, Lebastchi J, Jayavelu AK, ...Kahn CR. Signaling defects associated with insulin resistance in nondiabetic and diabetic individuals and modification by sex. *J Clin Invest* 131: e151818, 2021.

## ADVANCING PARATHYROID DISEASE DIAGNOSIS AND TREATMENT

**Case Studies Identify New Autoimmune Form of Parathyroid Hormone Impairment:** A recent case study has identified how a misguided autoimmune reaction to the parathyroid hormone type 1 receptor (abbreviated PTHR or PTH1R) can cause parathyroid hormone (PTH) resistance, a condition that can cause serious disruptions of the body's mineral levels. Normally, PTH helps control calcium and phosphorus levels. PTH resistance occurs when the body fails to respond to PTH, causing high calcium levels and low phosphorus levels in the blood.

Most cases of PTH resistance are congenital, due to genetic mutations or gene-related effects on one of the signaling proteins that mediates PTH activity. However, the PTH resistance of two women referred to the National Institutes of Health Clinical Center did not fit this pattern, prompting researchers, including those with the NIDDK Intramural Research Program, to dig deeper into the cause of their symptoms. Though these two women demonstrated classic signs of PTH resistance—high calcium levels, low phosphorus levels, and other common symptoms such as muscle cramps, tingling, and numbness—these symptoms had started later in life, and the women did not have genetic traits known to cause PTH resistance. Additionally, the women had elevated PTH levels that were difficult to correct with standard medication regimens. The scientists tested the women's blood to look for autoimmune irregularities and found that both women had high levels of antibodies directed against PTH1R, which were impairing the receptor's ability to bind PTH. Further tests also found that the women had higher-than-usual levels of an immune cell type sometimes seen in other autoimmune diseases.

Together, these results identified how autoimmunity against PTH1R can lead to PTH resistance. Further

research will be needed to determine how common this cause of PTH resistance is, and, since both people in this case study were Black women, whether it is affected by ancestry or biological sex. These findings could also have important implications for PTH resistance treatment, suggesting that people with an autoimmune-associated form of the condition may benefit from immune-suppressing therapies.

Mandl A, Burbelo PD, Di Pasquale G, ...Weinstein LS. Parathyroid hormone resistance and autoantibodies to the PTH1 receptor. *N Engl J Med* 385: 1974-1980, 2021.

**Novel Computational Pipeline Approach Leads to Discovery of Possible New Treatments for the Endocrine Disorder Hyperparathyroidism:** Scientists recently used a new strategy to identify, screen, and test possible new drugs to treat hyperparathyroidism by targeting the parathyroid hormone type 1 receptor (abbreviated PTHR or PTH1R) protein. Overactive PTHR signaling can result in hyperparathyroidism, an endocrine disorder in which the parathyroid gland makes too much parathyroid hormone. This hormone is vital for maintaining normal calcium and vitamin D levels and for proper bone turnover. However, excess parathyroid hormone works through its receptor, PTHR, to cause elevated calcium levels in the blood, which can lead to health problems such as bone thinning and kidney stones.

Seeking new ways to treat hyperparathyroidism, researchers devised a computational pipeline approach to identify and screen for compounds to affect PTHR's function. Using a series of computer models and simulations, researchers predicted how various parts of the PTHR protein interact with each other. This approach identified specific sites on PTHR that were "druggable" (i.e., where a small molecule could bind and change the receptor's shape and function). Scientists then used another set of simulations to screen a library of compounds virtually, looking for those predicted to bind well to the identified sites on PTHR. This computational strategy identified several promising compounds, and one of these compounds, Pitt12, was tested in both cells grown in the lab and in male mice. In both sets of experiments, Pitt12 inhibited the effects of parathyroid hormone, possibly by disrupting PTHR's interactions with other signaling proteins. In mice, Pitt12 also reduced blood calcium levels, indicating that this compound might be useful in preventing the elevated calcium levels associated with hyperparathyroidism. Preliminary experiments also suggested that Pitt12's

inhibitory effects on PTHR did not seem to extend to other similar receptors tested. Such specificity would be desirable in a therapeutic, though additional experiments will be needed to determine Pitt12's suitability for further drug development.

*Researchers devised a new computational pipeline to identify and screen for compounds to treat the disorder hyperparathyroidism.*

In addition to identification of Pitt12, this study also provided broadly valuable information on PTHR. This data could inform work on drugs targeting this receptor for other purposes, such as treating bone and mineral disorders. The researchers' new computational pipeline approach could also be adapted to identify small molecules targeting receptors other than PTHR, and thus could improve the drug development process for a wide variety of diseases.

