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Diabetes, Endocrinology, and Metabolic Diseases

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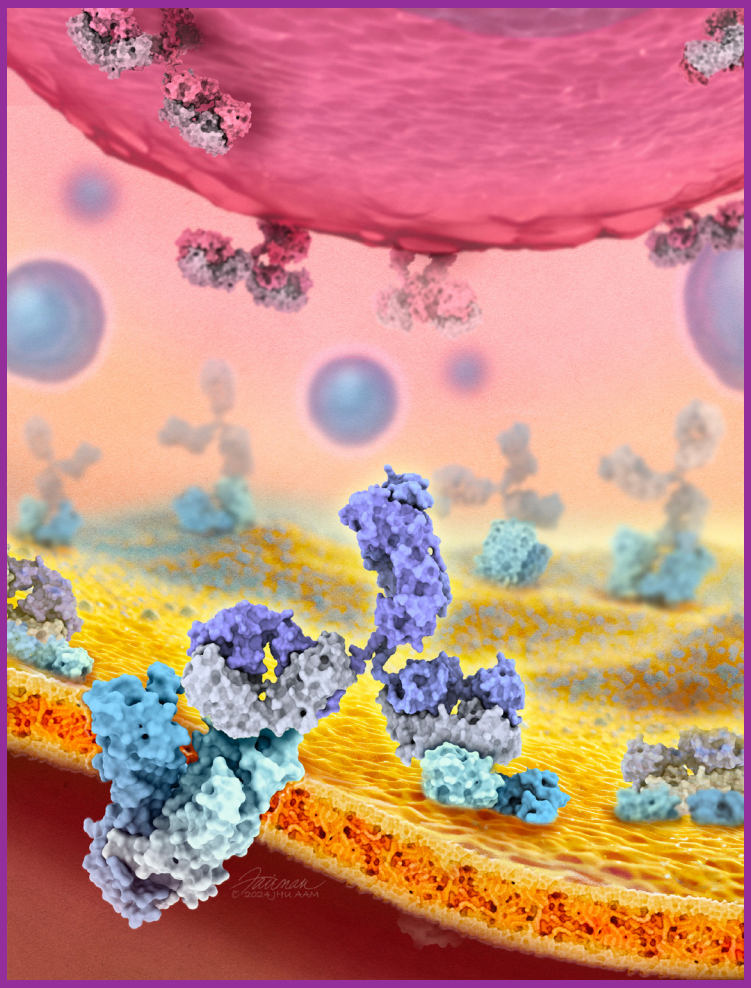

In type 1 diabetes, the immune system attacks and destroys insulin-producing β (beta) cells of the pancreas, so researchers are studying ways to thwart this attack. As described in this chapter and depicted in this artist's rendition, scientists showed that an antibody drug (the purple and grey wishbone-shaped molecule at center) binds to a protein called zinc transporter 8 (ZnT8, light blue molecules at lower left and right) that is found on the surface of β cells (indicated in yellow/orange at bottom). Antibody binding to ZnT8 shields β cells from attack by destructive immune cells (pink cell at top of image) and prevents type 1 diabetes in a mouse model of the disease. Because ZnT8 is a major target of the autoimmune attack in human type 1 diabetes, this therapeutic approach holds promise for being translated to people.

This image illustrates the mechanism by which a cell surface ZnT8 antibody shields the insulin-producing β-cell from antigenic exposure to the B-cell receptor of autoreactive B cells, leading to the induction of regulatory T cells within the pancreatic islet. The artwork is by Jennifer E. Fairman of the Department of Art as Applied to Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD. This visual depiction corresponds to Fig. 6L in the article Kasinathan D, Guo Z, Sarver DC, et al. Cell-Surface ZnT8 Antibody Prevents and Reverses Autoimmune Diabetes in Mice. Diabetes. 2024;73(5):806-818. doi:10.2337/db23-0568.

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, thyroid dysfunction, 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 38.4 million people in the United States—11.6 percent of the total population—and is the eighth leading cause of death.[1] Although overall rates of diabetes-related complications have declined substantially in recent years, disease burden remains significant, as the number of people with diabetes is still very high.[2] Diabetes can affect many parts of the body and is associated with serious complications, such as heart disease and stroke, blindness, kidney failure, and lower-limb amputation. In addition to these human costs, the estimated total financial costs of diagnosed diabetes in the United States in 2022—including costs of medical care, disability, and premature death—was $413 billion.[3] Effective therapy can prevent or delay diabetic complications, but 23 percent of U.S. adults with diabetes are undiagnosed and therefore not receiving therapy.[1]

Diabetes affects an estimated 38.4 million people in the United States—over 11 percent of the population. Another 97.6 million U.S. adults have "prediabetes," which puts them at elevated risk of developing type 2 diabetes.

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone that is necessary for cells to absorb and use glucose (sugar) as a 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.

Diabetes increases the risk for complications such as vision loss, kidney failure, and amputation, as well as doubling the risk for heart disease, many forms of cancer, some forms of dementia, and many other common diseases.

Type 1 diabetes affects approximately 5.7 percent of adults diagnosed with diabetes and the majority of children and youth diagnosed with diabetes.[1] It most often develops during childhood but may appear at any age. Type 1 diabetes is an autoimmune disease in which the immune system launches a misguided attack that destroys insulin-producing β (beta) cells in the pancreas. Thus, people with type 1 diabetes require lifelong insulin administration to regulate their blood glucose levels. NIDDK's landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that

[1] *Centers for Disease Control and Prevention. National Diabetes Statistics Report.* https://www.cdc.gov/diabetes/php/data-research/index.html. *Accessed September 16, 2024.*

[2] *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.*

[3] *Parker ED, et al. Economic costs of diabetes in the U.S. in 2022.* Diabetes Care *47: 26-43, 2024.*

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 developing novel technologies that can improve blood glucose management with less burden, such as new methods to improve blood glucose monitoring and insulin delivery. NIDDK has supported pivotal research that contributed to the development or testing of multiple U.S. Food and Drug Administration (FDA)-approved diabetes management technologies, including artificial pancreas devices that automatically link glucose monitoring and insulin delivery. NIDDK has also supported research that culminated in the FDA approval of islet transplantation as a treatment for some people with type 1 diabetes, and NIDDK currently supports research building on this progress to further develop and enhance β-cell replacement therapies toward the goal of curing type 1 diabetes.

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

Type 2 diabetes is the most common form of the disease. The risk for developing type 2 diabetes is associated with many factors, including older age, obesity, family history of diabetes, impaired glucose metabolism, and physical inactivity. The percentage of adults with diagnosed diabetes in the United States is highest among racial and ethnic minority populations, including American Indians and Alaska Natives, non-Hispanic Black people, and people of Hispanic origin.[1] Gestational diabetes is also an important risk factor: People who develop gestational diabetes during pregnancy are at increased risk of developing type 2 diabetes in the future. In people with type 2 diabetes, their muscle, fat, and liver cells do not properly respond to insulin, a condition called "insulin resistance." Gradually, the pancreatic β cells lose their ability to secrete enough insulin to compensate for the resistance, resulting 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. Also, an estimated 97.6 million U.S. adults have prediabetes, in which blood glucose levels are higher than normal but not as high as in diabetes.[1] This population is at elevated risk of developing type 2 diabetes.

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. NIDDK-supported research has shown that the disease may be more aggressive and difficult to treat in youth compared to adults. This is worrisome because those with early disease onset are at especially high risk for developing complications. In addition, increasing rates of type 2 diabetes in youth and adolescents may lead to more people entering pregnancy with diabetes, and diabetes during pregnancy—either gestational diabetes or pre-existing type 2 diabetes—is associated with an increased risk for negative effects on the fetus. Also, 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 cycle of ever-growing diabetes rates, in addition to increasing risks for pregnancy complications.

