

Pancreatic islets contain many different cell types, including β (beta) cells that release the hormone insulin into the bloodstream when glucose (sugar) levels are high. Effective insulin secretion from the pancreas depends on well-functioning islet blood vessels. Islets contain an extensive network of small blood vessels called capillaries, which are covered by cells called pericytes. Research described in this chapter shows that pericytes play an important role in regulating blood flow through pancreatic islets by controlling capillary diameter, and that β cells play an active role in controlling their own blood supply by regulating the pericytes. Additionally, as illustrated in the images above, the research shows that islets from a person with long-standing type 2 diabetes (right panel) have fewer pericytes (green) covering capillaries (red) compared to a person without diabetes (left panel). The loss of pericytes in type 2 diabetes suggests that β cells lose the ability to control their own blood supply, which could contribute to defects in insulin release associated with the disease.

Image courtesy of Joana Almaça, Ph.D. and Alejandro Caicedo, Ph.D., University of Miami Miller School of Medicine. Almaça J, Weitz J, Rodriguez-Diaz R, Pereira E, and Caicedo A. The pericyte of the pancreatic islet regulates capillary diameter and local blood flow. [Cell Metabolism](#) 27: 630-644, doi: 10.1016/j.cmet.2018.02.016, 2018. Reprinted with permission from Elsevier, copyright 2018.

Diabetes, Endocrinology, and Metabolic Diseases

NIDDK support of basic 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.

Not only is diabetes chronic and relentless, but its slow accumulation of insults to the body can rob a person of the ability to see, hear, feel, think, and walk. In addition to increasing the risk for complications of vision loss, kidney failure, and amputation, diabetes doubles risk for heart disease, many forms of cancer, some forms of dementia, hearing loss, erectile dysfunction, urinary incontinence, and many other common diseases.¹ NIDDK is vigorously pursuing research to combat diabetes and its associated health consequences.

Diabetes is a debilitating disease that affects an estimated 30.3 million people in the United States—or 9.4 percent of the total population—and is the seventh leading cause of death.² Although rates of diabetes-related complications have declined substantially in the past two decades, disease burden remains significant as the number of people with diabetes is still very high.³ 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.⁴ Effective therapy can prevent or delay diabetic complications, but nearly one-quarter of Americans with diabetes are undiagnosed and therefore not receiving therapy.²

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

result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of disease complications. The most common forms of diabetes are type 1 diabetes, in which the body loses its ability to produce insulin, and type 2 diabetes, in which the body becomes resistant to insulin signaling, with subsequent impaired insulin production. In addition, a significant proportion of pregnant women each year are diagnosed with gestational diabetes, a form of diabetes that is similar to type 2 diabetes but unique to pregnancy. Untreated, any form of diabetes during pregnancy increases the risk of serious complications for the

¹ *Diabetes in America*, 3rd ed. Cowie CC, et al., Eds. Bethesda, MD, National Institutes of Health, NIH Pub No. 17-1468, 2018.

² Centers for Disease Control and Prevention. *National Diabetes Statistics Report*, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2017.

³ Gregg EW, et al. *N Engl J Med* 370: 1514-1523, 2014.

⁴ American Diabetes Association. *Diabetes Care* 41: 917-928, 2018.

mother and baby before, during, and after delivery. Type 1 diabetes, formerly known as juvenile diabetes, affects approximately 5 percent of diagnosed diabetes cases in adults, and the majority of diagnosed cases in children and youth.² It most often develops during childhood but may appear at any age.

Type 1 diabetes is an autoimmune disease in which the immune system launches a misguided attack and destroys the insulin-producing β (beta) cells of the pancreas. If left untreated, type 1 diabetes results in death from starvation: without insulin, glucose is not transported from the bloodstream into the body's cells, where it is needed. Thus, people with type 1 diabetes require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—to regulate their blood glucose levels. The NIDDK's landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that keeping blood glucose levels as near to normal as safely possible reduced the risk of eye, kidney, nerve, and heart complications associated with type 1 diabetes. However, despite vigilance in disease management, with current technologies to test blood glucose levels and administer insulin, it is still not possible for people with type 1 diabetes to control blood glucose levels as well as functional pancreatic β cells do. Thus, researchers are actively seeking 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 diabetes management technologies recently approved by the U.S. Food and Drug Administration, including the first commercial "hybrid artificial pancreas" device that automatically links glucose monitoring and insulin delivery, and next-generation continuous glucose monitors, including the first fully implantable device. Researchers are also working to develop β cell replacement therapies, such as islet transplantation, to cure type 1 diabetes.

Type 2 diabetes is the most common form of the disease, accounting for about 90 to 95 percent of diagnosed diabetes cases in U.S. adults.² 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.⁴ Type 2 diabetes occurs at higher rates among racial and

ethnic minority populations in the United States, including African Americans, Hispanic and Latino Americans, American Indians, some Asian Americans, and Native Hawaiians and Pacific Islanders.² 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.⁵

In people with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. As a result, the pancreas initially produces more insulin to compensate. Gradually, however, the pancreatic β cells lose their ability to secrete enough insulin to restore balance, and the timing of insulin secretion becomes abnormal, causing blood glucose levels to rise. Treatment approaches for controlling glucose levels include diet, exercise, and oral and injected medications, with insulin often required as the disease progresses. There are also an estimated 84 million U.S. adults who have a condition called "prediabetes," in which blood glucose levels are higher than normal but not as high as in diabetes.² 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 can dramatically reduce their risk of developing type 2 diabetes with diet and exercise changes designed to achieve a 7 percent reduction in body weight. To a more limited degree, the safe and well-tolerated drug metformin can also help prevent or delay type 2 diabetes. Moreover, follow-up research has shown that the benefits of reduced diabetes risk from weight loss or metformin can persist for at least 15 years.

Type 2 diabetes was previously called "adult-onset" diabetes because it is predominantly diagnosed in older individuals. However, this form of diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects youth from racial and ethnic minority populations in the United States. Believed to be related to increasing rates of pediatric obesity, this is an alarming trend for many reasons. For example, results from the NIDDK-supported Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial and the Restoring Insulin Secretion (RISE) Pediatric Medication Study showed that the disease

⁵ Kim C, et al. *Diabetes Care* 25: 1862-1868, 2002.

may be more aggressive and difficult to treat in youth compared to adults. This is worrisome because the onset and severity of disease complications correlate with both the duration of diabetes and control of blood glucose levels; thus, those with early disease onset are at especially high risk for developing complications. In addition, increasing rates of type 2 diabetes in girls may lead to more women who enter pregnancy with diabetes, and maternal diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or the development of gestational diabetes during pregnancy—confers an increased risk of type 2 diabetes in offspring. Thus, the rising rates of diabetes and prediabetes in young women could contribute to a cycle of ever-growing rates of diabetes. Therefore, 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 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 the NIDDK's mission; such research will ultimately spur the design of potential new intervention strategies. In parallel, based on knowledge from past scientific research investments, the NIDDK is vigorously pursuing studies of prevention and treatment approaches for these diseases.

PANCREATIC CELL BIOLOGY

Understanding How Cells in the Pancreas Change with Age: Researchers have used sophisticated technologies to examine individual cells from healthy human pancreata to understand how the cells change with age. As people and other organisms age, cells become damaged—*e.g.*, they accumulate changes in their DNA sequence that could potentially be harmful. This damage eventually leads to reduced tissue and organ function, or could lead to diseases such as cancer. It is known that aging processes affect cells randomly, so it is possible that individual cells in an organ or tissue could be affected differently with age and that different organs or tissues may respond in varying ways to aging processes overall. However, changes at the level of a single cell have been difficult to tease out

because of experimental limitations. Now, scientists are using a technique called single-cell RNA sequencing (sc-RNAseq) to examine gene activity in individual cells. In new research, scientists used this technique to study the effects of aging on cells in the pancreas, an organ that is associated with age-related diseases, such as type 2 diabetes.

The scientists used sc-RNAseq to measure gene activity in 2,544 human pancreas cells from 8 female and male non-diabetic organ donors ranging in age from 1 month to 54 years old. They found increased “transcriptional noise” in endocrine cells—*i.e.*, pancreatic cells that secrete hormones—from older donors compared to cells from young adults and children. Transcriptional noise refers to differences in gene activity among cells from the same individual. This suggests that aging is a process of random, rather than programmed, changes in gene activity, but the functional significance of the increased transcriptional noise remains unknown. Researchers also observed that the glucagon-producing pancreatic α (alpha) cells and insulin-producing pancreatic β (beta) cells from older people were more likely to produce both hormones simultaneously compared to cells from younger people. These so-called bi-hormonal cells have been observed previously, and have been linked to β -cell failure and type 2 diabetes. It is possible that the age-related increase in transcriptional noise could be driving this effect—*i.e.*, the increased random variation in gene activity could give rise to bi-hormonal cells; this intriguing possibility remains to be tested. Finally, the scientists found a range in the number of genetic mutations in individual pancreatic cells, and, overall, discovered that the number of mutations increased with age. Further experiments suggested that oxidative stress, which can cause DNA damage, contributed to the age-related increase in the observed mutations. Oxidative stress has also been implicated in the development of type 2 diabetes.

The findings in this study are consistent with the notion that aging processes affect cells randomly, and provide an important look at how aging affects cells in the pancreas. They also show some surprising ways in which individual cells in a healthy pancreas change with age, stimulating questions about the factors driving these changes and the functional significance of them. Similar single-cell studies of pancreata from people with type 1 or type 2 diabetes could provide

key information about the development of these diseases.

Enge M, Arda HE, Mignardi M,...Quake SR. Single-cell analysis of human pancreas reveals transcriptional signatures of aging and somatic mutation patterns. *Cell* 171: 321-330, doi: 10.1016/j.cell.2017.09.004, 2017.

New Insights into the Regulation of Islet Blood Flow in Health and Diabetes: Researchers have discovered that cells called pericytes play an important role in regulating blood flow through pancreatic islets and may contribute to islet dysfunction in people with type 2 diabetes. Pancreatic islets contain many different cell types, including β (beta) cells that release the hormone insulin into the bloodstream when glucose (sugar) levels are high. It is known that effective insulin secretion from the pancreas depends on well-functioning islet blood vessels. As such, islets contain an extensive network of small blood vessels called capillaries, which are covered by pericytes—cells that have long, finger-like projections. Little is known about islet pericytes, but studies of pericytes in other parts of the body suggest that they are contractile cells that regulate the width (diameter) of capillaries. Much like hands squeezing a garden hose to slow the flow of water, when pericytes contract, the capillary tube narrows, and blood flow is restricted. Conversely, when pericytes relax, capillary diameter and blood flow increase. In new research, scientists set out to determine if pericytes play a similar role in controlling capillary diameter and blood flow in islets.

First, the researchers visually examined pericytes in healthy mouse and human (female and male) islets. They found that pericytes made up only about 3 percent of the islet cell population, but, because of their finger-like projections, covered about 40 percent of capillaries in both mouse and human islets. Additional experiments of mouse islets showed that about half of the pericytes had contractile properties, and that activating the pericytes to make them contract decreased capillary diameter and islet blood flow. These findings suggest that pericytes play an important role in controlling blood flow in the islet. Next, the researchers studied the effect of glucose on the islet pericytes. They found that when glucose levels were high—and β cells needed to secrete insulin into the bloodstream—mouse pericytes were inhibited and

relaxed, resulting in increased capillary diameter and islet blood flow. Other experiments suggested that under the high-glucose conditions, the β cells themselves secreted a molecule along with insulin that was involved in inhibiting the pericytes. These observations suggest that β cells play an active role in controlling their own blood supply. Interestingly, the researchers observed a large decrease in the number of pericytes in islets from people with type 2 diabetes. In fact, the longer a person had type 2 diabetes, the fewer islet pericytes were present. The loss of pericytes in type 2 diabetes suggests that β cells lose the ability to control their own blood supply, which the scientists suggest could potentially contribute to defects in insulin release associated with the disease, although more research is needed to delve further into the finding and examine that intriguing possibility. Additionally, future research to understand when and why pericytes are lost in type 2 diabetes could illuminate new therapeutic targets for maintaining a healthy islet blood supply and promoting efficient insulin secretion.