*Sutkeviciute I, Lee JY, White AD,...Villardaga J-P. Precise druggability of the PTH type 1 receptor. Nat Chem Biol 18: 272-280, 2021.*

# Research on Type 2 Diabetes in Youth

Type 2 diabetes affects many millions of adults in the United States, but it has also been increasing in children and young adults. The SEARCH for Diabetes in Youth (SEARCH) study, a joint effort supported by NIDDK and the Centers for Disease Control and Prevention, revealed that while type 2 diabetes is still uncommon in young people, its numbers have been rising steadily as a result of the obesity epidemic, especially among racial and ethnic minority populations and populations with low socioeconomic status.

Children with type 2 diabetes are at higher lifetime risk than adults of developing serious diabetes complications such as blindness, kidney failure, diabetic foot ulcers, strokes, and heart attacks because their likelihood increases with duration of diabetes. According to the SEARCH study, almost three out of four teenagers and young adults with type 2 diabetes already have at least one complication or associated health condition. What makes these statistics truly devastating is that these young people are experiencing debilitating and life-threatening complications during what should be the most productive period of their lives.

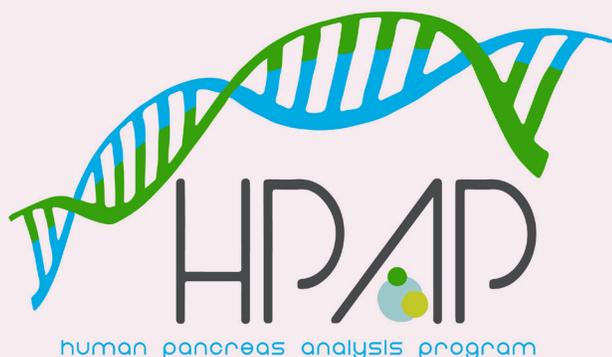
Unfortunately, we now also know that some of the medications most commonly used to treat type 2 diabetes in adults are either not as effective in controlling blood glucose (sugar) or have not been well studied in young people with the disease. For example, the NIDDK-supported Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial has shown that neither the most commonly used adult type 2 diabetes drug, metformin, nor a lifestyle intervention program was sufficient to control the disease in young people. TODAY also demonstrated that insulin resistance (an impaired response to insulin that both precedes and accompanies the disease) was greater and loss of insulin-producing  $\beta$  (beta) cell function occurred much more rapidly in youth-onset type 2 diabetes than when the disease arises during

middle age. These findings have been reinforced by similar results from another NIDDK-funded research effort, the Restoring Insulin Secretion (RISE) Consortium, again highlighting the urgent need to identify better treatment options for young people with type 2 diabetes.

To address this growing public health challenge, NIDDK continues to support and stimulate research to shed more light on the mechanisms underlying youth-onset type 2 diabetes and to determine what makes it so difficult to treat. TODAY2, an ongoing observational study, is providing long-term follow-up data on the progression of type 2 diabetes and various complications in participants from the TODAY trial. Data from TODAY2 may help identify and understand the unique factors that accelerate type 2 diabetes progression in youth so that researchers can leverage that knowledge to slow down or stop progression of the disease.

Another research area of particular interest is prevention. Given how aggressive and difficult to treat the pediatric form of the disease is, it is crucial to find effective prevention methods and better ways to detect the earliest warning signs of the disease so that treatment can begin before significant disease progression has occurred. Therefore, NIDDK issued a funding opportunity announcement in 2021 to create a clinical consortium to further study the disease in youth. The consortium will aim to recruit a large, diverse cohort of young people at risk for diabetes and gather data that may improve our ability to predict those with highest risk of developing the disease and increase our understanding of the factors that drive progression to type 2 diabetes in youth. This knowledge may one day help guide future development of effective prevention and treatment approaches to reduce the burden type 2 diabetes places on young people with the disease.

## Human Pancreas Analysis Program— New Insights into Diabetes



Diabetes occurs when the body's blood glucose (sugar) levels are too high. Glucose is the body's main source of energy and comes from the foods we eat. Normally, the hormone insulin, which is made by the pancreas, acts in tissues of the body to promote glucose absorption from the blood for use as fuel. In type 1 diabetes, the body's immune system launches a misguided attack on the insulin-producing cells of the pancreas, destroying them and leading to a rise in blood glucose levels. The onset of type 1 diabetes can be predicted using autoimmune and genetic markers. However, approaches to prevent or modify disease development are needed. Progress in this area could be greatly facilitated by a deeper understanding of the physical and functional organization of the human pancreatic environment and the interactions between the pancreas and the immune system at the cellular and molecular level.

To fill this knowledge gap, in 2016 NIDDK established the Human Pancreas Analysis Program (HPAP), an integral component of the Human Islet Research Network (HIRN). HPAP's initial aims were to procure pancreata from people with and without type 1

diabetes to conduct extensive cellular analyses and to generate integrated molecular signatures of the human pancreas at various stages of disease progression, providing information on type 1 diabetes risk and development.