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. There are also unusual forms of diabetes, called "atypical diabetes," that differ from known types. 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. It is critical to study various types of diabetes, including discovering and defining rare and atypical forms of diabetes, to move toward better diagnoses, improved treatments, and potential prevention of these diseases. NIDDK also supports 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 research investments, NIDDK is vigorously pursuing studies of prevention and treatment approaches for these diseases.

Type 2 diabetes is increasingly being diagnosed in children and adolescents, disproportionately affecting American youth from racial and ethnic minority populations.

IMPROVING DIABETES DIAGNOSIS IN YOUNG PEOPLE

Developing New Tools to Improve Accuracy of Diabetes Diagnosis in Youth: Researchers created new clinical prediction models that can help differentiate between type 1 and type 2 diabetes in a diverse cohort of young people. Diabetes diagnoses continue to rise in U.S. youth, and better tools are needed to accurately distinguish type 1 diabetes (which can occur at any age but is usually diagnosed in children and young adults) from type 2 diabetes (historically more common in adults but increasingly being diagnosed in children). Both diabetes subtypes result in impaired ability to maintain normal blood glucose (sugar) levels, but they can require different treatments. Type 1 diabetes involves destruction of insulin-producing cells in the islets in the pancreas and requires insulin treatment, while people with type 2 diabetes often still make insulin but have an impaired response to it and can benefit from glucose-lowering medications. Diagnosis can be complicated by the overlapping features of type 1 and type 2 diabetes and by the rise in obesity, which is associated with type 2 diabetes but also can co-occur in people with type 1 diabetes. Currently available tools—such as calculating a person's diabetes genetic risk score or testing for islet autoantibodies that indicate the autoimmune attack that causes type 1 diabetes—cannot always definitively diagnose diabetes type and may not be available.

Aiming to improve diabetes diagnosis tools, researchers from the SEARCH for Diabetes in Youth study and their collaborators developed multiple models to predict which youth were making enough insulin to be accurately diagnosed with type 2 diabetes. These models used various combinations of factors present at diabetes diagnosis, including the presence of islet autoantibodies, genetic risk score, and readily available clinical characteristics (such as age, sex, and waist circumference). All models, including those without the genetic risk score, were able to distinguish type 1 from type 2 diabetes more accurately than a clinical diagnosis alone or islet autoantibody tests alone. Furthermore, these models performed equally well for people of varied racial and ethnic backgrounds, as well as for a particularly challenging population to diagnose accurately: older children with obesity.

Overall, these new clinical prediction models may aid health care providers in accurately diagnosing—and providing the most appropriate treatments for—the diverse population of young people with diabetes in the United States.

Jones AG, Shields BM, Oram RA,...Redondo MJ. Clinical prediction models combining routine clinical measures have high accuracy in identifying youth-onset type 2 diabetes defined by maintained endogenous insulin secretion: The SEARCH for Diabetes in Youth study. Diabetes Care 47: 2110-2119, 2024.

PREVENTING AND TREATING TYPE 1 DIABETES

Investigating a Promising Therapy for Preventing Type 1 Diabetes: Researchers discovered that an antibody drug that binds to a protein on the surface of insulin-producing β (beta) cells prevented type 1 diabetes in a mouse model of the disease. Type 1 diabetes is an autoimmune disease in which the immune system attacks and destroys pancreatic β cells found in clusters called islets. This attack involves immune system cells targeting proteins present on the surface of β cells, including the hormone insulin and a protein called zinc transporter 8 (ZnT8). Scientists have long been studying strategies aimed at thwarting this autoimmune attack to protect β cells and prevent or reverse type 1 diabetes.

Scientists showed that an antibody drug that binds to a protein on the surface of insulin-producing β cells protected mice from developing type 1 diabetes.

In a new study, scientists tested an experimental drug called mAb43 that binds to ZnT8, to see if the antibody could shield ZnT8 from being targeted by the immune system and thus preserve β-cell function. Using a mouse model of type 1 diabetes, they compared female mice with no treatment to female mice treated with the mAb43 antibody every week starting at 10 weeks of age. At 35 weeks of age, all the untreated mice had type 1 diabetes, whereas none of the mice treated with mAb43 had the disease. When the mAb43 treatment was stopped, the mice gradually developed type 1 diabetes, showing that the protection against disease required ongoing treatment. The scientists also reported that, compared to untreated mice, mAb43-treated mice had significantly more β cells in their islets, along with fewer destructive immune cells and higher numbers of protective immune cells. Additional studies showed that mAb43 bound to ZnT8 on human islets in the laboratory, and this

binding also made insulin less visible to immune proteins. Together, these observations suggest that mAb43 may protect against type 1 diabetes by shielding not only ZnT8 but also nearby insulin from being targeted by destructive immune cells.

It is known that ZnT8 is a major target of the autoimmune attack in human type 1 diabetes, which suggests that the therapeutic approach described in this study holds promise for being translated to people.

Kasinathan D, Guo Z, Sarver DC,...Fu D. Cell-surface ZnT8 antibody prevents and reverses autoimmune diabetes in mice. Diabetes 73: 806-818, 2024.

Hydroxychloroquine in Early Type 1 Diabetes Does Not Delay Progression: An international clinical trial testing an immune-modulating drug's ability to delay type 1 diabetes progression was stopped early because the treatment was ineffective. Hydroxychloroquine is an anti-malarial drug also used to treat autoimmune diseases, such as rheumatoid arthritis and lupus. It is particularly effective at dampening the immune response early in these diseases, and previous research suggested that the drug might offer similar benefit in another autoimmune disease, type 1 diabetes. Type 1 diabetes progresses through different stages where the immune system launches a misguided attack on the body, which is detected by increasing numbers of self-attacking proteins called autoantibodies in the blood (stage 1), followed by the destruction of the insulin-producing β (beta) cells leading to impaired blood glucose (sugar) management (stage 2), and results in eventual clinical diagnosis of type 1 diabetes (stage 3).

To test whether hydroxychloroquine could slow or halt type 1 diabetes progression, scientists from the Type 1 Diabetes TrialNet randomly assigned 273 study participants, mostly children with stage 1 type 1 diabetes, to take either hydroxychloroquine or a placebo and then followed them for a median of 23 months. A pre-planned interim analysis to assess treatment effectiveness found that hydroxychloroquine was ineffective at preventing type 1 diabetes progression, and the trial was halted early. The study data collected showed that hydroxychloroquine affected the immune system, since treatment reduced the amount of autoantibodies and the appearance of new autoantibodies, but that was not sufficient to block type 1 diabetes progression in those already in stage 1. Hydroxychloroquine use also was associated with changes in blood glucose levels in the first 6 months, but that effect disappeared by 12 months of treatment. No safety concerns were noted in those who received hydroxychloroquine compared to those who received placebo.

Though hydroxychloroquine was unable to slow type 1 diabetes progression, this trial expanded existing knowledge on how early immune processes might affect the course of the disease and could inform future studies on how to prevent type 1 diabetes.

Libman I, Bingley PJ, Becker D,...Herold KC, for the Type 1 Diabetes TrialNet Study Group. Hydroxychloroquine in stage 1 type 1 diabetes. Diabetes Care 46: 2035-2043, 2023.

Equitable Continuous Glucose Monitor Access and Support Can Improve Youth Type 1 Diabetes Management: Researchers recently showed that providing continuous glucose monitors (CGMs) at type 1 diabetes diagnosis along with remote monitoring and support can help young people of varied backgrounds better manage their blood glucose (sugar) levels. Type 1 diabetes treatment requires frequent monitoring and insulin administration to keep blood glucose within a healthy range. This intensive routine can be challenging, and young people often do not reach the optimal treatment targets that can reduce the risk of developing diabetic complications. Using CGM technology that continuously reports blood glucose levels can improve type 1 diabetes management, but CGM use can be limited due to cost, insurance coverage, and/or technical limitations.

Providing a digital health program, including a continuous glucose monitor and remote support, to a diverse group of young people with type 1 diabetes helped them better manage their blood glucose levels.