Almaça J, Weitz J, Rodriguez-Diaz R, Pereira E, and Caicedo A. The pericyte of the pancreatic islet regulates capillary diameter and local blood flow. *Cell Metab* 27: 630-644, doi: 10.1016/j.cmet.2018.02.016, 2018.

NOT SO SIMPLE SUGAR METABOLISM

A Tale of Two Sugars—Fructose and Glucose Cause Differing Metabolic Effects: Researchers have found that the sugars fructose and glucose cause different metabolic effects and health outcomes in mice, but only in animals eating a high-fat diet. Overconsumption of high-fat foods and sugar-sweetened beverages is a risk factor for developing obesity, type 2 diabetes, and nonalcoholic fatty liver disease. Most food and beverages are sweetened with table sugar and/or high-fructose corn syrup, both of which contain fructose and glucose. Though both sugars promote fat build-up in the liver, the liver metabolizes fructose and glucose differently. It is unclear whether those differences lead to different health outcomes, and there is scientific debate about whether one sugar or the other is less harmful to people's health. In a new study, researchers sought to tease out whether there are metabolic differences when mice consume similar caloric amounts of fructose and glucose.

To do this, researchers added fructose or glucose to the drinking water of male mice for 10 weeks, keeping their total caloric intake similar. There were no major health differences when the animals ate a standard, low-fat diet—both groups gained similar amounts of weight and had mild accumulation of fat in their livers compared to control mice drinking only water. However, the story was different in mice eating a high-fat diet. In those mice, fructose consumption caused them to have more obesity and other indicators of metabolic dysfunction (e.g., reduced tolerance to glucose, impaired insulin signaling) compared to mice drinking the same caloric levels of glucose. Surprisingly, glucose appeared to protect animals eating a high-fat diet: their glucose tolerance and sensitivity to insulin were similar to control mice eating a standard chow diet, and they did not gain more weight than animals eating a high-fat diet alone even though they were consuming extra calories from the glucose. In mice eating a high-fat diet, both fructose and glucose led to the accumulation of high levels of liver fat, but experiments suggested that the underlying mechanisms leading to fat accumulation differed between the two sugars. Because fructose was associated with poor metabolic outcomes as described above, the researchers next studied a protein called ketohexokinase (KHK) that is involved in the first step of fructose metabolism. They found that *Khk* gene activity in the liver was increased in mice consuming fructose compared to animals consuming glucose or water. Experimentally decreasing the activity of the *Khk* gene in the liver resulted in improved health outcomes in fructose-consuming mice eating a high-fat diet—e.g., they had less weight gain, improved glucose tolerance, and less fatty liver compared to animals with normal *Khk* gene activity eating the same diet. Extending their observations to people, the researchers found that *KHK* gene activity and protein levels were higher in liver biopsy samples from obese adolescents with more advanced fatty liver disease compared to adolescents with no or less severe fatty liver disease. Taken together, these findings suggest that KHK may be a target for treating fatty liver disease in people.

This research has found that, in mice eating a high-fat diet, fructose leads to poor metabolic outcomes, whereas glucose appears to be protective. Further research could determine whether the observed differences between the two sugars hold true in women and men, and if adjusting sweetener use could have beneficial health effects.

Softic S, Gupta MK, Wang GX,...Kahn CR. Divergent effects of glucose and fructose on hepatic lipogenesis and insulin signaling. *J Clin Invest* 128: 1199, doi: 10.1172/JCI 99009, 2018.

A Surprising Result Improves Understanding of Processes Controlling Blood Glucose Levels: An unexpected result has shed new light on pathways affecting blood glucose (sugar) levels, while suggesting a potential new therapeutic approach for people with type 2 diabetes. The body needs a certain level of glucose in the blood in order to sustain life, so during periods of fasting, the pancreatic hormone glucagon signals the liver, stimulating it to produce glucose for release into the blood. In people with type 2 diabetes, this pathway is often active even when not needed, with excess glucose production from the liver contributing to high blood glucose levels. Glucagon acts by binding to a receptor on liver cells, activating a protein in the cell called a G protein, which in turn sends molecular signals that lead to glucose production and secretion. This arrangement—a hormone outside the cell binding to a receptor that extends inside, where it is coupled to a G protein that in turn triggers the response to the hormone—is quite common. The G proteins come in several different types that have differing effects within the cell—sometimes completely opposite effects.

The glucagon receptor is typically associated with a G protein designated G_s , which when stimulated increases glucose production from the liver. Research on receptors in other parts of the body has shown that G_s -coupled receptors can be counteracted by the effects of other receptors bound to a different G protein designated G_i . Therefore, researchers thought it might be possible to counteract the glucagon pathway in people with type 2 diabetes by stimulating G_i signaling in the liver. To test the idea, they created mice that contain a special, G_i -linked receptor they could stimulate using a chemical that has no effect on ordinary mice. When they used the chemical to simulate G_i in male mice, however, they did not see the expected result: instead of going down, liver glucose production increased—significantly. In contrast, an experiment that effectively eliminated G_i in the livers of male mice greatly improved blood glucose control, even protecting the mice from the effects of a diet that otherwise would have induced them to develop type 2 diabetes. Experiments with human liver cells suggested that G_i signaling increases liver

glucose production in people as well. Thus, this new, if surprising, discovery in mice is encouraging, as a therapeutic that acts to reduce G_i signaling in the liver could turn out to be an attractive approach to help control blood glucose in people with type 2 diabetes. However, because G_i has important functions in many tissues other than the liver, time will tell whether a safe and effective liver-targeted approach can be found that avoids undesirable side effects.

Rossi M, Zhu L, McMillin SM, ...Wess J. Hepatic G_i signaling regulates whole-body glucose homeostasis. *J Clin Invest* 128: 746-759, doi: 10.1172/JCI94505, 2018.

CLINICAL RESEARCH ON TYPE 1 DIABETES

Preserving Insulin Production in People with Newly Diagnosed Type 1 Diabetes: Researchers have discovered that treatment with a medicine that suppresses the immune system, called anti-thymocyte globulin (ATG), preserved insulin production and improved blood glucose (sugar) control for at least a year in people with newly diagnosed type 1 diabetes, as compared to placebo (no medicine). Type 1 diabetes is an autoimmune disease in which a person's immune system destroys β (beta) cells in the pancreas that make insulin. Previous research has shown that people whose bodies continue to produce some insulin had better blood glucose control, less hypoglycemia, and reduced rates of disease complications. Therefore, current research is examining ways to preserve more insulin production in people with type 1 diabetes. For example, a pilot study previously showed that treatment with ATG in combination with a modified protein called GCSF preserved insulin production for 1 year in people with established type 1 diabetes (duration of disease of 4 months to 2 years). ATG is a medicine used to prevent or treat immune system rejection of a transplanted organ; GCSF is used to increase white blood cell counts in people undergoing chemotherapy. Researchers in NIDDK's Type 1 Diabetes TrialNet built on the results of the pilot study to determine whether treatment with ATG alone or in combination with GCSF could preserve insulin production when used close to the initial diagnosis of type 1 diabetes.

To examine this question, researchers enrolled 89 female and male children and adults, ages 12 to 42 years, with newly diagnosed type 1 diabetes (less than 100 days since diagnosis) in a three-arm clinical trial. One group received a single course of ATG administered via intravenous infusions; another group received the single course of ATG followed by treatment with GCSF administered through an injection every 2 weeks for a total of 6 doses; and the control group received placebo. The study was blinded, meaning that all participants received the infusions and injections, but did not know whether they were getting medicine or placebo. After 1 year of follow-up, the researchers found that the group receiving ATG alone produced more C-peptide, a measure of insulin production, compared to the placebo group. However, C-peptide levels in the ATG/GCSF group were similar to the placebo group. People in both the ATG and ATG/GCSF groups had better average blood glucose control, as measured by hemoglobin A1c levels, than those in the placebo group. Trial participants continue to be followed to determine if the treatment effects persist for 2 years.

The findings show that a single course of ATG could preserve insulin production in people with newly diagnosed type 1 diabetes for at least 1 year, as compared to placebo, but that GCSF did not enhance benefit. These results differ from the pilot study that found benefit from ATG/GCSF combination therapy, although the pilot study did not examine ATG alone and those participants had more established type 1 diabetes. Like most drugs that target the immune system, ATG treatment has side effects of administration, and its therapeutic effects wane over time after treatment. TrialNet is continuing to follow the study participants, and the data from the 2 year follow-up will help researchers determine whether treatment with ATG alone or in combination with other agents should be pursued for preventing or delaying type 1 diabetes in individuals prior to clinical diagnosis.

Haller MJ, Schatz DA, Skyler JS, ...Greenbaum CJ; Type 1 Diabetes TrialNet ATG-GCSF Study Group. Low-dose anti-thymocyte globulin (ATG) preserves β -cell function and improves HbA1c in new-onset type 1 diabetes. *Diabetes Care* 41: 1917-1925, doi: 10.2337/dc18-0494, 2018.

DIABETES TREATMENT AND VITAMIN D STATUS

Diabetes Drug Alters Vitamin D Levels, Possibly Explaining Increased Bone Fracture Risk: Scientists found that the diabetes drug canagliflozin reduces vitamin D levels and calcium uptake, which may explain why this drug can increase the risk of bone fractures. Canagliflozin is one of a class of drugs called sodium glucose cotransporter-2 (SGLT2) inhibitors, which lower blood glucose (sugar) levels by preventing glucose reabsorption from urine in the kidney. Several SGLT2 inhibitors are U.S. Food and Drug Administration-approved to treat type 2 diabetes, and they can also reduce kidney and heart complications, two major causes of death in people with diabetes. However, SGLT2 inhibitors such as canagliflozin can also have detrimental side effects, including an increased risk of bone fractures.

In a study conducted by intramural scientists and led by NIDDK, in conjunction with other NIH Institutes, scientists hypothesized that canagliflozin may affect bone health by reducing calcium uptake. In addition to its effects on glucose, the SGLT2 protein transports sodium into kidney cells. Inhibiting SGLT2 lets sodium build up outside the cells, causing another transporter to increase the cells' uptake of phosphate. Based on results from previous studies, the researchers suspected that this increase in phosphate could trigger body-wide signals that ultimately reduce calcium absorption in the gastrointestinal tract. To test this theory, 9 female and 16 male healthy, non-diabetic volunteers received courses of canagliflozin and a placebo for 5 days each, with participants blinded to which course they received first. The participants ate a standardized diet before and during the study, so the researchers could investigate how canagliflozin affects levels of nutrients like phosphate, sodium, vitamin D (which promotes calcium absorption in the gut), and calcium. Consistent with their prediction, canagliflozin rapidly increased phosphate uptake, resulting in signals that, on average, reduced vitamin D levels in the blood as well as calcium uptake from food. The magnitude of these reductions varied from person to person, however, and were generally small enough that they might only affect the health of certain people with already low vitamin D and/or calcium levels. Though the study was too brief to measure bone fracture risk, canagliflozin's effects on calcium uptake, a key contributor to bone health, provides

a likely explanation for the increased fracture risk with canagliflozin use observed previously.

The researchers noted that it is not yet known if all SGLT2 inhibitors affect vitamin D to the same extent. Future research will also be required to confirm whether baseline vitamin D levels affect fracture risk when taking SGLT2 inhibitors, and, if so, whether modifying vitamin D levels could help protect bone health. Overall, this research revealed new insights about a possible side effect of a commonly prescribed, heart-protective diabetes drug that could be crucial to people and their doctors seeking to personalize their diabetes treatment.