In addition to performing in-depth characterizations of the pancreatic tissue ecosystem, an overarching goal of HPAP investigators is to accumulate, analyze, and distribute high-value datasets to the diabetes research community through a searchable database called PANC-DB. The latest version of PANC-DB, called version 2.0, was released in May 2022, and it provides researchers with an intuitive search interface and the ability to perform interactive analyses and comparative studies of diverse datasets. PANC-DB 2.0 offers new and improved capabilities enabling the diabetes research community to explore HPAP data more effectively while also providing a model for open-access data sharing.

Based on the success of HPAP's original focus on human type 1 diabetes, NIDDK announced in 2018 an expansion of HPAP to include the study of pancreata recovered from tissue donors with type 2 diabetes and related metabolic disorders. Type 2 diabetes develops when the body becomes resistant to the effects of insulin and the pancreas loses the capacity to produce enough insulin to keep blood glucose at a healthy level. The goal of this HPAP expansion is to better understand the molecular mechanisms responsible for pancreatic cell dysfunction in type 2 diabetes by studying pancreatic tissue from people with the disease using a range of experimental approaches and technologies.

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These two efforts are now referred to as HPAP-T1D and HPAP-T2D, and they are integrated in the HIRN consortium. Many of the HPAP investigators are involved in both of these programs, which greatly facilitates shared data management and comparison of the pathophysiology of these two types of diabetes. Both the HPAP-T1D and the HPAP-T2D teams collect tissues from diverse donor populations to explore differences in how these diseases manifest in and affect populations with different backgrounds.

Data produced and new biological insights gained through HPAP's efforts will help advance the common goals of diabetes researchers to improve understanding of disease origins and progression and may ultimately lead to new strategies to reverse or prevent disease.

## Understanding the Pancreas, Inside and Out: Efforts in Pancreatic Disease

*This Feature also appears in the “Digestive Diseases and Nutrition” chapter.*

The pancreas is a key player in many diseases, including diabetes and digestive diseases such as pancreatitis. Understanding the various roles of the pancreas in human health and disease—and how pancreatic diseases interact with each other—is therefore an important NIDDK research goal. In addition to supporting a robust investigator-initiated research portfolio on pancreatic diseases, NIDDK also continually seeks to identify and encourage study in areas of new opportunity. From establishing research consortia to encouraging dialogue between scientists with complementary expertise, NIDDK uses a multi-pronged approach to facilitate and pursue the most compelling research, with the long-term goal of reducing the burden of disease and improving public health.

The pancreas is an elongated gland behind the stomach, close to the first part of the small intestine, and it has two main functions, called the “endocrine” and “exocrine” functions. The pancreatic endocrine functions are carried out by structures called islets, which make the hormones insulin and glucagon that help regulate the body’s blood glucose (sugar) levels. Meanwhile, the pancreatic exocrine cells make digestive enzymes that break down food in the intestine. When either of these functions is compromised, serious disease can result. In type 1 diabetes, for instance, the body loses the ability to make insulin due to a misguided autoimmune attack on the pancreatic islets, leading to a lifelong need to take insulin. Also, any disruptions of the carefully orchestrated steps needed to safely produce and secrete digestive enzymes can cause inflammation of the pancreas (pancreatitis). Pancreatitis has many underlying causes, and this disease can be either

acute (short term) or chronic (long lasting). Both forms of pancreatitis can lead to complications, including damage to the pancreas and other organs.



### PROMOTING COLLABORATION TO UNDERSTAND THE PANCREAS AS A WHOLE

Traditionally, diseases related to endocrine and exocrine pancreatic functions—such as diabetes and pancreatitis, respectively—have been treated by different medical specialists and studied by different researchers. Increasingly, however, scientists are finding that intricate and crucial crosstalk occurs between the pancreas’s endocrine and exocrine functions as the body co-regulates digestion and metabolism. This crosstalk can also be seen in how disruptions in one function can adversely affect the other, such as when diabetes arises after chronic or acute pancreatitis. However, the mechanisms underlying these relationships and how they affect both health and disease are not fully understood.

To encourage discussion and investigation of the connections between the endocrine and exocrine pancreatic functions, NIDDK hosted a workshop on this topic in June 2022. This workshop, titled “Integrated Physiology of the Exocrine and Endocrine Compartments in Pancreatic Diseases,” brought together researchers from the endocrine and exocrine

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pancreas research communities to share new findings and expertise. Scientific presentations highlighted cutting-edge research on pancreas anatomy and physiology, as well as the latest perspectives on the links between endocrine and exocrine pancreatic disease. Researchers also discussed available tools for holistic analysis of the pancreas and identified knowledge gaps and key steps needed to support further study of its interdependent functions. The workshop's chairs closed the session with a plan to summarize and submit the workshop's proceedings for publication.