To test a strategy to enhance CGM access and use early in type 1 diabetes treatment, scientists offered a team-based, remote digital health program to all youth recently diagnosed with the disease at a pediatric clinic. This study—called Teamwork, Targets, Technology, and Tight Control (4T Study 1)—used an equitable approach to include participants whose insurance did not cover a CGM and also those from racial, ethnic, and socioeconomic backgrounds often underrepresented in research. CGMs were provided to all participants along with a compatible device to interface with the CGM, if they did not already have one. The study set

a relatively stringent treatment goal consistent with current guidelines: to maintain HbA1c, a measure of blood glucose management over time, under 7 percent. Participants then received weekly remote monitoring and significant support to help overcome logistical and technical hurdles. The program also aimed to reduce burden on both participants and their health care providers by sending automated alerts when CGM data might need review. After 1 year, 64 percent of study participants were still reaching their treatment target, with participants overall achieving significantly better blood glucose management than expected from historical data.

This study demonstrated how an equitable, technology-enabled, team-based approach can benefit a diverse, real-world population of young people with type 1 diabetes. It also showed how a remote digital health program can support health equity, reduce burden, and improve diabetes care. This approach could be adapted and expanded for use in other settings and to treat other chronic diseases.

Prahalad P, Scheinker D, Desai M,...Maahs DM. Equitable implementation of a precision digital health program for glucose management in individuals with newly diagnosed type 1 diabetes. Nat Med 30: 2067-2075, 2024.

STUDYING TYPE 2 DIABETES TREATMENTS

Effects of Type 2 Diabetes Treatments on Diabetes Distress and Depressive Symptoms: Researchers observed that adults with early type 2 diabetes taking metformin experienced decreases in emotional distress when they started taking an additional glucose (sugar)-lowering drug. Emotional distress, including depression and diabetes distress, is common among individuals with diabetes. Diabetes distress includes emotional burden of living with diabetes, burden related to diabetes management, interpersonal distress from lack of social support, and distress due to lack of expertise or guidance from physicians. Previous research suggested that insulin therapy in people with type 2 diabetes may increase emotional distress, but this relationship has not been rigorously studied. Insulin therapy, even when warranted, may be delayed if patients and health practitioners anticipate increased burden and decreased quality of life. Therefore, it is important to understand the link between type 2 diabetes treatments, especially insulin therapy, and emotional health to inform treatment decisions.

Launched in 2013, the Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) study was designed to directly compare the long-term effectiveness of four commonly used blood glucose-lowering drugs (insulin glargine, liraglutide, glimepiride, and sitagliptin) in adults who were already taking the drug metformin to manage type 2 diabetes. Because the GRADE cohort is large, diverse, well-characterized, and randomized, it offers a unique opportunity to study the glucose-lowering drugs' effects on the study participants' emotional well-being. For this study, researchers assessed depressive symptoms and diabetes distress. After the GRADE participants were randomly assigned one of the four drugs and followed up to 3 years, all four groups showed decreases in depressive symptoms and diabetes distress over time. Surprisingly, participants taking insulin glargine had lower diabetes distress after 1 year compared with all other groups combined. Participants assigned to liraglutide also experienced lower diabetes distress after 1 year compared to people taking glimepiride and sitagliptin. The data analysis also revealed that Hispanic individuals, non-Hispanic Black individuals, and people from non-White ethnic backgrounds were more likely to experience higher diabetes distress when receiving an additional glucose-lowering drug such as liraglutide, glimepiride, and sitagliptin, compared to non-Hispanic White individuals. More research is needed to understand and address these disparities.

Researchers found that adults with early type 2 diabetes taking metformin experience significantly lower diabetes-related distress when they started taking another glucose-lowering drug such as insulin glargine or liraglutide.

The GRADE study's findings challenge existing dogma and show that insulin, in combination with metformin, can lead to an overall decrease in emotional distress over time in adults with type 2 diabetes. These findings provide helpful information to providers and patients when considering treatments and effects on emotional health.

Gonzalez JS, Bebu I, Krause-Steinrauf H,...Cherrington AL; GRADE Research Group. Differential effects of type 2 diabetes treatment regimens on diabetes distress and depressive symptoms in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care 47: 610-619, 2024.

UNDERSTANDING DIABETES HEALTH DISPARITIES

Newly Identified Gene Variants May Help Predict Response to Metformin Treatment in African Americans With Type 2 Diabetes: Researchers have identified novel gene variants associated with metformin treatment response in African Americans with type 2 diabetes. Metformin has long been recommended as the initial drug of choice for managing blood glucose (sugar) in people with type 2 diabetes. However, studies suggest that how a person responds to metformin is often genetically determined, highlighting the importance of identifying genetic factors that can help predict individual variability in treatment response. Even though African Americans are at higher risk of developing diabetes than people of European ancestry, there is a significant knowledge gap in genetic variability associated with metformin response in African Americans, as previous studies have mostly been focused on data from people with ancestry from European countries. Thus, this new study aimed to fill this knowledge gap by studying genetic variability related to treatment response in African American participants with type 2 diabetes.

Researchers examined data from the Diabetes Multi-omic Investigation of Drug Response (DIAMOND) study, which includes a diverse cohort of people with type 2 diabetes from Southeast Michigan and the Detroit metropolitan area. Using genomic and clinical data from 447 participants who self-identified as African American and used at least 425 mg of metformin per day, researchers carefully mapped regions of the genome with known markers associated with ancestry from an area of western Africa. They searched for gene variants linked with changes in blood glucose levels in the study participants receiving metformin treatment, and they discovered two variants in a gene called *ARFGEF3* that were associated with the greatest changes in blood glucose while taking the drug. Interestingly, prior research on this gene in mice suggested a potential role for it in regulating insulin and blood glucose levels. Researchers in the current study found significant differences in improvement of blood glucose levels in response to metformin depending on the *ARFGEF3* gene variant that an individual had, suggesting that people with a certain *ARFGEF3* gene variant experience a bigger decrease in blood glucose levels than those with another *ARFGEF3* variant. However, this effect was not observed in people who took less than 425 mg of metformin per day and was not seen in people with ancestry from countries in Europe.

This is the first study in which a cohort consisting only of African Americans was used to discover novel gene variants that impact treatment response to metformin. The unique study method allowed researchers to discover new gene variants that are more commonly found in African Americans, not only helping to predict treatment responses more accurately across diverse populations but also providing mechanistic insight into how metformin works to decrease blood glucose levels. These findings and further studies using a similar method may help guide treatment decisions and advance precision medicine approaches for everyone with type 2 diabetes.

Wu B, Yee SW, Xiao S,...Williams LK. Genome-wide association study identifies pharmacogenomic variants associated with metformin glycemic response in African American patients with type 2 diabetes. Diabetes Care 47: 208-215, 2024.

Genetic Study of Diabetes Complications Reveals Insight Into Health Disparity: Scientists identified a genetic variant, more common in some populations with African ancestry, associated with an increased risk of diabetic complications, a finding that could suggest new ways to combat health disparities. Diabetic complications—including diseases of the heart, kidneys, eyes, and nerves—greatly affect the health and quality of life of people with diabetes, making preventing and treating them critically important. For reasons not fully understood, these complications occur more often in individuals of African ancestry. To understand why some people are more likely to develop a specific diabetic complication (eye disease), scientists collected genetic and electronic health record data from over 197,000 people with diabetes, 68,000 of whom had eye disease. Most of the data were from people with European backgrounds, but the collection also included information on a large number of males of African ancestry, allowing a specific analysis of this population.

From this wealth of data, the scientists identified unique genetic variants that were more likely to be found in people with eye disease, including a variant which causes a condition known as "G6PDdef" or glucose-6-phosphate dehydrogenase deficiency. This genetic variant is common in some populations with African ancestry and confers resistance to malaria. Previous research has shown that hemoglobin A1c levels (HbA1c; a test commonly used to provide information about average levels of blood glucose [sugar] over time) are lower in people with G6PDdef. In this study, the

scientists found that, in participants with this variant, the HbA1c tests were masking their blood glucose levels: Despite having high blood glucose, they had lower HbA1c results than expected. Higher blood glucose levels are known to increase the risk for diabetic complications, and the scientists showed that the increased risk of eye disease in participants with the risk variant was caused by these high blood glucose levels. Additional analyses revealed that having this genetic variant also increased risk for another diabetic complication—nerve damage—indicating that the masked high blood glucose levels in this population affected risk of multiple diabetic complications. Further research is needed to determine if these results extend to other populations where the genetic variant occurs, such as females of African ancestry or people of Asian ancestry.