Blau JE, Bauman V, Conway EM, ... Taylor SI. Canagliflozin triggers the FGF23/1,25-dihydroxyvitamin D/PTH axis in healthy volunteers in a randomized crossover study. JCI Insight 3: pii: 99123, doi: 10.1172/jci.insight.99123, 2018.

UNCOVERING CLUES TO METABOLIC CONTROL AND THE TREATMENT OF TYPE 2 DIABETES

Studies Show Difficulty in Treating Type 2 Diabetes in Youth and Highlight Unique Aspects of the Disease in Young People: New research reveals that two diabetes medications do not prevent rapid progression of prediabetes or recent onset type 2 diabetes in young people with the disease, even though these are the only two medications approved for pediatric type 2 diabetes. More encouragingly, however, analyses comparing metabolic tests of adults in a companion study and the youth study participants are helping scientists understand how the disease differs with age, which may one day lead to better treatment approaches. Resistance to the glucose-lowering effects of insulin is often associated with overweight, obesity, or advancing age. At first the pancreas can compensate for this problem by simply secreting more insulin, but type 2 diabetes results if the pancreas gradually loses its ability to do so. Although long thought of as a disease of middle-aged and older adults, type 2 diabetes has been appearing in teenagers in small but increasing numbers in recent years. This trend is alarming for many reasons—for example, because the complications of the disease, which can be both debilitating and life threatening, are more likely to develop the longer someone has diabetes.

Furthermore, the recent Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study found that type 2 diabetes was very difficult to treat when it occurred in younger people, and that the disease progressed much more rapidly than it did in those who develop it in middle age or later. TODAY compared metformin alone with metformin together with a lifestyle intervention, and with metformin plus another medication that was then commonly used to treat adults with diabetes; none of these approaches was found to be effective. One encouraging observation from that study was that participants who had been enrolled in the study earlier in the course of their disease fared better than those whose diabetes was already more advanced. This finding suggested that focusing on preventing disease progression in young people with prediabetes or recent onset type 2 diabetes might be beneficial.

Indeed, the idea for the Restoring Insulin Secretion (RISE) studies comes from earlier observations that use of the diabetes drug metformin and/or a long-acting form of insulin can improve the function of the insulin-producing β (beta) cells of the pancreas in adults with prediabetes or recent-onset type 2 diabetes. The theory is that by taking some of the burden off the pancreas through early treatment—giving it a “rest”—it may be possible to slow or even reverse the progressive loss of its capacity to respond to glucose by secreting insulin. RISE is actually a group of three clinical trials testing this idea in different ways. Two trials are testing approaches to restoring insulin secretion in adults with prediabetes or recent-onset type 2 diabetes, and one studied younger participants, who were between 10 and 19 years of age at study enrollment. This RISE Pediatric Medication Study focused on preventing progression of the disease by utilizing the two drugs approved for treating type 2 diabetes in children, metformin and insulin. The RISE study randomly assigned the 91 participants to take metformin for 1 year, or to take a long-acting form of insulin for 3 months, followed by metformin for 9 months. (Insulin had not been tested in the TODAY study.) Unfortunately, neither approach was successful, as the disease progressed markedly in both groups over the course of the study, underlining the great importance of finding better approaches to preventing and treating type 2 diabetes in young people.

To try to understand the physiological reasons why type 2 diabetes is so much harder to treat when it develops at a young age, researchers

also compared metabolic test results from participants in the pediatric RISE study with tests in adult participants in the other two RISE studies. Regardless of age, the RISE participants at entry into all three clinical trials had similar fasting blood glucose levels, and similar glucose levels 2 hours after ingesting a drink containing a standardized amount of sugar, referred to as an oral glucose tolerance test (OGTT). However, researchers examined the OGTT in greater detail, checking two measures of insulin levels before and after the glucose challenge and found a striking difference: at each time tested, the 10- to 19-year-old participants had markedly higher insulin levels than did the adults. This suggests that young people with prediabetes or early type 2 diabetes are different from older people with these conditions in that they retain a more robust capacity to produce insulin, but that this capacity is masked by a more severe degree of insulin resistance. Another analytic method supported these findings: researchers used an IV to increase blood glucose levels—holding them first at one level, and then at a higher level—and then measured how the participants’ pancreases and other tissues responded. Insulin levels rose significantly higher in the young RISE participants than in the adults, often beyond the amount of insulin that was needed or desirable. These results further confirm previous observations that puberty can aggravate insulin resistance, suggesting that improving insulin sensitivity may be a key therapeutic strategy; yet metformin—the only commonly used anti-diabetes drug that is known for improving insulin resistance—was ineffective for youth. These studies together underline the importance of finding new and better ways to treat and prevent type 2 diabetes in young people.

The RISE Consortium. Impact of insulin and metformin versus metformin alone on β -cell function in youth with impaired glucose tolerance or recently diagnosed type 2 diabetes. Diabetes Care 41: 1717-1725, doi: 10.2337/dc18-0787, 2018.

The RISE Consortium. Metabolic contrasts between youth and adults with impaired glucose tolerance or recently diagnosed type 2 diabetes: II. Observations using the oral glucose tolerance test. Diabetes Care 41: 1707-1716, doi: 10.2337/dc18-0243, 2018.

The RISE Consortium. Metabolic contrasts between youth and adults with impaired glucose tolerance or recently diagnosed type 2 diabetes: I. Observations using the hyperglycemic clamp. Diabetes Care 41: 1696-1706, doi: 10.2337/dc18-0244, 2018.

New Insights on Risk Factors for Severe Hypoglycemia in People with Type 2 Diabetes:

Results of NIDDK-supported research have improved understanding of factors that can help predict vulnerability to severe hypoglycemia in African American and White individuals with type 2 diabetes. Although untreated diabetes results in blood glucose (sugar) levels that are too high, accidental over-treatment can lead to blood glucose levels that are too low, a condition known as hypoglycemia. If glucose levels fall far enough, severe hypoglycemia can cause seizures, loss of consciousness, and even death. More mild instances of hypoglycemia can be disorienting, and may raise the odds of accidental injury. Hypoglycemia can occur not only when a person accidentally takes too much of a diabetes medication such as insulin or sulfonylurea, but also when a prescribed dose is accompanied by either more physical exercise or fewer calories consumed than usual, or when an unrelated illness such as an infection temporarily alters a person's metabolism. Importantly, while people with diabetes can live many years without a serious hypoglycemic episode, some people seem to be more susceptible to the problem.

To find ways to assess the risk of severe hypoglycemic episodes in people with diabetes, researchers examined outcomes from a well-characterized cohort of 1,206 African American and White women and men with diabetes who had participated in a prior study. The participants, who averaged 64 years of age at the beginning of the study, were followed for a median of about 15 years—that is, half of the study participants were followed for that long or longer, and half for that long or less. During the study, 185 participants were treated at least once for severe hypoglycemia in emergency rooms, via an ambulance call, and/or by hospitalization. The study confirmed some prior research that showed, for example, that risk of severe hypoglycemia increases with age, with poor cognitive function, and with poor kidney function, and is higher in African Americans than in Whites.

In addition, the study found some intriguing new risk factors. Not only is cognitive dysfunction a risk, but physical disability, assessed by the inability to perform activities of daily living, was found to be a new risk for hypoglycemia. Another demographic risk factor identified by this study is the use of Medicaid insurance, which may reflect socioeconomic disparities. Interestingly, researchers found that people with greater fluctuations in blood glucose

control—indicated by low blood levels of a compound called 1,5-anhydroglucitol (1,5-AG)—were at elevated risk for an episode of severe hypoglycemia. This means 1,5-AG may be a valuable new laboratory test of hypoglycemia risk, since HbA1c levels reflect a person's average blood glucose levels over several weeks, but indicate nothing about how much blood glucose has fluctuated around that average during that time period. Taken together, these results may help health care providers predict which people with type 2 diabetes may benefit from additional monitoring to prevent episodes of severe hypoglycemia.

Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, and Selvin E. Risk factors for severe hypoglycemia in Black and White adults with diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care 40: 1661-1667, doi: 10.2337/dc17-0819, 2017.

Treating Type 2 Diabetes in Adolescents with Severe Obesity:

In a new analysis comparing data from two different studies that evaluated treatments for adolescents with severe obesity and type 2 diabetes, researchers determined that bariatric surgery led to improved outcomes over treatment with medication. Type 2 diabetes is increasingly being diagnosed in youth, and it disproportionately affects youth from racial and ethnic minority populations in the United States. The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial showed that the disease may be more aggressive and difficult to treat in youth compared to adults. Because the onset and severity of disease complications correlate with both the duration of diabetes and control of blood glucose (sugar) levels, those with early disease onset are at greater risk for complications than those who develop the disease later in life. Thus, it is imperative to find treatments that help this vulnerable population manage their disease and achieve better glucose control.

To glean more information to compare treatment options, researchers returned to the outcomes of two NIDDK-supported studies: TODAY and the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS). In the TODAY clinical trial, youth with type 2 diabetes received either the anti-diabetes medication metformin alone; metformin in combination with another medication, rosiglitazone; or metformin with an intensive lifestyle intervention. The trial showed that metformin alone and metformin with lifestyle intervention were insufficient to control blood glucose adequately in

about half of the participants. The trial also showed that, although the combination of metformin with rosiglitazone worked somewhat better than metformin alone, this drug combination failed to maintain adequate blood glucose control in a high proportion of participants. Teen-LABS is an observational study that has been evaluating health outcomes of adolescents with severe obesity who underwent bariatric surgery. Teen-LABS found that bariatric surgery resulted in major weight loss and improvement in overall health and quality of life. However, questions remained regarding treatment options for youth with severe obesity and type 2 diabetes.

Because some of the Teen-LABS and TODAY participants had both type 2 diabetes and severe obesity, researchers embarked on a new analysis to compare bariatric surgery and medication for treatment of these conditions in youth for the first time. They analyzed data for 30 adolescents with severe obesity and type 2 diabetes who underwent bariatric surgery in Teen-LABS in comparison with data from 63 adolescents with these conditions who received medication in the TODAY study. The researchers found that hemoglobin A1c levels (HbA1c, a measure of average blood glucose control) worsened over 2 years of follow-up in adolescents treated with medication (an average increase from an HbA1c of 6.4 percent to an HbA1c of 7.8 percent, with a higher value indicating worse control), whereas HbA1c levels improved in adolescents treated with bariatric surgery (an average decrease in HbA1c from 6.8 percent to 5.5 percent). Adolescents treated with medication were also more likely to gain weight (an average increase of nearly 13 pounds), have worse diabetes (as indicated by HbA1c and other measures), and show no improvement in blood pressure or kidney function. In contrast, adolescents treated with bariatric surgery showed weight reduction (an average loss of over 94 pounds), remission of their diabetes, and improvements in blood pressure and kidney function.

The striking improvements in those treated with bariatric surgery indicate that this could be a treatment option for adolescents with severe obesity and type 2 diabetes. Bariatric surgery, however, has serious surgical risks that need to be balanced with the potential benefits. For example, within 2 years of having bariatric surgery, 23 percent of adolescents with type 2 diabetes treated with

bariatric surgery required subsequent operation and/or hospitalization for conditions related to the bariatric surgical procedure. Further research is needed to understand the long-term outcomes of bariatric surgery in this population. These results also continue to highlight the pressing need for better treatments for youth with type 2 diabetes—and for better prevention of diabetes in youth.