## INVESTIGATING LINKS BETWEEN TYPE 1 DIABETES AND PANCREATITIS

Another NIDDK effort to shed light on the links between different pancreatic diseases is the Type 1 Diabetes in Acute Pancreatitis Consortium or T1DAPC. Formed in 2020, the Consortium's purpose is to study type 1 diabetes and other forms of diabetes that occur during or after one or more episodes of acute pancreatitis. The T1DAPC is composed of 10 clinical centers and one data coordinating center, which will support the T1DAPC's main clinical effort: the Diabetes RElated to Acute pancreatitis and its Mechanisms (DREAM) study.

DREAM's main goal is to understand the connections between pancreatitis and diabetes. High blood glucose during acute pancreatitis can sometimes last only a few weeks before getting better, or it can persist and lead to a diabetes diagnosis. Diabetes can also appear a year or more after the acute pancreatitis has resolved. Little is known, however, about how often or why diabetes occurs in these situations. The DREAM study is designed to answer some of these questions, helping researchers better understand what types of diabetes develop after acute pancreatitis and who is at risk. The DREAM study began recruiting participants in fall 2021 and is expected to continue recruiting through summer 2024.



## FACILITATING NEW CLINICAL TRIALS IN PANCREATITIS

There are currently no U.S. Food and Drug Administration (FDA)-approved drugs to treat recurrent acute and chronic pancreatitis. Thus, there is an urgent need to develop effective therapies for these diseases, as well as a growing interest in best practices for pancreatitis clinical trials. To help address these needs, in July 2022, NIDDK—with additional support from the National Pancreas Foundation and participation of the FDA—held a 1-day workshop on clinical trials in recurrent acute and chronic pancreatitis.

This workshop covered a range of topics centered on the opportunities and challenges of designing and conducting patient-focused pancreatitis clinical trials. Presentations by researchers, as well as NIDDK and FDA staff, discussed considerations for designing successful trials, from identifying appropriate participant populations to defining suitable outcome measurements. Also covered were topics such as integrating patient perspectives, resolving ethical considerations, and forming successful public-private partnerships. Participants were also informed about currently available opportunities for investigators, including early-stage investigators. The final panel discussion focused on identifying knowledge gaps and ways to move the field forward. NIDDK developed a summary of the workshop for publication, and ideas gained from the workshop will help inform future NIDDK research directions.

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## **MOVING PANCREATIC DISEASE RESEARCH FORWARD**

As researchers study the pancreas's various roles in disease, their findings continue to highlight previously unappreciated connections between digestive and metabolic health. As described above, NIDDK is taking a holistic approach to advancing the study of pancreatic diseases, seeking to improve public health by promoting collaborative research, supporting important clinical trials, and encouraging the development of new treatments for pancreatic diseases.

## Advancing Research on Artificial Pancreas Devices for Type 1 Diabetes Treatment

In type 1 diabetes, the insulin-producing  $\beta$  (beta) cells of the pancreas are destroyed by a misguided immune system attack. People with the disease must measure blood sugar (glucose) levels throughout the day and night and administer insulin to survive. While insulin therapy helps keep blood sugar from climbing too high, it brings with it the risk of potentially life-threatening episodes of hypoglycemia (dangerously low blood sugar). The risk of hypoglycemia can complicate keeping blood sugar within the range recommended to reduce the risk of long-term complications such as blindness and heart, kidney, and nerve disease.

A major goal of NIDDK-supported research has been to develop technologies, such as artificial pancreas devices (also called closed-loop systems or bionic pancreas), that help people manage their type 1 diabetes and keep their blood sugar levels in a healthy range while lowering the risk of hypoglycemia. Recent progress was reported from an NIDDK-supported clinical trial testing the iLet<sup>®</sup> Bionic Pancreas, a closed-loop system that requires minimal input from the user. Such research advances have relied on the contributions of dedicated volunteers with type 1 diabetes participating in clinical trials testing new and emerging technologies for managing blood sugar levels. (See inset for the story of a participant in the iLet<sup>®</sup> Bionic Pancreas clinical trial.)

### RESEARCH TO DEVELOP CLOSED-LOOP TECHNOLOGIES

Historically, people with type 1 diabetes have administered insulin through multiple daily injections or through an insulin pump, and most people with the disease continue to use those management strategies today. In more recent years, scientists have made significant progress on developing closed-loop technologies that aim to automate type 1 diabetes management. These systems consist of a continuous glucose monitor (CGM) that measures blood sugar levels, an insulin pump, and a computer algorithm on the device itself or through a smartphone app that calculates the amount of insulin needed based on the CGM's data and instructs the pump to deliver it. These features of closed-loop technology enable people with type 1 diabetes to achieve recommended blood sugar levels without the enormous burden associated with older methods of type 1 diabetes management—thus improving their health and quality of life.