By identifying a genetic variant associated with increased risk of diabetes complications in men of African ancestry, scientists uncovered an opportunity to improve diabetes diagnosis and treatment for people carrying the variant.

These important findings indicate that, for people with G6PDdef, HbA1c tests may not accurately indicate high blood glucose levels. Screening for G6PDdef, coupled with more accurate monitoring of blood glucose levels, could thus improve diabetes diagnosis and treatment in this population. The scientists further estimated that such changes could prevent nearly 12 percent of diabetic eye disease and 9 percent of diabetic nerve disease in individuals of African ancestry in the United States, combating health disparities and significantly improving public health.

Breeyear JH, Hellwege JN, Schroeder PH,...Edwards TL. Adaptive selection at G6PD and disparities in diabetes complications. Nat Med 30: 2480-2488, 2024.

INVESTIGATING LINK BETWEEN SLEEP AND INSULIN RESISTANCE

Chronic Sleep Deficiency Elevates Insulin Resistance in Women: Researchers have found that chronic sleep restriction can increase insulin resistance in otherwise healthy women, especially those who are postmenopausal. Previous studies have shown that insufficient sleep can elevate the risk for certain conditions such as cardiovascular disease, high blood pressure, and disordered glucose (sugar) metabolism—which may include insulin resistance, elevated insulin levels, and high glucose levels and can ultimately lead to type 2 diabetes. However, most studies have been conducted in men and for short durations. Given that women report poorer sleep than men, the researchers enrolled only women in the current study and sought to determine if mild sleep restriction in a real-life setting (*i.e.*, not in a sleep lab) impacted the participants' blood glucose and insulin levels.

Researchers have found that chronic sleep restriction can increase insulin resistance, a risk factor for type 2 diabetes, in otherwise healthy women, especially those who are postmenopausal.

The researchers recruited a group of racially diverse women who had healthy sleep habits (at least 7 to 9 hours per night) and normal blood glucose levels but were at increased risk of cardiometabolic disease due to having overweight/obesity or a family history of type 2 diabetes or cardiovascular disease. Among the 38 participants for whom the researchers collected and analyzed data, more than a quarter were postmenopausal. The women wore a wrist sensor and kept sleep logs for 2 weeks to establish baseline sleep patterns. Participants then completed two, randomly assigned, 6-week study phases—one phase where they maintained their typical sleep patterns, averaging 7.5 hours a night, and another where sleep was restricted by delaying bedtime by 1.5 hours. During the sleep-restricted phase, they averaged 6.2 hours of sleep per night. At the beginning and end of each phase, the women completed tests to measure glucose and insulin levels and had a scan to measure body fat tissue. After limiting sleep for 6 weeks, the researchers found that the participants' insulin resistance increased by about 15 percent in all participants, with more pronounced effects for postmenopausal women relative to premenopausal women. Limiting sleep induced elevated insulin levels in all women. Other measurements indicated that the effects of sleep restriction on insulin resistance were independent of body fat despite longer wake times.

These findings provide new insight into the health impact of sleep deficits in women, especially postmenopausal

women, and highlight the importance of adequate sleep in reducing the risk for type 2 diabetes. More research is needed to better understand how even mild sleep deprivation in all people affects metabolism, so health care providers can better inform patients about the importance of sleep duration as a tool for type 2 diabetes prevention.

Zuraikat FM, Laferrère B, Cheng B,...St-Onge MP. Chronic insufficient sleep in women impairs insulin sensitivity independent of adiposity changes: Results of a randomized trial. Diabetes Care 47: 117-125, 2024.

STUDYING METABOLIC REGULATORS OF HEALTH

Studying Regulation of "Clock" Genes Important for Metabolism: Scientists have defined mechanisms that regulate the rhythmic control of gene activity in mouse liver, shedding light on the crucial processes of turning genes on and off dynamically at the right time. It is known that in animals and humans, biological "circadian clocks" regulate behavior and bodily processes, harmonizing them with daily, rhythmic changes in the environment, most notably day/night cycles. Transcription factors—proteins that bind to DNA and control gene activity (also called gene transcription)—play a crucial role in translating environmental stimuli into biological process by regulating clock-controlled genes. Appropriately regulating these genes is critically important to metabolic physiology. Recent advances in understanding gene transcription have suggested that transcription factors can dynamically congregate at DNA hubs or "condensates," and that condensate formation is driven by specific sections of the transcription factor proteins called "intrinsically disordered regions (IDRs)." Because this is an emerging area of research, most studies on condensates have been done in laboratory cell culture, so their biological function in mammals is unknown.

Scientists have defined new mechanisms that regulate the rhythmic control of gene activity in mouse liver, contributing to understanding how the environment regulates health and informing future approaches for treatment and prevention of metabolic diseases.

In recent research, scientists studied a transcription factor called Rev-erb-α that is involved in regulating many physiological processes, including circadian control of metabolic functions in the liver. The scientists discovered that an IDR located within Rev-erb-α is required to recruit another protein called NCOR1 to form circadian condensates in liver cells of male mice. The condensate complex of Rev-erb-α and NCOR1 turns off metabolic rhythmic gene transcription in mouse liver. Based on these findings, the scientists speculate that the formation of clock protein condensates through IDRs may be a general mechanism for regulating circadian gene transcription, although more research is needed to confirm the role of this mechanism, as well as to extend the findings to people. This study provides important information on the complex processes that cells use to regulate gene activity at appropriate times, contributing to understanding how the environment regulates health and informing future approaches for treatment and prevention of metabolic diseases.

Zhu K, Celwyn IJ, Guan D,...Lazar MA. An intrinsically disordered region controlling condensation of a circadian clock component and rhythmic transcription in the liver. Mol Cell 83: 3457-3469.e7, 2023.

New Insights Into the Regulation of Glucagon Release From Pancreatic Alpha Cells: Researchers have identified proteins involved in controlling the release of glucagon from pancreatic α (alpha) cells in mice, representing novel targets for modulating glucagon release for therapeutic purposes. Glucagon is a hormone that raises blood glucose (sugar) levels and is involved in other metabolic activities; it is produced by α cells found in clusters called islets in the pancreas. Dysregulated, elevated blood glucagon levels contribute to the high blood glucose levels that are a hallmark of both type 1 and type 2 diabetes. Therefore, identifying ways to regulate glucagon release could inform novel approaches for treating diabetes and other metabolic disorders.

In new research, scientists studied whether signaling proteins, called G_s-coupled receptors, played a role in glucagon release. These receptors are found on cells throughout the body, so the researchers generated novel mouse models that allowed them to explore the receptors' role specifically in α cells. In one mouse model, activating these receptors led to an increase in blood glucagon levels. High glucagon levels in turn caused insulin levels to rise, consistent with recent studies suggesting that glucagon can signal to neighboring β (beta) cells in islets to promote insulin release. Activating G_s-coupled receptors also led to improved glucose tolerance, a measure of metabolic health, in both lean and obese mice; the scientists think

that this improvement is due to the increased insulin levels stemming from glucagon release. Using another mouse model, the researchers showed that lack of G_s-coupled receptors in α cells was associated with lower levels of both glucagon and glucagon gene activity. Together, these findings show that G_s-coupled receptors are involved in controlling glucagon release from α cells in mice. If these receptors play a similar role in people, they represent potential targets for treating metabolic diseases, such as diabetes.

Liu L, El K, Dattaroy D,...Wess J. Intra-islet α-cell Gs signaling promotes glucagon release. Nat Commun 15: 5129, 2024.