*Inge TH, Laffel LM, Jenkins TM, ... Zeitler PS; for the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) and Treatment Options of Type 2 Diabetes in Adolescents and Youth (TODAY) Consortia. Comparison of surgical and medical therapy for type 2 diabetes in severely obese adolescents. *JAMA Pediatr* 172: 452-460, doi: 10.1001/jamapediatrics.2017.5763, 2018.*

NEW INSIGHTS ON THE COMPLICATIONS OF DIABETES

Immune Cells Convert into New Tissue To Close Wounds: Scientists have shed light on a long-standing mystery: what happens to macrophages, a type of immune cell, during skin wound healing? A new study has found the answer: the macrophages change their properties to become part of healed skin, and this process is crucial for wound closure and may be impaired in diabetic wound healing. Previous work had suggested that wound inflammation can cause macrophages responding to the injury to “transdifferentiate,” or convert into another type of cell. However, what triggers transdifferentiation, what happens to macrophages after the wound heals, and what controls how quickly and how well wounds heal is still unknown.

To investigate these questions, researchers used microscopy to study macrophages in male and female mice’s skin wounds. They found that macrophages rushed to wound sites, then converted into cells similar to a type of connective tissue cell (fibroblasts) and eventually made up nearly two-thirds of new tissue formed to close the studied wounds. Researchers also found macrophage-derived fibroblast-like cells in healing chronic human skin wounds, suggesting a role for this process in human disease.

The scientists next investigated what was causing this transdifferentiation. Interestingly, they found that treating human macrophages with fluid from healing,

but not non-healing, wounds promoted conversion of the macrophages to fibroblast-like cells. This result suggested that a factor in the wound fluid played a role in macrophage transdifferentiation. Several experiments searching for this factor demonstrated that wounded human skin cells secreted more of a small molecule called miR-21 into the fluid of healing wounds than of non-healing wounds. Adding miR-21 to macrophages in the laboratory caused them to convert into fibroblast-like cells, and removing miR-21 from a new wound in mice impaired healing. These results indicated that miR-21 plays a critical role in signaling macrophages to become fibroblast-like cells and that this process is critical to wound healing. Additionally, researchers asked whether miR-21 and transdifferentiation have roles in chronic, slow-healing wounds, such as those seen in diabetes. They found that diabetic mice secreted less miR-21 than non-diabetic mice when wounded and that macrophage transdifferentiation and healing at the wound site was impaired. These differences were reduced if the mice's wounds were treated with miR-21.

These links between miR-21 and the transdifferentiation of macrophage cells into cells that become part of healed skin give new insight into how wound healing is impaired during diabetes. Further research is needed to test whether therapies targeting macrophage transdifferentiation could improve wound healing in humans.

Sinha M, Sen CK, Singh K,...Roy S. Direct conversion of injury-site myeloid cells to fibroblast-like cells of granulation tissue. Nat Commun 9: 936, doi: 10.1038/s41467-018-03208-w, 2018.

NEW TOOLS TO TREAT GENETIC DISEASES

Turning Pancreatic Alpha Cells into Insulin-Producing Beta-like Cells via Gene Therapy: Scientists have developed a new way to replace lost β (beta) cells in mouse models of type 1 diabetes. Type 1 diabetes stems from a misguided autoimmune attack destroying the pancreas' insulin-producing β cells, which reside in cell clusters called islets. Insulin therapy is a life-saving treatment for this disease, but it is difficult to keep blood glucose (sugar) levels within the recommended range with current therapies. Scientists are studying new ways to replace lost β cells, and one approach is

to "reprogram" other pancreatic cells—such as glucagon-producing α (alpha) cells, which are also in the islets—to take over β cells' function. Toward this end, one group of scientists has used a repurposed virus as a vehicle to deliver extra copies of two genes involved in β cell maturation and function (*Pdx1* and *Mafa*) into the mouse pancreas. They gave this gene therapy to mice who had diabetes because their β cells had been destroyed. After the therapy, the mice no longer had diabetes, and their blood glucose levels stayed in the normal range until the experiment's end 6 months later. Researchers found that the *Pdx1* and *Mafa* genes were delivered to pancreatic α cells, where the genes prompted the α cells to become β cell-like and produce insulin.

However, could this approach effectively treat diabetes in a mouse model mimicking the ongoing autoimmune attack seen in people with type 1 diabetes, or would this autoimmune response destroy the newly reprogrammed insulin-producing cells? To answer these questions, the researchers gave the *Pdx1* and *Mafa* gene therapy to mice made diabetic due to an ongoing autoimmune attack that destroyed their β cells. Mice that received the therapy soon after the onset of diabetes had increased insulin production and more β -like cells when compared to controls. Importantly, their blood glucose levels stayed in the normal range for about 4 months before returning to the diabetic range, indicating that the newly formed β -like cells could evade immune attack during that time. Also, the researchers were able to reprogram human α cells directly in cell cultures in the laboratory. Human pancreatic islets isolated from male and female deceased donors were experimentally treated to destroy their β cells and then treated with the *Pdx1* and *Mafa* gene therapy. When these reprogrammed islets were transplanted into an autoimmune diabetic mouse model, insulin production went up, and the mice had significantly better blood glucose control than similar mice given placebo-treated islets.

Overall, these results describe a new method to reprogram mouse pancreatic α cells to functionally replace destroyed β cells. The researchers cautioned that more research is needed to determine if this approach would work in people with type 1 diabetes, including whether human β -like cells would survive

for any length of time or if they would need extra protection against the ongoing autoimmune attack that occurs in type 1 diabetes.

Xiao X, Guo P, Shiota C,...Gittes GK. *Endogenous reprogramming of alpha cells into beta cells, induced by viral gene therapy, reverses autoimmune diabetes. Cell Stem Cell* 22: 78-90, doi: 10.1016/j.stem.2017.11.020, 2018.

Improved Treatment Targeting Root Cause of Cystic Fibrosis May Be on Horizon:

A clinical trial led by a pharmaceutical company with additional support from other organizations and from an NIDDK-supported Cystic Fibrosis Center that facilitated the conduct of the trial has shown that a combination of two medications provides significant clinical benefit in a subgroup of patients with cystic fibrosis (CF). CF occurs when people lack a functional copy of the *CFTR* gene, which encodes a protein required for transporting chloride, one of the two chemical components of salt, in and out of our cells. People with CF develop severe lung disease, and digestive problems, and commonly develop a form of diabetes once they reach adulthood; these complications significantly diminish both lifespan and quality of life. People have two copies of this gene, but in people with CF inactivating mutations affect both copies. While many *CFTR* mutations are known, the one that is the most common by far is designated Phe508del (also known as F508del or delta F508). This mutation not only dramatically reduces the amount of *CFTR* protein that reaches the cell surface where it is needed to function, but also practically eliminates the chloride transporting capability of the small amount of *CFTR* that does get there. The combination of these effects means people with two copies of Phe508del—about half of CF patients—have a very severe form of CF. About another 40 percent of people with CF have one copy of Phe508del paired with one of the rarer *CFTR* mutations. A few dozen of these rarer forms of the gene are termed “residual function mutations” as they encode forms of *CFTR* protein that retain a limited capacity to transport chloride. People with one copy of a residual-function mutation and one copy of Phe508del typically develop a less severe form of CF than those with two copies of Phe508del.

Using knowledge of the different *CFTR* mutations, scientists have developed candidate medicines that may help restore sufficient *CFTR* function

to partially alleviate CF symptoms. Already, a combination of ivacaftor, a compound that facilitates transport of chloride through mutant forms of the *CFTR* protein, plus lumacaftor, a compound that stabilizes *CFTR* proteins so they reach the cell surface more easily and in greater amounts, was approved by the U.S. Food and Drug Administration (FDA) in 2015 for use in CF patients with at least one copy of Phe508del. However, benefits are modest, and some patients experience significant side effects. The current study tested a combination of ivacaftor and a promising new (not yet FDA-approved) *CFTR*-stabilizing drug, tezacaftor, in people who have one copy of Phe508del and one copy of a residual-function *CFTR* mutation. The study had an unusual design that included two 8-week treatment periods, separated by 8 weeks in which the 248 male and female participants with CF (who were at least 12 years old) did not receive study medications. Each participant was randomly assigned to receive either combination therapy, ivacaftor alone, or a placebo during the first treatment period, and (after the break) to have one of the other two regimens during the second. As a result, all of the participants received at least one of the experimental therapies for at least one of the two treatment periods.

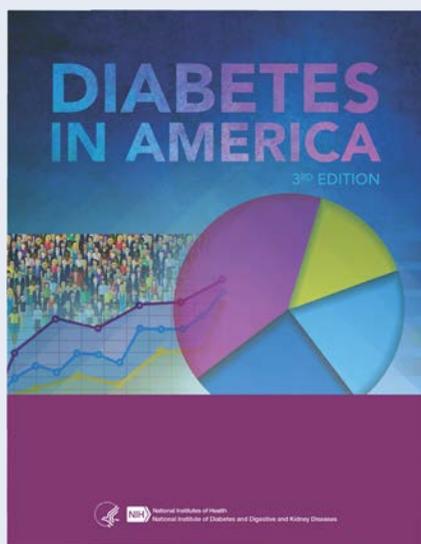
The researchers found that the amount of air that participants were able to exhale per second—a standard measure of lung function in people with CF—rose by an average 4.7 percentage points with ivacaftor treatment alone, and 6.8 percentage points with the combined ivacaftor-tezacaftor treatment, compared to a placebo. (That is, placebo-taking participants able to exhale 50 percent as much as expected for people without CF would be able to exhale an average of 54.7 percent with ivacaftor alone, or 56.8 percent with the combination therapy.) These improvements may seem small, but they suggest either therapeutic approach could confer clinical benefit. Indeed, participants—who did not know whether they were taking one of the medication regimens or placebo at any given time—reported significantly better measures of respiratory-related quality of life after taking ivacaftor or ivacaftor-tezacaftor than after taking placebo. Importantly, there were no differences in the adverse event frequency between placebo and drug treatments.

An important caveat is that the 8-week intervention periods of the study were too short to ascertain definitive effects on long-term clinical outcomes. However, all participants were enrolled in an ongoing follow-on study that should provide greater insights into the longer-term effects of the two treatments. Moreover, results from a different trial supported entirely by the same pharmaceutical company suggest that the drug combination may also benefit people with two copies of Phe508del. Together, these studies

may form the basis for eventual FDA approval of the tezacaftor-ivacaftor combination to treat the molecular cause of CF in a large proportion of people with the disease. If results from the two trials are borne out, this treatment approach may one day significantly improve the health and quality of life of many people with CF.

Rowe SM, Daines C, Ringshausen FC,...Davies JC. Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. N Engl J Med 377: 2024-2035, doi: 10.1056/NEJMoa1709847, 2017.

NIDDK’s “Diabetes in America, 3rd Edition” Provides Preeminent Source for Scientific Information on Diabetes and Its Complications



Diabetes affects nearly everyone, from the more than 110 million Americans with or at risk for the disease to the many more people who care for them. It is chronic and relentless and increases the risk for many devastating conditions and diseases. To understand the burden of diabetes in the United States, in August 2018, the NIDDK completed the third edition of a resource designed to be a preeminent source for crucial scientific information on diabetes and its complications: *Diabetes in America, 3rd Edition*. Developed by researchers at NIDDK with contributions from leading diabetes experts from around the world, *Diabetes in America* is an assessment of epidemiologic, public health, clinical, and clinical trial data on diabetes and its complications in the United States. The resource covers the spectrum of diabetes, describing data and trends, complications of diabetes and related conditions, and prevention and medical care for diabetes, including outlining major diabetes research findings.

Diabetes in America is designed to be useful to a variety of audiences, presenting data patients can use to gain a fuller understanding of their condition, practitioners can use to determine the likelihood that their patients will develop diabetes or associated complications, health policymakers can use to help guide decision-making related to diabetes, and researchers can use to identify areas of needed research to advance care for people with or at risk for diabetes.

Diabetes in America also describes the effects the disease has on the entire body—from head to toe. Diabetes not only increases the risk for complications such as vision loss, kidney failure, nerve disease, and amputation, but also doubles the risk for heart disease, many forms of cancer, some forms of dementia, hearing loss, and urinary incontinence. *Diabetes in America* provides comprehensive information about the link between diabetes and those and other conditions, such as osteoarthritis, bone fractures, gum disease, and depression.