In 2016, the U.S. Food and Drug Administration (FDA) approved Medtronic's MiniMed<sup>™</sup> 670G, making it the first commercially available closed-loop system in the United States. In 2019, the FDA approved a second closed-loop device, the Tandem Control-IQ<sup>™</sup> system. More recently in 2022, the FDA approved the Omnipod<sup>®</sup> 5 Automated Insulin Delivery System. NIDDK-supported research contributed to the early development or testing of these devices.

# PERSONAL PERSPECTIVE

Many other closed-loop systems are now under development and being tested in clinical trials, as it is important to give people with type 1 diabetes—who have diverse needs and range in age from very young children to older adults—a variety of available devices so they can choose one that best fits their needs.

## DEVELOPING AND TESTING A BIONIC PANCREAS DEVICE

The iLet® Bionic Pancreas (abbreviated here as Bionic Pancreas) was first developed by researchers at Boston University and Massachusetts General Hospital with support from NIDDK and the Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program), which NIDDK administers.

One feature of the Bionic Pancreas is that it requires minimal input from the user. For example, to initiate the device, users input only their body weight. Another example is that the Bionic Pancreas does not require counting carbohydrates, which affect blood sugar levels more than other foods do. Instead, it only requires that people input the meal type (breakfast, lunch, or dinner) and whether the carbohydrates at that meal are “usual for me, more, or less.” The device’s computer algorithms, which were designed to adapt to users’ needs, then calculate the insulin dosing.

A randomized controlled clinical trial conducted at 16 sites across the United States and supported by the Special Diabetes Program tested a Bionic Pancreas device that delivers insulin. (Another version of the Bionic Pancreas, not tested in this trial, delivers both insulin and its counteracting hormone, glucagon.) An important aspect of the trial was that it specifically included participants from groups who can be underrepresented in clinical research, including individuals from racial and ethnic minority populations, people with low income and education levels, and people with high hemoglobin A1c (HbA1c)

levels (a measure of average blood sugar levels) that put them at increased risk for developing long-term complications.

The researchers assigned over 300 participants, aged 6 to 79 years, to an intervention group that used the Bionic Pancreas or to a control group in which participants practiced their usual care by using their own diabetes management strategies (e.g., insulin injections, insulin pump, or a commercially available closed-loop system). After the 13-week trial, the researchers reported that both children and adults using the Bionic Pancreas showed improvements in HbA1c levels compared to participants in the control group. This is an encouraging result, as improved HbA1c levels over time have been shown to correspond with fewer diabetes complications. Trial results also showed that Bionic Pancreas users spent more time with their blood sugar levels in the recommended target range. Importantly, these benefits were achieved without increasing the occurrence of hypoglycemia. These exciting results suggest that the Bionic Pancreas outperformed the control group’s usual care.

## HOPE THROUGH RESEARCH

NIDDK continues to support research to improve and test closed-loop technologies to develop next-generation devices, with a focus on testing artificial pancreas use in groups for which blood sugar control is particularly challenging, such as racial and ethnic minority populations, children, adolescents and young adults, older adults, pregnant women, and people who have frequent, severe episodes of hypoglycemia. Research is also ongoing toward improving technology adoption in individuals from underrepresented backgrounds with type 1 diabetes. Continued research could give people with type 1 diabetes a range of available devices to address their unique management needs.

## Lauryn's Story



Lauryn participated in an NIDDK-supported clinical trial testing an iLet® Bionic Pancreas

When Lauryn was in eighth grade, she listened to a lesson on diabetes given at her medical magnet middle school in her hometown of Jacksonville, Florida. This information helped her when, a couple of weeks later, she started experiencing the symptoms of type 1 diabetes that she had just learned about. “I had frequent urination, I was thirsty, and I was falling asleep in class,” Lauryn recalls. “Normally, I never fall asleep in class.” Because of her lesson, she was confident that she had type 1 diabetes, even before her diagnosis was confirmed.

Adjusting to life with type 1 diabetes as an adolescent “was definitely rough,” Lauryn says. She remembers how tough it was for her to always think about when

to take insulin and how much to take depending on what she was eating. Another challenge for Lauryn was that when her blood sugar levels fell, she felt terrible. Because she feared having low blood sugar, “I’d try to keep my [blood] sugar on the higher side and not take as much insulin as I needed to,” she admits. As a result, her hemoglobin A1c (HbA1c) levels were about 9 percent, while the recommended level is below 7 percent.

Lauryn was not alone—most teenagers and young adults with type 1 diabetes have higher than recommended HbA1c levels. This worrisome trend underscores the importance of research to identify strategies to help young people manage their disease and improve their short- and long-term health.