FEATURE

Sugar-Sweetened Beverage Taxes—Potential Sweet News for Public Health

High consumption of added dietary sugar increases the risk for the development of obesity; type 2 diabetes; and heart, kidney, and liver diseases. Despite this risk, cutting back on added dietary sugars is often difficult due to its presence in cheap, convenient, and hyperpalatable processed foods. Sugar is often a main ingredient in bottled beverages such as soda, iced teas, and fruit-flavored drinks, which increase sugar consumption without providing additional nutritional value. Sugar-sweetened beverage (SSB) taxes have been proposed as a stimulus to limit the consumption of these high-caloric drinks by giving people an economic incentive to think twice about consuming that added sugar. However, determining the effects of SSB taxes is difficult given the extended time between consumption of SSBs and the development of chronic disease. New NIDDK-funded research is finally offering evidence that these taxes can promote healthier habits to decrease the burden of disease.

SSB taxes can only decrease disease burden if they are effective in limiting the purchase and consumption of SSBs. While studies have been conducted in other countries to show the effectiveness of SSB taxes, data from the United States has been limited. A new 2024 study used advanced statistical techniques to analyze SSB prices and purchasing trends in cities before and after they adopted SSB taxes, as compared to areas that did not adopt SSB taxes but were similar in other ways. This method allowed the researchers to analyze data from five cities that had implemented SSB taxes at different times: Philadelphia, Pennsylvania; Oakland, California; San Francisco, California; Seattle, Washington; and Boulder, Colorado. The researchers found that following implementation of the tax, prices of SSBs increased by an average of 33.1 percent, and this increase was sustained through at least the following 2 years, which was the timeframe of the study. Over the same period, there was a corresponding 33 percent decrease in the volume of SSBs purchased within the taxed areas. They also analyzed whether more SSBs were purchased in border zones surrounding the taxed cities where prices were still lower, but the data did not show an increase in purchases there, suggesting residents of the taxed area were not going elsewhere to buy SSBs.

Another recent study of the effects of SSB taxes overcame the problem of extended time between SSB consumption and chronic disease development by utilizing a time-limited life stage where SSBs have been shown to have acute negative effects: pregnancy. Increased consumption of SSBs while pregnant is associated with adverse outcomes for the pregnant individual, including the development of gestational diabetes, increased weight gain both during and after pregnancy, and high blood pressure. It is also associated with adverse outcomes for the baby, including early delivery and a birth weight that is much lower than average for the number of weeks of pregnancy. Given that the development of these complications occurs within a 9-month period, researchers compared the incidence of adverse pregnancy outcomes before and after the implementation of SSB taxes. For the study, researchers examined data from five cities that have implemented SSB taxes: Berkeley, California; Philadelphia, Pennsylvania; Oakland, California; San

Francisco, California; and Seattle, Washington. Using national birth certificate data from a total of more than five million births, they were able to compare rates of gestational diabetes and excess weight gain in the time before and after SSB tax implementation and also use data from comparably sized cities that did not implement SSB taxes to control for confounding factors. The results demonstrated that SSB taxes were associated with a decrease in risk for the development of gestational diabetes, beginning 6 months after implementation of the tax, as well as a reduction in the weight gain experienced by pregnant people.

Together, these new results provide evidence that SSB taxes may be an effective policy to improve public health by changing consumption habits. More research will be needed in the future to understand if these benefits extend to longer-term health and the prevention of chronic disease, but the results from the pregnancy study already offer a positive outlook for better long-term outcomes, as having gestational diabetes and excess weight gain during pregnancy can lead to a higher risk of developing cardiovascular disease and type 2 diabetes later in life for both the parent and child. While these studies do not address whether SSB taxes have a positive effect on preventing chronic disease in the general population, including in other geographic areas such as rural communities, the results observed in purchasing patterns and pregnancy health suggests there is cause for hope.

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FEATURE

Human Islet Research Network: Celebrating 10 Years of Innovative Research on Type 1 Diabetes

In 2024, the Human Islet Research Network (HIRN) celebrated 10 years of making significant progress conducting innovative research to better understand how insulin-producing β (beta) cells are lost in type 1 diabetes and how to protect or replenish them in people with the disease.

Establishing HIRN as a Forward-Looking, Interdisciplinary Research Approach

NIDDK established HIRN to create an interdisciplinary community of scientists (*e.g.*, cell biologists, immunologists, bioengineers, bioinformaticians, chemists) who would work together to explore type 1 diabetes biology in ways that would be difficult for individual laboratories to tackle, toward an overarching goal of identifying strategies to protect or replace β cells in type 1 diabetes. Other goals for HIRN included developing transformative technologies, investigating understudied areas of the type 1 diabetes disease process, generating datasets to be shared with the broad research community, and fostering the next generation of type 1 diabetes researchers.

HIRN is composed of several complementary consortia, each one defined by its own scientific mission. (Information on the current HIRN consortia is available under the "Our Research" tab at the top of the page at: *https://hirnetwork.org*.) This modular structure has allowed HIRN to evolve over time, with some consortia sunsetting as research goals were met, some consortia merging, and new consortia forming as novel opportunities arose. HIRN's Human Islet Research Enhancement Center coordinates network operations, providing support for the over 100 HIRN scientists.

Transforming Type 1 Diabetes Research

HIRN has been extremely productive, publishing about 1,000 scientific papers and contributing unprecedented insights into the type 1 diabetes disease process. For example, HIRN researchers reported a groundbreaking discovery that pancreatic α (alpha)-cell dysfunction precedes β-cell loss in people who have a single type 1 diabetes autoantibody (a protein made by the immune system that signals an early stage of type 1 diabetes). This finding is paradigm changing and defines a new, distinct, early stage of type 1 diabetes. Additional studies of this early stage could pave the way to developing clinical interventions to protect or replenish β cells.

HIRN has also been extremely successful in identifying potential type 1 diabetes therapeutic targets. For example, HIRN researchers have been studying the role of thioredoxin-interacting protein (TXNIP), which is elevated in people with type 1 diabetes and can trigger β-cell death. They showed in a small clinical trial that the drug verapamil, which targets TXNIP and is already approved for treating high blood pressure, can delay type 1 diabetes progression and lower insulin requirements in people with newly diagnosed

disease. The researchers are now developing more potent and specific drugs to target TXNIP.

Furthermore, HIRN has made significant progress in developing new models of type 1 diabetes that are enabling novel studies of disease pathophysiology and serving as platforms for pre-clinical testing of new therapies, such as sophisticated mouse models that mimic key features of human disease. Additionally, HIRN scientists have bioengineered "islet chips," which are three-dimensional models of human islets in the laboratory setting. These microenvironments incorporate or mimic diverse elements that support islets in the body, such as blood vessels, and are therefore a better representation of human islet physiology than other islets grown by themselves on flat plastic dishes.

Along with its own scientific accomplishments, the network's community resources, such as datasets shared through a public database called PANC-DB, are also benefitting the type 1 diabetes research field. Scientists both within and outside of HIRN have used these datasets to publish dozens of research papers that have advanced knowledge of islet biology and the type 1 diabetes disease process.

Efforts to Foster the Career Development of Diabetes Researchers

Both NIDDK and HIRN have placed a high priority on fostering the next generation of type 1 diabetes researchers by supporting career development programs for talented early career stage scientists from diverse backgrounds interested in pursuing HIRN-related research. These programs include:

- **HIRN Emerging Leaders Awards**: HIRN awards given to experienced senior postdoctoral fellows to enhance their transition toward independent research careers.

- **HIRN New Investigator Awards**: HIRN awards given to early career scientists to apply bold and innovative new research approaches to biological problems under investigation in HIRN, which could be used as a foundation to apply for their own independent NIH research awards.

- **NIDDK New Investigator Gateway Awards**: NIDDK awards given to early career stage investigators in which awardees join relevant HIRN scientific consortia to increase their understanding of key research questions, establish collaborations to propel their careers forward, and enhance their ability to compete for their own independent NIH research awards.