Diabetes in America shows that though much research progress has been made, there is still much work to be done to achieve the goal of good health for all people with or at risk of diabetes. The NIDDK hopes that this new edition of *Diabetes in America*, the first in more than 20 years, will help educate people about diabetes and its many complications, to lessen this burden for everyone.

Diabetes in America, 3rd Edition, is available, in individual chapters and online only, on the NIDDK website at: www.niddk.nih.gov/about-niddk/strategic-plans-reports/diabetes-in-america-3rd-edition

Workshop Highlights

State-of-the-Science in Diabetes Genetics

On April 23–24, 2018, the NIDDK hosted a workshop in Bethesda, Maryland, to accelerate the identification and characterization of genetic factors related to diabetes. This workshop—titled “Towards a Functional Understanding of the Diabetic Genome”—featured presentations by an international group of experts on recent findings and innovative approaches, as well as identification of knowledge gaps and future opportunities in the field.

Diabetes is a complex disease that can be affected by both genetic and environmental factors. In type 2 diabetes, the body does not make enough insulin or does not use insulin well, while in type 1 diabetes a misguided autoimmune attack destroys the insulin-producing cells in the pancreas. Understanding the genetic factors that affect diabetes development or progression could lead to new therapies and better disease outcomes. To find these factors, researchers have compared the genetic information of people with and without diabetes. These studies produced a wealth of data and identified many genetic regions related to the disease. It has been more difficult to connect all of these diabetes-associated genetic factors to their functions in the body, and this is an area ripe with opportunity. This knowledge could advance precision medicine approaches, allowing the tailoring of diabetes treatment plans to counter or take advantage of a person’s unique genetic makeup.

Workshop attendees presented their recent research progress using diverse approaches and multiple data types to “connect the dots” between genetic

factors and diabetes. Integrating all these data types with genetic association data will be important to build a complete picture of how particular genomic regions influence diabetes. One of the important themes that emerged from the workshop was that although the pancreas—the major organ responsible for controlling blood glucose (sugar) levels—plays an important role in diabetes development, other tissues such as fat, liver, skeletal muscle, and brain also play a part. Presentations highlighted new findings on diabetes disease mechanisms and on various ways that diabetes-associated genetic differences can control gene function. Workshop participants also shared information on cutting-edge genetic analysis techniques and valuable research model systems, as well as giving demonstrations of useful diabetes genetics resources such as the Type 2 Diabetes Knowledge Portal (www.type2diabetesgenetics.org; part of the Accelerating Medicines Partnership) and the Diabetes Epigenome Atlas (www.t2depigenome.org). Much of the workshop focused on type 2 diabetes, though the studies and resources discussed could eventually benefit all people with diabetes.

At the end of the workshop, attendees discussed how to fill research gaps, what resources are needed to build upon previous findings, and how to take advantage of opportunities in this developing field. This information is expected to inform NIDDK planning efforts to support diabetes genetics research and will help advance precision medicine approaches for predicting, preventing, and treating diabetes.

Diabetes Mellitus Interagency Coordinating Committee Meeting Focuses Attention on the Importance of Research in Older Americans with Diabetes Receiving Long-term Care

On May 29, 2018, the Diabetes Mellitus Interagency Coordinating Committee (DMICC) held a meeting about “Fostering Research on Older Adults with Diabetes Receiving Long-term Care.” U.S. adults over age 65 have a very high prevalence of elevated blood glucose (sugar) levels. In fact, nearly one-third have diabetes, and almost half have prediabetes (glucose levels higher than normal, but lower than in diabetes) according to recent Centers for Disease Control and Prevention (CDC) data. Over 61 percent of all health care expenditures attributed to diabetes in the United States are for health resources used by older adults with diabetes, yet many studies do not focus on this group, especially when they receive long-term care services rather than dwelling independently in the community. Critical gaps of knowledge on this understudied population were identified at this meeting, and ways to address these gaps were discussed.

There was a call for better understanding how different factors alone and in combination can alter an older adult’s ability to manage diabetes, including the presence of cognitive and functional impairments, numerous competing health issues referred to as “multimorbidity,” and complex medication regimens referred to as “polypharmacy.” Who assists with diabetes care and variations in the level of assistance in different settings can also impact how well glucose levels are controlled

for older adults with diabetes. Furthermore, it is critical not just to understand how older adults with diabetes can control elevated glucose levels, but also how they can do so while avoiding hypoglycemia (low blood glucose), which can increase the risk of falls, hospitalization, and worsening of other medical conditions.

Opportunities to address these issues were discussed at the meeting. For example, representatives from the Centers for Medicare & Medicaid Services, the Veterans Health Administration, the CDC, and the NIH's National Institute on Aging presented information about sources of data that their agencies have assembled on large numbers of older adults with diabetes, particularly in long-term care settings. These presentations were paired with talks by researchers who have found innovative ways to mine these substantial quantities of data to yield key insights on how better to care for our large and growing older adult population, highlighting both the strengths and limitations of these data. Importantly, the Committee addressed how these sources of data may be utilized to fill gaps in our existing knowledge of diabetes treatment in older, managed care populations, so that we may one day achieve better long-term health outcomes for older adults with diabetes.

STORY OF DISCOVERY

Newborn Screening for Lysosomal Storage Diseases

For most people, having a baby is one of the greatest joys in life. When an infant is born with a rare genetic disorder, parental joy can be mixed with fear; but fortunately, recent decades have also brought good news for many families of children born with an inherited disease, as progress in the treatment of some of these disorders is improving health and quality of life for many affected infants.

In some cases, therapies achieve the best possible health outcomes if they are initiated before outward signs of the disorder develop. For this reason, it is critically important that advances in treatment for genetic disorders be matched with development of newborn screening programs that help quickly identify children who need them.

Newborn screening programs in most U.S. states test for dozens of genetic disorders, including several that are within the NIDDK's mission area. These include sickle cell anemia, cystic fibrosis, as well as some lysosomal storage diseases, a constellation of rare diseases whose detection in newborn screening has undergone a revolution in recent years.

WHAT ARE LYSOSOMAL STORAGE DISEASES?

The body's cells recycle many of the substances they no longer need by digesting them with proteins inside cellular compartments called lysosomes. The proteins that are missing or damaged in people with lysosomal storage diseases are considered "enzymes," meaning that each functions to promote the conversion of one chemical compound into another. Specifically, lysosomal enzymes convert toxic cellular waste products into materials that the cell can recycle or safely excrete. When one of

these enzymes is missing or inactive, toxic waste products are not properly degraded. Instead, they build up in the lysosomes where they can lead to severe organ damage. Diseases caused by such enzyme deficiencies—lysosomal storage diseases—are individually rare, but collectively affect about 1 in 7,700 infants born in the United States. Symptoms vary, and are often not apparent at birth; however, as the undigested materials accumulate, they can cause serious problems such as weakness, severe pain, brittle bones, intellectual disability, corneal clouding, organ failure, and death. Dozens of lysosomal storage diseases have been characterized, including Gaucher disease; Pompe disease; Fabry disease; and several forms of mucopolysaccharidosis (known as MPS I, MPS II, etc.), a subset of the lysosomal storage diseases resulting when someone lacks any of several enzymes needed to recycle one particular class of biological molecules.

Built on the discoveries of scientists supported by the NIDDK and other NIH Institutes and Centers and product development by pharmaceutical companies, lysosomal storage disease research is a classic story of translating remarkable findings from basic research into U.S. Food and Drug Administration (FDA)-approved treatments for many of these diseases. To take the greatest advantage of these developments, the NIDDK has also invested in developing improved methods for identifying infants who would benefit from these therapies.

BLOOD SPOT SCREENING: THE BEGINNING OF THE REVOLUTION

The first widely utilized newborn screen for a genetic disease did not detect a lysosomal storage disease; rather, it tested for phenylketonuria (PKU),

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a genetic disorder caused by the inability to break down an amino acid called phenylalanine. Amino acids are the building blocks of proteins. In PKU, phenylalanine can build up to harmful levels in the body, causing intellectual disability and other serious health problems. By the 1950s, physicians understood that the serious symptoms of PKU could be greatly reduced by carefully limiting the amount of phenylalanine in the diet of people with the disease. However, PKU can have serious, lasting effects on a child's development if the problem is not detected—and the dietary intervention initiated—early enough.

Thus, it was a landmark development when, in 1959, researchers developed a straightforward method to test for PKU. First, they saturated a small piece of paper with a drop of blood, usually collected by pricking the heel of an infant to be tested. After the spot had dried, they placed the paper onto a petri dish containing bacteria that can only grow in the presence of supplemental phenylalanine. Since healthy people store very little phenylalanine, and people with PKU accumulate significant amounts of the amino acid, this bacterial growth test made it much easier to identify babies with PKU during their first few days of life. First tested on a large scale in 1962 using blood spots from 400,000 babies, the approach was a tremendous success, allowing early dietary intervention that greatly improved outcomes for children with PKU. Within a few years, states throughout the Nation had adopted the PKU screen; a 1968 World Health Organization report led to screening in many foreign countries as well.

A METHOD TO IDENTIFY SEVERAL DISEASES AT ONCE

Similar tests using dried blood spots and bacterial growth soon followed for other genetic diseases, but there were limits to the number of such tests that could be performed with a single blood spot, and limits to the number of blood spots that could reasonably be collected from every infant. Researchers found a solution to this problem by utilizing “mass spectrometry,” a method for

simultaneously measuring the amounts of multiple chemical components from a small sample.

Early models of mass spectrometers, developed more than 120 years ago, relied on differences in the mass and charge of chemicals in a sample in order to separate them. Modern mass spectrometry methods take advantage of other chemical differences, and are powerful enough to separate and quantify thousands of molecules at once. This technology has been widely adopted by clinical laboratories to perform a wide variety of diagnostic tests. Importantly, these tests can include simultaneous screens for dozens of genetic diseases, provided that each of those diseases has a measurable effect on the chemical components of a dried blood spot or other easily obtained sample.

THE DEVELOPMENT OF TREATMENTS FOR LYSOSOMAL STORAGE DISEASES CREATES A NEED FOR EARLY DETECTION

Although mass spectrometry was utilized to detect a growing number of genetic diseases in newborns, for at least two reasons, lysosomal storage diseases were not initially among them. First, it turns out that the levels of the metabolites that accumulate in lysosomal storage diseases can be quite variable in both healthy babies and those with lysosomal storage diseases, which can lead to test inaccuracy. A second reason was that in the late 1990s, when mass spectrometry screening of dried blood spots was becoming more common, there were no effective treatments for lysosomal storage diseases. It is not considered useful or cost-effective to test for a condition if a positive result would only make parents worry that their children are likely to develop a disease when there is no treatment their pediatrician can suggest to keep them healthy.

Fortunately, research in the early 2000s—supported by the NIDDK, other components of NIH, and voluntary groups—led to significant improvements in the treatment of many lysosomal storage diseases. Scientists studying the basic biology of the

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lysosome discovered that healthy cells do not simply synthesize the enzymes and deposit them directly into their lysosomes. Rather, each enzyme is initially synthesized in an inactive, precursor form, which the cell excretes. Either the same cell or another cell nearby reabsorbs the precursor and directs it to a lysosome, where it is converted into its mature, active form. To treat a lysosomal storage disease, therefore, clinicians can periodically inject some of the needed enzyme in its precursor form, taking advantage of these final processing steps to deliver it to lysosomes and activate it.

While by no means a cure, “enzyme replacement therapy,” as the treatment approach is called, significantly improves health for people with a variety of lysosomal storage diseases. Several such therapies are FDA-approved, while still more are under consideration. Importantly, just as with PKU, best results are obtained when treatment begins early, before organ damage has occurred. So once treatments were available, there was a need for corresponding improvements in methods to screen for lysosomal storage diseases in newborns.