***“It was probably one of the best things that has happened.... It introduced me to an easier life,” says Lauryn, talking about how participating in a Bionic Pancreas clinical trial showed her a less burdensome approach to managing her type 1 diabetes.***

Lauryn’s opportunity to contribute to that research came in the summer of 2021 when she was 20 years old. She got a phone call from one of her health care providers at Nemours Children’s Health, Jacksonville. He encouraged her to join a new clinical trial being done at Nemours—one of 16 participating U.S. sites—that was testing an iLet® Bionic Pancreas device (Bionic Pancreas). Until then, Lauryn had only used multiple daily insulin injections for managing her type 1 diabetes, but she was interested in trying a system with an insulin pump. “I thought it would make life easier, so I didn’t have to do injections all the time,” she says. Lauryn signed up for the 13-week trial and was happy she was randomly selected for an arm of the trial that would test the Bionic Pancreas.

# PERSONAL PERSPECTIVE

Lauryn feels that joining the trial was the right choice. “It was probably one of the best things that has happened” since her type 1 diabetes diagnosis, she says. “It introduced me to an easier life.” Lauryn explained that one big advantage of being on the new device was that it greatly reduced the number of needed injections. With the Bionic Pancreas, she only had to change the needle at her insulin infusion site once every 3 days—a dramatic decrease from the six insulin injections each day she was administering before the trial.

Another major benefit was that her HbA1c levels drastically improved by the end of the trial—decreasing from about 9 to 7 percent. When asked if the HbA1c improvement made her feel better, she responds, “I felt like it did. I wasn’t as tired, and I was more active.” Another plus was that she used less insulin while on the Bionic Pancreas. Although the insulin and other supplies she used as part of the trial were paid for by the research study, paying for insulin and other diabetes management supplies is a challenge for her and her mom. Not only was she able to further type 1 diabetes research through her participation in the trial, but she also says she benefitted from the helpful break from the costs of managing her diabetes.

Lauryn notes that there were some aspects of the device that did not work well for her. For example, she disliked the wire that delivered insulin because it got caught on things. She also did not feel that the feature that eliminated carbohydrate counting worked well for her all the time, though she did like it in some instances. Such research participant feedback is important because it helps scientists improve devices to enhance patient satisfaction.

***“I wasn’t as tired, and I was more active,” says Lauryn, speaking about how she felt after her hemoglobin A1c levels dramatically improved during her participation in a clinical trial.***

Overall, Lauryn appreciated that the Bionic Pancreas helped improve her health while reducing the burden of managing her type 1 diabetes. Importantly, it also introduced her to a new way of managing her diabetes other than injecting insulin. As a result, at the end of the trial when she had to return the Bionic Pancreas to the researchers, she decided to start using a commercially available insulin pump. At the time of this interview, Lauryn’s health insurance had stopped covering her commercial pump, so she was back to using insulin injections. “I’m trying to stay as healthy as I can until I get back on the pump,” she says.

An unexpected benefit of the trial was the bond that Lauryn developed with the research team. “I really enjoyed working with them,” she says. Lauryn particularly bonded with a Senior Clinical Research Coordinator at Nemours whom she worked with very closely during the trial, and the Coordinator has become a mentor. “She’s an endocrinologist, and I want to be a reproductive endocrinologist, so there’s a lot of things I could learn from her. That was a great aspect of doing the trial,” Lauryn says.

Now a 21-year-old senior in college, Lauryn is majoring in chemistry/pre-med with a minor in physics. She plans to attend medical school, pursue that goal of becoming a reproductive endocrinologist, and work as a physician on a military base. When she’s not busy studying, she enjoys going to theme parks or watching videos of them—she loves their atmosphere and the feeling they give of being away from the real world.

“I would encourage everyone to try a clinical trial at least once,” Lauryn says. She explains that research is important to her because “we need to know if things will work or if things won’t work.” In particular, she thinks it was important for her to participate in the Bionic Pancreas clinical trial as a person of color. “For me to have done the trial, I feel like it will show other people who look like me: ‘I can do it too. I can be healthy and have diabetes,’” she says. “It’s about helping my culture, helping my community, and showing them there are other people out there

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just like me with diabetes living a healthy life, living a normal life.... I'm definitely glad that I did the trial."

***Lauryn thinks it was important for her to participate in the Bionic Pancreas clinical trial as a person of color. "For me to have done the trial, I feel like it will show other people who look like me: 'I can do it too. I can be healthy and have diabetes.'"***

In the true spirit of a person with a calling to help others, Lauryn has also spent time online sharing

her experiences of living with type 1 diabetes and educating others about the disease. She says that when she was first diagnosed, she felt alone. "I didn't see a lot of people like me with diabetes, but then I realized there *are* a lot of people out there like me with diabetes." She shares her experiences with others to help them realize that they aren't alone.

Through her participation in the Bionic Pancreas clinical trial and her sharing of her personal experiences of living with type 1 diabetes, Lauryn is making a positive impact on the lives of other people with the disease. And at 21, she is just getting started.