These programs have not only provided support for conducting innovative research, but have also given awardees invaluable opportunities to learn from and collaborate with established HIRN scientists and to gain experience taking on leadership roles. Thus, these efforts have been instrumental in advancing awardees' research careers while ensuring a pipeline of researchers contributing to HIRN's mission. (See next page for quotes from awardees on the impact these programs had on their research and careers.)

Looking to the Future

As intended, HIRN is continuing to evolve as new scientific opportunities arise. For example, NIDDK recently added a new component to HIRN called the Pancreas Knowledgebase Program. The knowledgebase is serving as a centralized community resource around the human pancreas, providing access to datasets and advanced data science tools to take advantage of the latest developments in data analysis (*e.g.*, artificial intelligence). Even as HIRN's scientific approaches change to capitalize on progress and the availability of new technologies, the network will remain steadfast in its commitment to performing top-tier islet biology research while also supporting the career development of diverse young scientists and sharing data to benefit the broad research community. Through these multifaceted efforts, HIRN is poised to continue its exceptional scientific track record for years to come.

FEATURE

"The HIRN New Investigator and NIDDK Gateway Awards have been instrumental in my success as an independent investigator. They gave me the opportunity to network and share my work in ways that significantly benefitted my research program and career development. Due in no small part to these opportunities, I expanded my network of collaborators, published several manuscripts, obtained additional research funding, was promoted to Associate Professor with tenure, and recently became Director of our NIDDK-funded Indiana Diabetes Research Center Optical Microscopy Core."

Amelia Linnemann, Ph.D., Associate Professor, Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, 2018 HIRN New Investigator awardee, and 2020 NIDDK New Investigator Gateway awardee.

"The NIDDK Gateway Award allowed me to perform experiments to investigate the longevity of beta cells in a mouse model of type 1 diabetes. Importantly, this award helped me establish my independent laboratory at Vanderbilt and to interact with leaders in the islet and diabetes research field. Since my HIRN award, I have been awarded my own lead principal investigator NIDDK-funded research project grant (R01) and additional grants from the National Institute on Aging (NIA) and the National Institute of General Medical Sciences (NIGMS)."

Rafael Arrojo e Drigo, Ph.D., Assistant Professor, Molecular Physiology and Biophysics, Vanderbilt University, and 2020 NIDDK New Investigator Gateway awardee.

"The HIRN New Investigator Award provided me with a platform to tackle a novel and exciting project, build a strong network with peers and senior scientists, and ensure my success as an early career faculty member. Findings from our HIRN-sponsored project were instrumental in securing my lab's first NIDDK-funded research project grant (R01) and have resulted in multiple publications. Being a member of HIRN provided me with greater visibility in the field and multiple opportunities to take on leadership roles, including organizing the annual HIRN investigator meeting. The HIRN award made these opportunities feasible, which collectively contributed to my promotion to Associate Professor with tenure."

Sangeeta Dhawan, Ph.D., Associate Professor, Arthur Riggs Diabetes and Metabolism Research Institute, City of Hope, and 2018 HIRN New Investigator awardee.

Norma: Receiving a Life-Enhancing Islet Transplant to Treat Type 1 Diabetes

Norma and her husband, John. Norma, who is living with type 1 diabetes, participated in an islet cell transplantation clinical trial.

Late in the summer of 1982, 14-year-old Norma began to sense that something was wrong. "It was August," she remembers, "I was feeling tired, losing weight, and I was thirsty all the time." She thought it might just be the heat, but her excessive thirst reminded her of a book her sister had lent her, describing the experiences of a girl with diabetes. "Hmm…," Norma thought. "This can't be good."

When Norma had her annual physical later that month, her blood sugar (glucose) levels were dangerously high, a condition called hyperglycemia that prompted a diagnosis of type 1 diabetes and a hospital stay.

She learned how to use blood glucose test strips and to administer her own insulin shots before meals to keep her blood sugar within the recommended range. Estimating how much insulin was needed and when to take it was an extremely imperfect science at that time. One morning in the hospital, Norma took her first dose of insulin ahead of her upcoming breakfast… and then the meal arrived late. While she waited, the insulin drove her blood sugar levels well below normal levels, a dangerous condition called hypoglycemia. She became sweaty and lightheaded, and later realized that she had experienced her first hypoglycemic reaction.

Recurring hypoglycemia would haunt Norma for years and significantly affected her daily life. Ultimately, this relentless struggle compelled her to volunteer for an experimental islet transplant, a decision that would profoundly change her life.

THE TIGHTROPE OF BLOOD SUGAR MANAGEMENT

After her type 1 diabetes diagnosis, Norma had little trouble keeping her blood sugar levels in a healthy range. She had the same schedule and mealtimes every day in high school, which helped her accurately meet her insulin needs. "Then I went off to college," Norma says wryly. "You want to blend in. You want to follow everyone else's hectic, crazy schedules. You don't want to be testing your blood sugar and taking insulin shots." Her sleep and eating schedules became inconsistent, and at the time she didn't have access to modern diabetes management technologies like an artificial pancreas, insulin pump, or a continuous glucose monitor.

PERSONAL PERSPECTIVE

Looking back, Norma says college was when she started having trouble managing her type 1 diabetes, and that trouble grew over the years. After her daughter and son were born, Norma found it very difficult to manage her diabetes while caring full time for young children on a very unpredictable daily schedule. She experimented with different strategies to adjust her insulin dosing and eventually turned to an insulin pump for better blood glucose management, but even vigilant effort and the best modern technologies cannot fully replace the pancreas' precise control of insulin levels.

College, Norma says, was when she started having trouble managing her type 1 diabetes. "You want to blend in. You want to follow everyone else's hectic, crazy schedules. You don't want to be testing your blood sugar and taking insulin shots."

For Norma, it was a challenge to keep her daily blood glucose levels within a normal range while balancing changing insulin needs, physical activity, and meal schedules for her and her family. When hypoglycemia struck, leaving her shaky and unable to concentrate, Norma would have to treat it by drinking juice or eating a snack. If her blood glucose levels rose too high, she worried about increasing her risk of diabetes complications such as kidney failure, heart disease, nerve damage, and blindness.

After over 20 years of managing type 1 diabetes, Norma's kidney function had severely declined. She had had eclampsia (a serious pregnancy-related high blood pressure disorder) during her first pregnancy, and her kidneys were also affected by the long-term effects of elevated blood glucose levels. Norma had a kidney transplant in 2006 and began a lifelong regimen of immunosuppressants to prevent organ rejection.

After the kidney transplant, Norma thought, "I *really* have to control my blood sugars, because I have to protect this kidney that my brother-in-law so selflessly gave me." By that time, however, Norma's ability to notice her own hypoglycemia was, she says flatly, "gone": she had a condition called impaired awareness of hypoglycemia, where she couldn't feel her blood sugar levels dropping and couldn't tell when she needed to administer treatment. Friends and family sometimes had to warn her when they thought she was hypoglycemic. Norma's young daughter was particularly helpful. "She knew, all the time," Norma says, describing how her daughter would sometimes just hand Norma juice and say, "Take this, Mommy."

This constant vigilance was like walking a tightrope, Norma says. "It just kept getting worse. I was so frustrated." The recurring hypoglycemia was affecting her ability to drive and care for her children. She knew something had to change. "I had two little kids at home who needed me, and … I really couldn't keep going like that."

A BREAK FROM TYPE 1 DIABETES

Aware of Norma's struggles with hypoglycemia, one of Norma's doctors suggested taking part in a Clinical Islet Transplantation Consortium research study. During islet transplantation, islets are extracted from a cadaveric donor pancreas and injected into a vein in the recipient's liver, allowing them to attach and produce insulin when needed. (For more details on islet transplantation, see inset below.) Islet transplantation was still experimental and only available as part of a research study at the time, but Norma recalls her response: "I didn't hesitate. I was ready to try anything that could give me even a temporary break from insulin." The need to take immunosuppressants to protect the transplanted islets didn't deter her, since she was already taking

When one of her doctors suggested she take part in a Clinical Islet Transplantation Consortium research study, Norma recalls, "I didn't hesitate. I was ready to try anything that could give me even a temporary break from insulin."

them to prevent rejection of her donated kidney. Even if the islet transplant only lasted a few months, Norma thought, it would still offer a break from insulin injections.