FLUORESCENCE TESTS FOR LYSOSOMAL STORAGE DISORDERS

Unlike with PKU, researchers found that the most reliable way to test for lysosomal storage diseases was to test for the activities of the lysosomal enzymes in a tissue sample from the person being tested. Early forms of such tests were both invasive—requiring a muscle or skin biopsy—and labor intensive, so they were not used unless there was a clear reason to suspect a child had a lysosomal storage disease (because he or she had developed the symptoms, or had an older sibling with the disease). Other tests were developed that measured the amount of the enzyme in the blood sample relative to the amount of other proteins, for example; but their usefulness was limited by the fact that some lysosomal storage disease-causing mutations do not eliminate the relevant enzyme, but rather make it unable to perform its chemical function.

A major step forward came in 2001, when researchers described a simple process whereby the activity of an enzyme called α -L-iduronidase (IDUA), which is missing or inactive in people with the lysosomal storage disease MPS-I, could be reconstituted from a dried blood spot. Just as importantly, they developed a straightforward test to check for that enzymatic activity. The test relied on a modified form of the chemical that IDUA normally acts on in the lysosome: IDUA splits the modified form of the chemical into two parts, one of which is highly fluorescent, and can be detected and quantified by a light sensor. The diagnostic test for MPS-I takes advantage of this fluorescent component—samples from people who lack normal levels of IDUA activity produce much less fluorescence than those from people without the disease. The principle utilized in the MPS-I test was extended to develop related fluorescence-based strategies for diagnosing Pompe, Gaucher, Fabry, and other lysosomal storage diseases.

Special tools allowed laboratories to perform these tests on blood spots from dozens of babies at once, suggesting that wide-scale screening might be possible. Therefore, other researchers conducted pilot studies in which they used these methods to screen for one or more lysosomal storage diseases in large numbers of children. One such study took place in Taiwan, where Pompe disease is more common than in the United States. Testing dried blood spots from over 200,000 newborns born in one region of the country, researchers diagnosed 6 babies with the disease. Compared to babies born in other regions of Taiwan at about the same time, those diagnosed earlier were also able to begin enzyme replacement therapy sooner and had better health outcomes. Taiwanese researchers later performed an analogous pilot study to diagnose Fabry disease with similar results. Other researchers supported these findings through pilot studies conducted in Europe, South America, and Missouri. The fluorescence assays were therefore the first practical approaches to screening for lysosomal storage diseases using dried blood spots from large numbers of newborns. The FDA has therefore

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approved tests using this technology for newborn screening to detect MPS-I, Pompe, Gaucher, and Fabry diseases.

THE NEXT GENERATION OF LYSOSOMAL STORAGE DISEASE TESTING METHODS

While these fluorescence tests were a critical stride toward allowing widespread newborn screening for lysosomal storage diseases, they are not perfect. For example, for reasons that are not fully understood, some people have low (but non-zero) IDUA activity, yet never develop MPS-I symptoms. And because the tests have a limited capacity to detect small differences in the enzyme activities, it was sometimes unclear whether babies with intermediate levels of IDUA activity were perfectly healthy or would go on to develop a mild form of MPS-I. A similar problem exists for the enzymes missing in some of the other lysosomal storage diseases. Another important limitation of the fluorescence approach is that all of the lysosomal storage disease tests utilize the same fluorescent product, meaning each must be performed separately.

Fortunately, researchers have identified a significantly more sensitive method for measuring the activities of lysosomal enzymes, and it allows testing for multiple lysosomal storage diseases at once. Their insight was to combine the enzyme reconstitution methods pioneered in the development of the fluorescence tests with use of mass spectrometry technologies to detect their activities—without the need for fluorescence. NIDDK-supported researchers first developed such an approach to diagnose a lysosomal storage disease known as Krabbe disease, in which people lack the enzyme galactosylceramidase (GALC). As described in a 2004 scientific publication, the scientists allowed enzymes extracted from a blood sample to mix with a normal, unmodified form of a chemical GALC splits into two products in lysosomes. With a few additional steps, they were able to use mass spectrometry to separate those products in the mixture, and measure how much of one of them

had been created, finding little or none if the sample was from someone with Krabbe disease.

Initially, the method relied on GALC extracted from a fresh blood sample, but later the researchers found they could reconstitute the enzyme from a dried blood spot, based on the same principles utilized for the fluorescence tests. And importantly, they also found that if they included chemicals acted on by IDUA and other enzymes missing in various lysosomal storage diseases, the mass spectrometry process could separate out each of the different reaction products. Thus, they were able to use just a small part of a single blood spot to check for at least six different lysosomal storage diseases simultaneously. In addition, the mass spectrometry screening methods are notably better than the fluorescence approach at reliably measuring small differences in the enzyme activities, making it easier for clinical testing labs to distinguish infants likely to develop lysosomal storage diseases from those with enough enzymatic activity to keep them healthy.

MOVING INNOVATIONS IN LYSOSOMAL STORAGE DISEASE TESTING INTO WIDESPREAD CLINICAL USE

Although there are tests for hundreds of other genetic diseases, in addition to the lysosomal storage diseases, it would be difficult and costly to screen every child for each of them. Some tests may be difficult, requiring a more invasive sample procedure than the use of a dried blood spot, or requiring expensive, unusual testing equipment, for example. Others may often yield ambiguous results, or cause needless worry among parents by misdiagnosing a disease in infants who are actually healthy. Even if the test is accurate and simple to perform, if there is no way to treat for the disease, or if it can be treated effectively even after symptoms develop, routine screening of most newborns would not be useful.

For these reasons, the U.S. Health Resources and Services Administration assembled a group of experts in diagnostic testing called the Advisory Committee on Heritable Disorders in Newborns

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and Children, which carefully considers evidence from clinical research to determine whether states throughout the Nation should routinely screen newborns for various genetic diseases. The Committee publishes and periodically updates a list, the Recommended Uniform Screening Panel, that now includes tests for MPS-I and Pompe disease among the dozens of diseases infants should be screened for. The bar is high for adding additional diseases, given limited resources, but the availability of reliable tests and treatments for several other lysosomal storage diseases suggest they may be added in the future. Indeed, many states require testing for lysosomal storage diseases not currently listed on the Uniform Panel.

THE FUTURE OF RESEARCH AND TREATMENT FOR LYSOSOMAL STORAGE DISEASES

In 2018, the FDA approved a simultaneous mass spectrometry test for Gaucher, Niemann-Pick A/B, Pompe, Krabbe, Fabry, and MPS I diseases. The availability of reliable testing means many children with lysosomal storage diseases may soon

be diagnosed earlier, and more accurately. This fact, combined with the therapeutic options now available, is reducing the burden of these serious diseases for affected children and families. Earlier diagnosis not only allows therapy to begin before irreversible organ damage may have occurred, it also potentially helps avoid costly diagnostic efforts to determine the cause of a child's health issues, as well as potentially ineffective therapies that might precede an eventual correct diagnosis. While lysosomal storage disease therapeutics currently in clinical use are not perfect and well short of a cure, further research to develop improved methods to treat these diseases is currently in development.

In addition, researchers have developed and are testing diagnostic methods for many more lysosomal storage diseases, including other forms of MPS (such as types II, IIIA, IIIB, IVA, and VI). Such developments would provide the opportunity to screen for many more lysosomal storage diseases, administer available therapy early, and greatly improve the lives of those affected by these disorders.

SCIENTIFIC PRESENTATION

Dr. Maike Sander—Harnessing Insights into Beta Cell Plasticity for Regenerative Therapies

Dr. Maike Sander is a Professor of Pediatrics and of Cellular and Molecular Medicine at the University of California San Diego (UCSD). She is also the Director of the Pediatric Diabetes Research Center at UCSD and is part of the Stanford Consortium for Regenerative Medicine. An expert in pancreatic stem cell biology with over 20 years of experience in medicine and diabetes research, Dr. Sander is an elected member of the American Society for Clinical Investigation, a member of the NIDDK-supported Human Islet Research Network, and the recipient of JDRF's Gerold and Kayla Grodsky Basic Research Scientist Award.

At the May 2018 meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council, Dr. Sander presented an overview of selected regenerative medicine approaches to diabetes treatment that are currently under investigation, including some of her own laboratory's work. The following summarizes the research highlights of her presentation.

HOW CAN REGENERATIVE MEDICINE BE APPLIED TO DIABETES?

Pancreatic β (beta) cells are crucial to the body's ability to manage blood glucose (sugar) levels. The insulin these cells secrete helps keep the body's constantly-cycling blood glucose levels within a healthy range. Loss of β cells (such as that caused by the misguided autoimmune attack that causes type 1 diabetes) or loss of the β cells' ability to produce enough insulin for the body's needs (as seen in type 2 diabetes) can lead to abnormally high blood glucose levels. These high blood glucose levels can, in turn, affect the eyes, nerves, heart, kidneys, and other organs, causing many of the long-term complications associated with diabetes.

Despite the current tools and therapies available, keeping blood glucose levels within a healthy range is still challenging, and better therapies are needed.

The field of regenerative medicine offers a promising avenue to these new therapies. Regenerative medicine is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to disease, damage, or other dysfunction. In the case of diabetes, regenerative medicine approaches usually focus on restoring or replacing the function of β cells. Many of these approaches capitalize on what is known as "cell plasticity," or the ability of one cell type to convert into another cell type with different functions. Some of these approaches include: stimulating stem cells in the laboratory to become insulin-producing cells for β cell replacement transplants, restoring existing β cells' ability to replicate, and reprogramming other pancreatic cell types to take over β cells' functions.

In her talk, Dr. Sander gave a broad review of the diabetes regenerative medicine field and then focused on two approaches that her lab is pursuing: β cell replacement and β cell replication.

INSIGHTS INTO BETA CELL GENETICS

One way to replace β cells lost to disease is by transplanting insulin-producing cells into the body. One challenge for this strategy, however, is procuring the large quantity of transplantable cells needed, since the supply of donated β cells, mostly derived from the pancreases of deceased donors, is limited.

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A promising strategy to overcome this shortage is to make insulin-producing cells in the laboratory from pluripotent stem cells (cells that are able to become any type of cell in the body). For decades, scientists—including those in the Beta Cell Biology Consortium (funded by the NIDDK and Special Statutory Funding Program for Type 1 Diabetes Research)—meticulously identified the factors needed to coax lab-grown stem cells to become insulin-producing, β -like cells. This work has yielded the recent ability to produce large quantities of insulin-producing cells in the laboratory and also resulted in a model to further study what genes control the stem cell plasticity that allows it to become a β cell.

Dr. Sander described how researchers, including herself and her colleagues, are studying these stem cell-derived, insulin-producing cells to identify exactly what genetic and cellular changes occur as they are made. For instance, what genes are “turned on” or “turned off” in cells that are more stem cell-like, compared with cells that are more β cell-like? And what cellular pathways and proteins are affected by those changes? By comparing the genes that are turned off/on in the β cells of people with type 1 and type 2 diabetes to those of people without diabetes, researchers are learning more about diabetes-associated genetic changes in β cells. Dr. Sander expressed hope that studies such as these will shed light on how diabetes occurs and reveal new targets for diabetes therapies.

INSIGHTS INTO IMPROVED BETA CELL MODELS

Insights from the genetic studies highlighted above are also helping scientists build more realistic laboratory models for studying β cells. Insulin-producing cells made from stem cells may have many of the characteristics of β cells, but they are still different in key ways from the β cells found in the human pancreas. These differences may limit how useful these lab-grown cells would be for testing new diabetes therapies, for instance, or for studying how β cells in the pancreas behave. Therefore, there is an ongoing need for better β cell models in the laboratory, especially those that realistically mimic the pancreatic islet, the complex pancreatic structure where β cells and other hormone-producing cells normally are found.