## Contributing to Research on Gestational Diabetes Mellitus

Pregnancy can be a joyous time. But it also places significant stress on the body. During pregnancy, virtually every organ system works harder to support the developing fetus, and the resulting physiological changes can induce adverse metabolic conditions in the pregnant person. For example, hormones produced by the placenta can prevent the body from using insulin effectively, which can cause sugar (glucose) to build up in the blood instead of being absorbed by cells. In some cases, blood sugar levels can rise during pregnancy to an extent that results in the diagnosis of a condition called gestational diabetes mellitus (GDM). GDM is a form of diabetes that is distinct from type 1 or type 2 diabetes, as it develops during pregnancy and usually resolves after pregnancy. However, GDM is known to confer short- and long-term health risks to pregnant people and their children, including babies with high birth weight, delivery complications, and a greater risk of developing type 2 diabetes and obesity. Traditional approaches to diagnosing GDM include a screening test 24 to 28 weeks into pregnancy, but research suggests that this may be too late to counteract some of the lasting adverse impacts of GDM. The NIDDK-supported study Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs) aims to address critical questions about GDM screening and diagnosis, toward improving the health of mothers and their children. (See inset for the story of a GO MOMs participant.)

### SETTING THE STAGE—THE HAPO STUDY

In 2008, the landmark NIH-funded Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study released findings of health issues associated with blood sugar levels during pregnancy that were above

normal (hyperglycemia) but not high enough to meet the traditional definition of GDM. In this prospective, observational study, the HAPO researchers studied a racially and ethnically diverse cohort of more than 23,000 pregnant women and their babies and found that elevated maternal blood sugar levels below those that would qualify as GDM were associated with multiple adverse outcomes for mother and child. These complications included high birth weight for the infants and the need for caesarean delivery. Because the HAPO participants' blood sugar levels, though elevated, did not meet the traditional diagnostic criteria for GDM, they were not treated for the disease.

In 2010, HAPO results led an international panel of experts to recommend new diagnostic criteria for GDM. However, these criteria were not widely used in the United States, largely due to findings from an NIH-convened expert panel that pointed out knowledge gaps regarding best treatment strategies using these alternate criteria and the need for more research. Additionally, the uncertainty regarding long-term health impacts of elevated blood sugar levels below the traditional threshold for GDM remained.

### PAVING THE WAY FOR CONTINUED RESEARCH ON GDM—THE HAPO FOLLOW-UP STUDY

Realizing the critical insights that could be gleaned from further study of HAPO participants, researchers began the HAPO Follow-up Study (HAPO FUS), funded by NIDDK with additional support from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. HAPO FUS enrolled more than 4,800 mother-child pairs from the original HAPO study and collected additional data 10 to 14

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years post-delivery to better understand the long-lasting effects of elevated maternal blood sugar levels. Mothers were evaluated for type 2 diabetes and prediabetes, and children were assessed for overweight and obesity using body mass index (a ratio of weight to height), body fat percentage, and waist circumference. Their blood sugar levels were also evaluated. In 2019, HAPO FUS researchers reported that the adverse outcomes of even modestly elevated blood sugar levels during pregnancy extend more than a decade. Among participating mothers whose pregnancies during HAPO met, in retrospect, the alternate criteria for GDM (although not traditional criteria), more than half of these women developed type 2 diabetes or prediabetes. Among participating children, the researchers found that the likelihood of developing obesity was significantly greater among those born to mothers whose pregnancies were affected by GDM based on the alternate criteria. Moreover, those children were also more likely to develop insulin resistance, a risk factor for type 2 diabetes.

## THE PROMISE OF FUTURE RESEARCH—GO MOMS

The HAPO FUS findings are important because they demonstrate that elevated maternal blood sugar levels below those traditionally defined as GDM are associated with long-term adverse health effects for mothers and children. However, knowledge gaps and research opportunities remain regarding how blood sugar metabolism changes across the entire course of pregnancy and if screening for and treating GDM earlier in pregnancy could reduce these health risks.

To address these important questions and build upon previous research, in 2021, NIDDK established the GO

MOMs study to improve GDM screening and diagnosis by better understanding blood sugar levels throughout pregnancy. The study, which is taking place at 9 sites throughout the United States and is ongoing, aims to enroll more than 2,000 women without diabetes in their first trimester of pregnancy and is using continuous glucose monitoring (CGM) technology to map blood sugar levels throughout pregnancy. CGM devices measure blood sugar levels every 5 minutes. Participants are asked to wear the device for 10 days at four different times during their pregnancy to provide the researchers with a picture of how blood sugar levels are changing over time. The study also uses oral glucose tolerance tests—a measure of how well a person's body is processing sugar—as a tool to diagnose GDM. By understanding more about blood sugar levels during pregnancy, the hope is that researchers can identify potential early indicators of GDM and pinpoint the best times to screen for and treat it. Because GDM disproportionately affects those from racial and ethnic minority populations, another important goal of the study is to recruit diverse participants so that results are applicable across affected groups.