When she arrived for the procedure in October 2011, the staff's excitement was infectious. Norma got the impression that preparation of the islets for her transplant had gone well, and that optimism proved prophetic: Norma's insulin needs plummeted post-transplant. After years of micromanaging her blood sugar levels, she was amazed at how they stayed in a healthy range day after day. Her health care team gradually reduced the insulin she took via her insulin pump, until one day she safely took no insulin at all. Then, Norma says with a smile, "My family had a pump removal celebration at my house." She ceremoniously tucked the device in a drawer.

Years passed, and still Norma did not need to take insulin. "I couldn't believe how long it was lasting," she says. In total, Norma enjoyed over 12 insulin-free years. She has since returned to taking insulin, but her experience is very different than what she endured prior to her islet transplant. She takes one long-acting insulin shot daily and monitors her blood sugar levels via a continuous glucose monitor, but the recurring low blood sugar episodes and impaired awareness of hypoglycemia are now gone.

A LIFE ENHANCED BY RESEARCH

"That break that I had?" Norma says, referring to her years of insulin independence. "It was huge." She says that her islet transplant enhanced her life in both physical and psychological ways. She is certain that her years of good blood sugar control have protected her heart and her donated kidney, reducing her risk of diabetic complications. The mental relief from the constant burden of diabetes management, though, is what she values most. Now Norma can travel, play the sports she loves, or just enjoy a walk without having to worry about sudden blood glucose drops. "It's such an incredible mental boost," she says.

"That break that I had?" Norma says, referring to the 12 years she didn't have to take insulin following her islet transplant. "It was huge."

Islet transplantation was approved by the U.S. Food and Drug Administration (FDA) in 2023 to treat some adults who, like Norma in 2011, have difficulty managing their type 1 diabetes due to repeated episodes of severe hypoglycemia. Though the need for immunosuppressive medicines makes islet transplantation appropriate for only a small subset of people with type 1 diabetes, it is still the first approved cellular therapy for the disease. "It's amazing," Norma says about this landmark achievement. She loves that she was a part of this groundbreaking research, but mostly she says she is grateful: to those who donated the islets, to her transplant team, and to the researchers who first developed islet transplantation.

Today, Norma stays active, playing golf and ice hockey. She and her family love to travel, and she volunteers for transplant-related and type 1 diabetes-related causes. She encourages others to seek out and participate in clinical research and looks forward to advances that might negate the need for immunosuppression. She's even willing to do her part: If such a trial needs her, Norma says, "I'd gladly volunteer for that, too!"

PERSONAL PERSPECTIVE

More Information on Type 1 Diabetes and Islet Transplantation

Type 1 diabetes is an autoimmune disease in which the immune system destroys insulin-producing β (beta) cells found in cell clusters called islets in the pancreas. Loss of insulin causes sugar to build up in the blood (called hyperglycemia). Persistent hyperglycemia raises the risk of serious complications of the eyes, kidneys, heart, and other organs.

Insulin—administered via injection, insulin pump, or artificial pancreas device—is a life-saving treatment for those with type 1 diabetes. However, even with modern diabetes management technologies, it can be difficult to keep blood sugar levels in a healthy range as they fluctuate in response to meals, activity, and other factors. Too much insulin can push blood sugar levels dangerously low (hypoglycemia). Even with careful diabetes management, some people experience episodes of severe hypoglycemia that are associated with confusion, behavior changes, seizures, unconsciousness, and difficulty awakening from sleep. Such episodes may make activities like driving or caring for young children unsafe. If left untreated, severe hypoglycemia can lead to coma or seizures, or be fatal. Repeated episodes of severe hypoglycemia can also lead to a condition called "impaired awareness of hypoglycemia," where a person cannot tell when their blood sugar is low, making it difficult for them to self-administer treatment.

Finding ways to replace or restore the body's ability to make insulin is a major, long-term goal of both NIDDK and the Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program). One such research avenue is islet transplantation, where islets are isolated from donated cadaveric pancreases and transplanted into a person with type 1 diabetes.

In 2004, NIDDK and the National Institute of Allergy and Infectious Diseases (NIAID) established the Clinical Islet Transplantation Consortium (CIT). Also supported by the Special Diabetes Program, the CIT studied an islet transplantation procedure where donated islets are injected into a major vein in the liver and then protected from rejection by a novel combination of immunosuppressive drugs. CIT investigators showed that in most cases islet transplantation could eliminate severe episodes of hypoglycemia, normalize blood sugar levels, and improve quality of life. Some recipients no longer needed to take insulin for years post-transplant.

These groundbreaking CIT results laid the foundation for the July 2023 U.S. Food and Drug Administration (FDA) approval of islet transplantation to treat adults with type 1 diabetes whose disease cannot be adequately managed due to repeated episodes of severe hypoglycemia, despite intensive diabetes management and education. This approval was the culmination of decades of collaborative work between NIH, nongovernmental organizations such as Breakthrough T1D (formerly JDRF), businesses, and the FDA.

Though islet transplantation can be life-changing, it still has limitations. One significant drawback is that the recipient must take immunosuppressants for the life of the transplant, which can increase their risk of infections and other serious health problems. The needed cadaver-derived islets are also in short supply. Thus, islet transplantation is only appropriate for a small subset of people with type 1 diabetes who have exhausted other treatment options. NIDDK continues to support research toward overcoming these hurdles, including developing new sources of insulin-producing cells for transplant and eliminating the need for immunosuppression.

PERSONAL PERSPECTIVE

Keisha: Contributing to Research on Long-Term Outcomes of Medical/ Lifestyle Management Versus Bariatric Surgery in Type 2 Diabetes

For 51-year-old Keisha, who resides in Pittsburgh, Pennsylvania, and works as a customer service representative for a large financial services and insurance company, family has always been important. In 1994, she and her husband welcomed twin girls, and 2 years later, a baby boy. Her first pregnancy resulted in a difficult delivery. "I almost died on the table," she recalled. When she became pregnant with her son, she felt that her doctor was not considering her complete health picture beyond her basic prenatal appointments. Notably, Keisha doesn't recall ever being screened for high blood sugar (glucose) or type 2 diabetes during either pregnancy. (More information on type 2 diabetes is provided at the end of this feature.) Her son weighed more than 9 pounds, and she experienced yet another very difficult delivery. Thankfully, all three babies were born healthy.

However, shortly after the birth of her son, Keisha began experiencing extreme fatigue and an overall loss of energy. Her symptoms were so intense that she lost her job at the time due to falling asleep at work. She sought out a new doctor who, based upon the results of her blood tests, suspected she may have developed gestational diabetes (a form of diabetes that develops during pregnancy and can lead to type 2 diabetes), and it had gone unrecognized and untreated. At age 23, Keisha was diagnosed with full-blown type 2 diabetes.

DEALING WITH DIFFICULT HEALTH ISSUES

The diagnosis of type 2 diabetes came as a surprise to Keisha as she had no family history of the disease, and she tried her best to maintain a healthy diet. However, she had a difficult time losing the weight she had gained after the birth of her son, despite her efforts. To get her blood sugar under control, her doctor prescribed insulin (a hormone treatment commonly used in people with type 2 diabetes), but her blood sugar continued to rise. Keisha's type 2 diabetes was difficult to manage, especially while she was caring for three young children, and she developed other health problems associated with excess weight. She had trouble breathing and could barely climb a flight of stairs. She also developed fibromyalgia, a musculoskeletal condition commonly diagnosed in women and people with type 2 diabetes that causes pain throughout the body, fatigue, and trouble sleeping.