Dr. Sander and her colleagues are working to develop such a model by creating an artificial islet system. Their goal is to model, in the laboratory, the islet’s complicated contents and support structure, including not only the β cells and other hormone-producing cells, but also blood vessels, surrounding structural cells, and other components that keep the artificial islet supplied with fluid and nutrients. They have had early success in constructing devices that can support primary (directly from the body) human pancreatic islets, and researchers hope that in the future this system will be useful for studying lab-grown insulin-producing cells, as well.

INSIGHTS INTO BETA CELL REPLICATION

Dr. Sander also discussed another promising regenerative medicine approach to treat diabetes: encouraging functioning β cells to replicate. Other types of cells in the body may constantly replicate to renew themselves, but β cells only seem to replicate under certain circumstances, such as during development or pregnancy. Younger β cells also appear to replicate more than older β cells, for reasons that are not well understood. Overall, much is still unknown about what triggers or prevents β cell replication.

Studying replicating β cells in the body, however, can be very difficult, as they are very rare. In the past, studying β cells required pooling data on many cells, which did not allow researchers to look specifically at replicating β cells. Now, however, cutting-edge technologies have allowed Dr. Sander and her colleagues to study individual β cells.

These single-cell technologies allow researchers to specifically identify and compare replicating β cells and their non-replicating counterparts. Dr. Sander and her colleagues are interested in differences between the RNA in replicating and non-replicating cells. The RNA molecules she studies act as messengers, carrying the cell’s instructions for making proteins from the genes to the protein-making machinery, much like an order being sent from a customer’s table to a restaurant kitchen. Many proteins are being made every second, and looking at a cell’s RNA at a specific moment in time

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can give a photo-like snapshot of what proteins a cell is making and thus what the cell is doing. Dr. Sander and her colleagues have analyzed these RNA snapshots in an effort to identify proteins that control the switch from a replicating to a non-replicating state.

They found significant variety in the RNA found in different β cells, even when those cells were the same age. To make sense of this information, they used computer algorithms to construct a timeline of β cell maturation from least mature (replicating most) to most mature (replicating least). Then, comparing cells at differing levels of maturity, they identified RNAs that corresponded with each state. As expected, some of the RNAs that differed between these two types of cells carried instructions to make proteins involved in replication and insulin secretion. However, they also found that as a cell lost its ability to replicate, it also contained fewer RNAs coding for proteins involved in a metabolic chemical process called oxidative phosphorylation. These findings provided an interesting new clue to β cells' inner workings.

INSIGHTS INTO BETA CELL METABOLISM

Oxidative phosphorylation is part of the process that creates reactive oxygen species (ROS), a type of metabolic byproduct. Dr. Sander's group hypothesized that replicating β cells might be more metabolically active. If this was true, they asked, then could the ROS itself be a trigger for β cell replication? Upon further investigation, they found that this was the case: replicating β cells had higher ROS levels than non-replicating β cells, and inhibiting ROS in mice resulted in those mice having fewer β cells. These results suggested that a β cell's metabolism regulated its ability to replicate. This finding was corroborated by the proteins found in β cells, as well. When the researchers compared snapshots of the proteins found in young, replicating β cells to those found in older, non-replicating β cells in mice, proteins involved in cellular metabolism were reduced in the older cells.

Dr. Sander and other researchers continue to perform targeted experiments to determine what aspects of metabolism are affected by β cell aging. For example,

what specific chemical reactions in the β cells are affected by ROS, and how do they change the β cells' function? And how does aging regulate metabolism, insulin secretion, and blood glucose levels? Answering these questions could be the key to future regenerative medicine approaches. Being able to manipulate β cell replication could lead to, for instance, increased production of β cells for transplantation therapies, or even to being able to induce β cell growth in people with diabetes.

INSIGHTS INTO THE FUTURE OF REGENERATIVE MEDICINE IN DIABETES

Having the ability to replace lost β cells would be a tremendous breakthrough in diabetes treatment. As regenerative medicine studies in diabetes continue, scientists are continuously discovering more about β cell biology and developing new technologies. These advances could lead, in the future, to safe, effective, long-lasting β cell transplantation therapies, or to identification of molecular triggers that could "turn back the clock" and allow older β cells to replicate again.

Future research will also be needed to surmount the challenges these strategies face in the clinic. For instance, therapies that replace or cause existing β cells to replicate may require a way to protect these new insulin-producing cells from the immune response. This will be particularly important in the case of those with type 1 diabetes, which is caused by a misguided autoimmune attack on the β cells that might also attack the new cells. Recent research demonstrating that some β cells can survive the ongoing autoimmune attack in type 1 diabetes offers hope that β cells can be protected from this attack, and research into this area is still ongoing. Solutions to these and other challenges in diabetes regenerative medicine will rely heavily on collaborative research. Researchers from different specialties, such as bioengineering and β cell biology, continue to work together to find ways to overcome these technical hurdles. Success could lead to revolutionary new treatments for diabetes and perhaps, in the future, a cure.

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Mike: Participating in a Long-term Type 1 Diabetes Research Study To Stay Healthy While Helping Others



Mike

Mike has been physically active his whole life, participating in sports like skiing, racquetball, baseball, and football in high school and college. Now, at age 58, outside of his work in the mortgage industry, he participates in competitive ski racing in his home state of Ohio and in places like New York, Vermont, Colorado, and Canada. “It’s a lot of fun—a lot of exercise,” Mike states. He’s even had success on the race course: “I actually won a pair of racing skis.” He also enjoys doing other outdoor activities like hiking, roller blading, and biking in his home city of Cleveland. “I try to stay as active as possible,” Mike says, “as healthy as possible.”

Contributing to his good health is a long-term, landmark NIDDK-supported research study that Mike has been participating in for the last 35 years: the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study. Mike, like other DCCT/EDIC participants, has type 1 diabetes. He credits his participation in DCCT/EDIC with helping him learn how to manage his type 1 diabetes on a day-to-day basis while living a full, active life.

A DIAGNOSIS OF TYPE 1 DIABETES

Mike remembers when he first had symptoms of type 1 diabetes. He was 16 years old, and his family was driving from Cleveland to a much-anticipated beach vacation in South Carolina. During the car trip, Mike was very thirsty and, as he recalls, “I was drinking what seemed like a gallon of iced tea, lemonade.... I’m just slugging it down and then within short order having to go to the bathroom.” His father was not too thrilled about having to make so many bathroom stops, and one stop was particularly memorable: “I came out of the bathroom and the family car was gone,” Mike says with a laugh. Turns out that after Mike’s mother and sister got into the car, his father took off without realizing they had left Mike behind. Fortunately, about 10 minutes later, the car pulled up, Mike got in, and the family made their way to the beach.

However, it wasn’t a great trip for Mike. “I just had no energy. There were days when I just sat around and didn’t feel like doing anything,” he recollects. Although he had no family history of type 1 diabetes,

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his mother was a nurse, so she recognized that his symptoms of excessive thirst, fatigue, and weight loss were hallmarks of the disease. He went to a general practitioner back in Cleveland who diagnosed him with type 1 diabetes—an autoimmune disease in which a person’s immune system destroys the cells that make the hormone insulin, which promotes the transport of sugar (glucose) from the bloodstream into the body’s cells where it is used as fuel. Over time, people with the disease can develop severe and often life-threatening complications, like eye, kidney, nerve, and heart disease.

Mike remembers when he first had symptoms of type 1 diabetes... “I just had no energy. There were days when I just sat around and didn’t feel like doing anything,” he recollects.

Mike didn’t get much information about how to manage his type 1 diabetes when he was first diagnosed because of the lack of tools and knowledge available in the mid- to late-1970s. Back then, there was debate about whether keeping blood sugar levels as low as safely possible would prevent the long-term disease complications. The debate didn’t matter much from a practical standpoint, though, because there were no available tools to help people achieve near-normal blood sugar levels—for example, blood sugar monitoring did not yet exist. Instead, people like Mike monitored their body’s sugar levels with urine tests, which had limited utility: they recognized high but not dangerously low sugar levels and reflected past, not current, sugar levels. Thus, at first, Mike was just given advice about managing his diabetes with diet and exercise, being told to watch what he ate and avoid foods with sugar. Then he started taking one or two shots of insulin a day.

That management regimen did not work well for him. Without a way to monitor his blood sugar levels, judging his body’s needs could be difficult. He recalls a bad experience at a high school marching band summer camp, where the extra exercise made it

extremely challenging for him to manage his diabetes: “I must have lost 10 to 15 pounds in that week from physical activity,” he recalls. On top of the physical challenges, Mike also remembers feeling different from his friends because of his type 1 diabetes. For instance, because of the required medical forms, he had to delay getting his driver’s license, when his other driving-age friends were getting theirs. At that time, Mike didn’t know that things would eventually change for the better because of a new research study.

JOINING THE DCCT

Mike calls himself fortunate: “One of my family members worked with one of the doctors, Dr. Saul Genuth, who was the lead research doctor for the DCCT in Cleveland. We were at a family event [and I found] out that this doctor may be willing to see me.” With that, Mike was introduced to the DCCT and ultimately became one of its 1,441 volunteer participants.

The DCCT began in 1983 to address the debate about the importance of controlling blood sugar levels to prevent long-term complications in people with type 1 diabetes. Importantly, in the late 1970s and early 1980s, there was significant progress in developing new tools and tests needed for blood sugar control—such as meters for self-monitoring of blood sugar and insulin pumps—enabling a trial like the DCCT to be conducted.

Specifically, the DCCT compared the effects of “intensive” versus conventional treatment of blood sugar levels on the development of eye, kidney, and nerve disease. Participants in the intensive treatment group followed a regimen that included self-monitoring of blood sugar at least four times per day and at least three insulin injections per day or use of an insulin pump. The goal was to keep their blood sugar levels and hemoglobin A1c levels (HbA1c, a measure of average blood sugar levels over the previous 3 months) as close to normal as safely possible. Conventional treatment—which was the standard treatment at the time and similar to the regimen that Mike was using before he joined the DCCT—consisted of one or two insulin injections per day, with once-a-day urine or blood sugar testing.

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When asked if it was a hard decision for him to enroll in the trial, Mike responds, “No, it wasn’t really hard because [of] the way I was feeling physically and knowing that things weren’t the way they should be.” Not knowing at that time whether one or the other treatment would have better outcomes, he also didn’t have much of a reaction when he found out that he was assigned—by chance—to the intensive treatment arm of the trial. “It was like, you’re either in Group A or Group B,” he says, meaning that neither group had much significance to him at the time.

Mike describes some of his early memories of being involved in the trial. Because he was in the intensive treatment arm, he says that the study “was strict on multiple testing and multiple injections, and constant follow-up.” As part of that follow-up, people in the intensive treatment arm visited the study center each month and were contacted even more often by phone to go over and adjust their treatment regimens. Mike remembers the DCCT study team being very accommodating of his busy schedule and making him feel like he was a partner in the research. “There were times I was on the phone with them in the evening,” he says. “They were great on just engaging and making you feel that you were part of things.”

Because the DCCT was determining if intensive blood sugar control could prevent the development of complications, Mike says that the researchers took many measurements at the start of the study so that they could then detect changes over time: “[They] were checking all kinds of things, from nerves to kidney function, eyesight...you name it and they were testing it.”

Mike states that even with implementing the more intensive treatment approach as part of the DCCT, his overall health didn’t improve immediately—it took him a year or two to feel like his diabetes was under good control. He explains that part of that was dealing with the mental aspect of having a chronic disease. “It’s not easy to say I’ve got this permanent [disease]—it’s never going to go away... and to be separate from the rest of the crowd.” For example, he said it was difficult being told around the time of his type 1 diabetes diagnosis to avoid

foods with sugar, even though his peers had no such restrictions, so he would sometimes sneak a candy bar. “I’m thinking I’m fooling everybody,” he says, “and it was kind of satisfying, but then my blood sugar is up and I’m feeling lethargic.”