The importance of GO MOMs is underscored by recent data showing that rates of GDM are rising in the United States, climbing 30 percent between 2016 and 2020.<sup>1</sup> Additionally, as other NIDDK-supported studies have shown the devastating impacts of type 2 diabetes in youth (see Feature in this chapter), GO MOMs and other future research could improve the health of future generations to come.

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<sup>1</sup> Gregory ECW, et al. *Trends and characteristics in gestational diabetes: United States, 2016–2020*. Centers for Disease Control and Prevention. *National Vital Statistics Reports*; vol. 71 no. 3, 2022.

## Angelica's Story



Angelica, pictured here with her son, participated in an NIDDK-supported clinical study to better understand how blood sugar levels change during pregnancy

Thirty-two-year-old Angelica is a teacher in the Chicago Public School system, and she recently graduated with a master's degree in English as a Second Language, to complement her first master's degree in Urban Education. "I'm the type of person who has to stay busy all the time!" she says. For the first 8 years of her career, Angelica taught seventh graders before transitioning out of the classroom and into a leadership role managing her school's bilingual program. After spending this first part of her career helping children, she decided the time was right to have a little one of her own, and she became pregnant with her first child in the summer of 2021.

At Angelica's first pre-natal doctor's appointment, medical staff approached her about enrolling in the Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs) study at Northwestern University. Diabetes runs in her family, and Angelica started thinking about the impact that gestational diabetes (GDM), if she were to develop it, could have on her and her baby's health. She wanted to do whatever she could to navigate her pregnancy as healthfully as possible. "Pregnancy can be scary. But the more information we have, the more we can advocate for the little humans inside of us. This is a service to my little one," Angelica says. She also acknowledged a heartbreaking reason she wanted to participate in this study—her partner of 8 years recently passed away from stage 4 cancer. He was a staunch proponent of research and had recognized the importance of people participating in clinical studies to advance medicine. In honor of him, she made the commitment to join GO MOMs. Angelica had advocated for her partner's health throughout his treatment, and now she wanted to do the same for their baby. And so, her journey through pregnancy and the GO MOMs study began.

***"Studies like GO MOMs empower us as pregnant women to have access to information, resources, and support that allow us to advocate for our little ones throughout the entire pregnancy," says Angelica.***

As a standard part of the study protocol, Angelica traveled to the study site at Northwestern several times throughout her pregnancy to be fitted with a continuous glucose monitor. A continuous glucose monitor measures blood sugar levels every 5 minutes. The device used in this study is about the size of a large coin, and it adheres to the body for 10 days. After 10 days, she simply returned it to the study site by mail for analysis or she dropped it off at one of her

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scheduled appointments. Angelica said these study site visits were always very quick and hassle-free. While the monitor did fall off twice, requiring her to return to have another one put on, she says she didn't mind because she knew how important this information gathering was to the success of the study. Also, as part of the protocol, she had two separate oral glucose tolerance tests—one test early on and one later in the pregnancy. This test required her to drink a sugary beverage and measured how well her body processed the ingested sugar. While Angelica didn't care for the taste of the drink much at all, during the final test she felt her baby move. "It was so rewarding knowing I was doing this to protect the health of my baby," she shared.

***"They were great at making me feel important. I felt they genuinely cared about me and my little human," says Angelica, referring to the GO MOMs study staff.***

Throughout her participation, only the study staff had access to the blood sugar data, and Angelica did not see the test results. Test results were only released to a participant if the results showed that she developed GDM. Thankfully, Angelica had a smooth pregnancy and never developed GDM. In May 2022, she delivered a healthy baby boy. Study staff were at the hospital to record her newborn baby's physical measurements including birth weight, length, and skinfolds (a fast, non-invasive method to explore infant nutritional status).

In describing her experience with study staff, Angelica says "they were great at making me feel important.

I felt they genuinely cared about me and my little human ... there was a strong relationship built over a short amount of time." She added that many people don't enjoy going to the doctor, "but I loved going to all of my GO MOMs appointments. When my participation ended at delivery, I thought 'I'm really going to miss you!'"

Reflecting upon her experience in this study, Angelica says she realizes how fortunate she was to have had access to this type of research that many others do not. "Studies like GO MOMs empower us as pregnant women to have access to information, resources, and support that allow us to advocate for our little ones throughout the entire pregnancy," she remarked. Results from GO MOMs are expected to shed critical new light on how blood sugar levels change throughout pregnancy, toward improving GDM diagnosis and treatment.

***"It was so rewarding knowing I was doing this to protect the health of my baby," says Angelica, speaking about her participation in the GO MOMs study.***

Angelica is back to work now and plans to take a couple of years off from furthering her education to enjoy being a mom. But her ambition knows no bounds. In the future, she plans to pursue doctoral studies and achieve her dream of becoming a school principal. As both a dedicated educator and a research participant in the GO MOMs study, Angelica has already had a tremendous impact on future generations.