PARTICIPATING IN CLINICAL RESEARCH AND UNDERGOING BARIATRIC SURGERY

After years of health issues, Keisha began seeing a new doctor at the University of Pittsburgh Medical Center (UPMC) who suggested bariatric surgery, also called metabolic surgery, to manage her obesity and

type 2 diabetes. She was told about a randomized clinical trial, being conducted right there at UPMC, that was designed to compare initial outcomes of bariatric surgery versus a structured weight-loss program for people with type 2 diabetes and overweight or obesity. Her doctor explained that the trial, called the Triabetes study, was randomizing participants into one of three interventions—one of two different surgical procedures or an intensive lifestyle weight-loss intervention. Keisha knew this meant there was no guarantee she would be assigned to one of the surgery groups. But she saw this as an opportunity to potentially improve her health and contribute to clinical research. So, in 2010, she enrolled in the study and underwent Roux-en-Y gastric bypass surgery, a type of bariatric surgery that staples the stomach to create a small pouch that holds less food and bypasses the rest. "I felt so lucky about my assignment! I was excited and ready to get back to my old self," she exclaimed. And that she did.

"Without these studies, my health would not be what it is today.... They gave me a lot of life back to raise my family," Keisha said, referring to her participation in clinical research.

Keisha underwent an initial assessment 2 weeks after surgery and then every 3 months for 1 year after her surgery, consistent with standard practice. At the follow-up visits, she was weighed, had her blood pressure checked, and had blood drawn. She was also counseled for lifestyle modifications, which included a diet program and increased physical activity. Keisha changed her diet, adhered to instructions, and noticed results almost immediately. She lost a substantial amount of weight, going from 170 to 125 pounds, and, remarkably, her type 2 diabetes went into remission—she no longer needed any medication to treat the disease.

THE UPS AND DOWNS OF TYPE 2 DIABETES AND OVERWEIGHT/OBESITY

A few years after the Triabetes study concluded, study coordinators approached Keisha and asked her if she would be willing to participate in a follow-up observational study, the Alliance of Randomized Trials of Medicine versus Metabolic Surgery in Type 2 Diabetes, or ARMMS-T2D. This study would combine data from four independent randomized trials conducted across the United States, including the Triabetes study, with a goal of determining long-term blood sugar control and safety and efficacy of surgery compared to lifestyle intervention for people with type 2 diabetes and overweight/obesity. Keisha jumped at the chance. "The study coordinators kept me grounded ... they made sure I kept doing what I needed to do to stay healthy," she said. And so, in 2016, she enrolled in the ARMMS-T2D study.

"The study coordinators kept me grounded ... they made sure I kept doing what I needed to do to stay healthy," Keisha said, referring to her decision to continue in the ARMMS-T2D study.

Everything was going very well for Keisha. For several years after her surgery, she experienced good health. And then the COVID-19 pandemic swept the world, presenting unprecedented challenges. Like many others, Keisha found it difficult to maintain her healthy habits. She began snacking frequently, and the weight she had lost crept back on. Even worse, her blood sugar increased significantly, and her diabetes was no longer in remission. But Keisha persisted. She began working closely with ARMMS-T2D study staff, and she remained diligent about going to follow-up appointments. "My doctor ... she really listens to me. She did what we needed to do to get things right," Keisha remarked. She worked hard to lose weight, and she began taking insulin. Her HbA1c

level (a measurement of blood sugar), which had been very high at 12 percent, dropped to 7 percent—an impressive accomplishment. She hopes to lose another 10 pounds and be medication-free once again.

"Before I joined these studies and had surgery, I had no strength. I was always tired. And now I have so much energy to play with my grandson!" Keisha said about her participation in clinical research.

When asked how she feels today, Keisha replied, "Before I joined these studies and had surgery, I had no strength. I was always tired. And now I have so much energy to play with my grandson!" Keisha is looking forward to a happy, healthy future. She plans to get out more, perhaps take a vacation, since the pandemic kept her isolated for so long. When asked what she would say to others who may be considering participating in a clinical trial, Keisha added, "Without these studies, my health would not be what it is today.... They gave me a lot of life back to raise my family."

More Information on the Alliance of Randomized Trials of Medicine Versus Metabolic Surgery in Type 2 Diabetes: ARMMS-T2D

Type 2 diabetes develops when the body can no longer overcome "insulin resistance" to keep blood sugar (glucose) levels from getting too high. Our bodies extract energy from the foods we eat, converting it into the form of blood sugar that is the main fuel used by our body's cells. The hormone insulin is made by the pancreas and acts in the tissues of the body (*e.g.*, muscle) to promote absorption of sugar from the blood. In some people, their bodies can become resistant to insulin, requiring the pancreas to produce more of the hormone to keep blood sugar at a healthy level. Type 2 diabetes occurs when the pancreas loses its capacity to produce enough insulin to compensate for the body's insulin resistance.

Type 2 diabetes and obesity continue to rise in the United States and worldwide, causing significant comorbidities such as cardiovascular disease and kidney disease, and they are a driving force behind preventable deaths. Together, type 2 diabetes and obesity contribute to substantial individual health burden and societal health care costs.

Despite recent advances in medications that achieve weight loss comparable to bariatric surgery, the drugs are costly and require continued use to maintain weight loss. In addition, their longer-term risks and benefits are still being evaluated. Several small randomized clinical trials (RCTs)—the gold standard for studying causal relationships between interventions and outcomes—and observational studies have suggested that bariatric surgery is superior to medical and lifestyle therapies for treatment of type 2 diabetes. But observational studies do not prove cause and effect, and the RCTs have been limited in number, participants enrolled, type of surgery, and follow-up duration. Therefore, long-term studies comparing bariatric surgery with a newer generation of medications (*e.g.*, GLP-1 agonists) for weight loss are needed. But, for now, despite increasing evidence supporting surgical options, many clinicians do not recommend surgery unless a person has a body mass index (BMI, a measure of weight relative to height) of 35 kg/m^2 or higher.

To evaluate long-term efficacy, durability, and safety of bariatric surgery to treat type 2 diabetes, the NIDDK-supported Alliance of Randomized Trials of Medicine versus Metabolic Surgery in Type 2 Diabetes (ARMMS-T2D) consortium

PERSONAL PERSPECTIVE

combined data from four, independent, single-center, randomized trials conducted in the United States between May 2007 and August 2013. The original studies (including the Triabetes study discussed earlier in this feature) evaluated the effectiveness of bariatric surgery compared to intensive lifestyle and medication therapy involving oral and injectable diabetes medications, including insulin, for adults with type 2 diabetes and overweight/obesity. While some participants in the study were prescribed GLP-1 agonists to help control blood sugar and boost weight loss as part of their medical management of diabetes, these drugs were not specifically examined in the study. Investigators from the four original studies pooled their results to provide a larger and more geographically diverse dataset. Follow-up data were collected through July 2022.

In total, 262 participants from the original studies enrolled in ARMMS-T2D. About 60 percent were randomized to surgery and underwent one of three different surgical procedures. The remaining participants were randomized to a medical/lifestyle management group with an intervention that had previously been shown to be effective for weight loss. Results were measured at 7 years with continued follow-up for 12 years.

At 7 years, participants who underwent surgery had an average 20 percent weight loss compared to 8 percent in the medical/lifestyle group. The surgery group had greater improvements in blood sugar control, measured by HbA1c, with 54 percent achieving an HbA1c of less than 7 percent, compared to only 27 percent of participants in the medical/lifestyle group. More participants who had surgery achieved diabetes remission compared to participants in the medication/lifestyle group, and the percent of participants using medications to treat diabetes in the surgery group decreased from 98 percent to 61 percent yet remained largely unchanged in the medication/lifestyle group. The results and differences between groups remained significant at 12 years.

The ARMMS-T2D findings provide important insights about the benefits of bariatric surgery in people with type 2 diabetes and obesity and exemplify how public investments in research can lead to clinical advances and long-term health improvements for millions of Americans with these diseases.