While in the trial, Mike experienced acute episodes of hypoglycemia, or dangerously low blood sugar, which is a limitation of implementing intensive insulin therapy. He recalls times when he would take insulin and then decide to do an outdoor activity like skiing or sled riding, which would lower his blood sugar levels even more and sometimes cause them to go too low. He depended on his friends to recognize the signs of hypoglycemia (e.g., being confused, dizzy, jittery), and give him a sugary drink to bring his blood sugar levels back up; sometimes he had to manage the hypoglycemia on his own. “That was the difficult part,” he states.

Why does Mike continue to participate in the DCCT/EDIC research study after all these years? “Honestly,” he says, “what motivates me the most is the avoidance of [diabetes] complications.”

DCCT RESULTS

The DCCT ended after 10 years in 1993—a year earlier than planned—when the study proved that participants in the intensive treatment arm, like Mike, who kept their blood sugar levels close to normal, greatly lowered their chances of having eye, kidney, and nerve disease compared to people in the conventional treatment arm. These landmark findings changed the way type 1 diabetes is treated worldwide, making intensive blood sugar control early in the course of the disease the standard treatment.

For Mike personally, the importance of these impressive results didn’t really hit him until later in life. At the time, he was happy that his tests through the DCCT indicated that he didn’t have complications, but it didn’t change the fact that he was still living with a chronic disease. “It’s the

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look-back part that puts it in perspective,” he explains. Now with the wisdom of hindsight, he recalls the time before he joined the trial when his diabetes wasn’t in good control, like when he was in marching band camp, and sees how things could have gone quite differently. He now realizes that if he hadn’t started implementing intensive glucose control, “I could have been one of those people that started to have complications,” he states.

CONTINUING IN THE EDIC STUDY

When the DCCT ended, participants who had received conventional treatment were taught the intensive treatment regimen, and all were encouraged to use it. Nearly every DCCT participant, including Mike, volunteered for the follow-on EDIC study, which began in 1994 and is ongoing. EDIC was established to determine the long-term outcomes of reducing exposure of the body’s tissues and organs to high blood sugar levels. EDIC is an observational study, so participants independently see their own health care team and participate in annual follow-up visits with EDIC.

The annual follow-up visits allow EDIC investigators to collect information about Mike’s health. He explains that each year, the research team may do different measurements: “[One year], it’s testing kidney function.... The next year it may be nerve testing.” He says that sometimes the tests could take a lot of time and not be too much fun. What makes it easier, though, he says, is that these important tests continue to indicate that he is free of complications.

Because of Mike and the other dedicated participants, there continues to be a wealth of important information emanating from EDIC. EDIC has shown that, compared to people formerly in the DCCT’s conventional treatment arm, people in the former intensive treatment arm have a reduced risk of cardiovascular disease (such as heart attack and stroke), eye disease and related eye surgery, kidney disease and kidney failure, and nerve disease. They also have been living longer. These findings underscore current clinical practice guidelines recommending that people with type 1 diabetes

practice early and intensive blood sugar control to improve their long-term health.

In addition to helping Mike stave off diabetes complications, his continuing participation in EDIC had an unexpected benefit related to finding a major health problem that likely resulted from a bacterial infection he had as a teenager before he developed type 1 diabetes. About 6 or 7 years ago, both the DCCT/EDIC study team and his personal endocrinologist “were hearing stuff within my heart and telling me to go to a cardiologist, and I ignored them for a couple of years,” Mike admits. Then, at one of his annual EDIC visits, the study team told him that the noise was getting worse. As a New Year’s resolution, he went to the cardiologist who broke the bad news: Mike had a damaged aortic valve. He was quickly scheduled for open heart surgery to replace it. “He [the cardiologist] said if I had waited probably 6 more months, I’d be having emergency surgery,” Mike recalls. The doctor told him that the damaged valve was probably caused by the bacterial infection he had as a teenager, and thus was unrelated to his diabetes. “So, I’m a survivor today of that [open heart surgery] and the longevity of diabetes,” he states.

When asked what it means to him to be part of a study that has changed so many lives for the better, Mike replies: “I feel good about it.... I want to continue because if there is anything more that can be learned or gained, I want to be able to be part of that, whether that be as a collective group or individually.”

Mike feels that so many years of intensively managing his type 1 diabetes during DCCT/EDIC, as well as leading a healthy, active lifestyle, helped him get through the surgery. “I actually skied 6 months after surgery,” he exclaims. A month after that, “My son and I drove out to the Grand Canyon and we hiked it. I was kind of proud of that.” The experience again made him realize what the DCCT has meant to his long-term health—he feels that if he had not started intensive control, his health

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today could be much worse, especially now knowing that he had underlying heart damage. Instead, he says, “I have more energy now than ever.”

PARTICIPATING IN A LONG-TERM RESEARCH STUDY

It’s been 35 years since the DCCT began in 1983, and over 90 percent of living DCCT/EDIC participants, including Mike, are still enrolled in the study. Why does Mike continue to participate in the DCCT/EDIC research study after all these years? “Honestly,” he says, “what motivates me the most is the avoidance of complications. [Losing] my eyesight is the number one thing that I worry about.” Thus, it’s a huge relief every time he gets a good bill of health from his eye tests done through EDIC.

“I’d encourage people that if they have a chance to do something research-wise to do it.”

Mike says that one of the biggest benefits of being in DCCT/EDIC was learning how to manage his type 1 diabetes daily. Now, instead of sneaking candy bars like he did as a teenager, he eats and does the activities that he wants, but knows he must be vigilant about checking his blood sugar levels. In other words, “I know how to adjust for some of the more day-to-day-stuff. I didn’t know that at the beginning [of the DCCT]. I have a better sense of it now—it’s only taken 30 years to figure it out,” he says with a laugh. Today, he continues to manage his type 1 diabetes with frequent blood sugar testing and insulin administration that he learned as part of the DCCT and has been able to keep his HbA1c levels below recommended levels, which has been shown by DCCT/EDIC to reduce his risk of long-term complications.

Mike’s personal experiences illustrate another important finding from DCCT/EDIC: overall, participants in the former intensive treatment arm have maintained a lower risk of complications for 25 years, even though after DCCT ended their blood sugar control gradually became indistinguishable from

that of the participants in the former conventional treatment arm. (After the DCCT ended, blood sugar control in participants from the former intensive treatment group was not as good as it was during the trial, when they had the advantages of the clinical trial setting—although they still had better control than before the trial. At the same time, those in the former conventional treatment group improved their blood sugar control when they began implementing more intensive therapy after the DCCT.) This long-term benefit of a period of intensive blood sugar control has been termed “metabolic memory.” These findings emphasize the importance of implementing intensive blood sugar control from the earliest stages of diabetes. They have also spurred NIDDK-supported research to develop new tools and technologies to help people with type 1 diabetes achieve recommended levels of blood sugar control, like artificial pancreas technologies that aim to automate insulin delivery in response to blood sugar levels. Mike is fortunate to have enrolled in the DCCT/EDIC when he did—at a young age when he could learn about adjusting for “some of the more day-to-day stuff,” as he says, and incorporate intensive blood sugar control as routine practice.

When asked what it means to him to be part of a study that has changed so many lives for the better, Mike replies: “I feel good about it.... I want to continue because if there is anything more that can be learned or gained, I want to be able to be part of that, whether that be as a collective group or individually.” He also has a message for others: “I’d encourage people that if they have a chance to do something research-wise to do it.”

Finally, Mike has advice for people facing a recent type 1 diabetes diagnosis: “Don’t give up and put aside what it is that you like.... You can manage it [the disease] *and* manage to continue to live the way you want to.” For Mike, that means continuing to participate in ski racing and other outdoor activities. At the same time, he and the other DCCT/EDIC participants can take pride in knowing that their remarkable and continuing dedication to research is a key reason why people with type 1 diabetes are living longer, healthier lives than ever before.

Angela: RISE-ing Above Diabetes



Angela

In 2015, Angela had just obtained health insurance, so she saw her doctor for an overdue physical examination. A massage therapist in her fifties who sees her clients at their homes and businesses, she is dependent on her health to be able to carry her equipment to appointments and stay on her feet to work. In general, her health was good, but her health care provider did identify one area of concern: elevated blood sugar (glucose) levels—termed prediabetes—that suggested she was at risk to develop type 2 diabetes. “When I was diagnosed as prediabetic, that made me very nervous,” says Angela, who was aware that her family history of type 2 diabetes also increased her risk of developing the disease.

A DISEASE THAT RUNS IN THE FAMILY

Born in Trinidad to a family of South Asian descent, Angela immigrated to the United States as a child and grew up in Miami with five of her siblings—three

sisters and two brothers. (Another sister moved from Trinidad to England.) Angela knew that her mother, who recently passed away, had type 2 diabetes for the last 2 decades of her life. The family history runs deeper, however. “My father died at 75,” Angela relates, and she and her siblings “didn’t know this [at the time]—but he also had diabetes.” The complications of the disease had taken their toll: her father developed kidney failure and was on dialysis for 10 years, before dying from cardiovascular complications of the disease. In fact, the family’s history “stems way back,” Angela says, as her mother’s father had the disease as well.

Two in her generation—Angela and one of her sisters—have developed prediabetes. Angela is concerned about her and her siblings’ health, but also is thinking of the next generation. “So far, none of my [three] kids have” developed diabetes or prediabetes, Angela notes, gratefully. “Thank you, God, for that.” But Angela isn’t taking her future health—or theirs—for granted. She agreed to participate in a clinical trial, she says, “for my years of life and my children’s, and the generations to come!”

DIABETES AND PREDIABETES

When we eat, sugars and other nutrients enter our bodies through the digestive process. The pancreas responds by producing the hormone insulin, which signals cells throughout the body to absorb sugar. However, while the body needs blood sugar levels to remain above a certain level to maintain brain and other functions, higher levels lead to organ damage. Thus, a healthy pancreas helps keep blood sugar levels within a narrow, optimal range.

Unfortunately, some people develop a condition called insulin resistance, in which their cells no longer respond as strongly to insulin. Aging and excess weight—as well as genetics and other

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factors—can increase risk for insulin resistance. At first, the pancreas compensates for this by simply producing more insulin, but gradually it may lose the ability to do so. At that point, blood sugar levels begin to rise, often reaching levels in excess of the diagnostic threshold for type 2 diabetes. Although this form of diabetes can occur in anyone, people of African, Hispanic, Native American, or Asian descent (like Angela) are at particularly high risk.

THE RESTORING INSULIN SECRETION CLINICAL STUDIES

In 2013, the NIDDK-supported Restoring Insulin Secretion (RISE) consortium formed to conduct three related clinical studies. Each stems from an important observation: previous research suggesting that lowering blood glucose levels with certain diabetes drugs during prediabetes or early in the course of type 2 diabetes may slow or perhaps even reverse the loss of pancreatic function. Although it is not clear why this works, possibilities include that such treatments may limit the exposure of the pancreas to damage from chronically high levels of sugar and other nutrients, or that they may simply relieve the burden on a person's pancreas.

The RISE studies, two in adults, and one in youth, were therefore designed to test the potential for different methods to improve and preserve the production of insulin in people with prediabetes or recently diagnosed type 2 diabetes. “I hope that is accomplished,” Angela says fervently. Fortuitously, her prediabetes diagnosis coincided with a timely offer to participate in one of the three RISE clinical trials. “I was very fortunate that RISE sent me a letter in the mail,” Angela relates, “and I said well, you know, there's no harm in trying ... to see if they can do something about it.” She was quick to call and was soon enrolled in a RISE study. As she says, “I am very happy to participate in the RISE study ... to help [people with or at-risk for diabetes] maintain function [and] a healthy life.”

PARTICIPATING IN THE RISE ADULT MEDICATION STUDY

The RISE clinical trial Angela is participating in—the RISE Adult Medication Study—is comparing the capability of various blood glucose-lowering medication regimens to preserve or restore the ability of the pancreas to secrete insulin. The four approaches being compared are: 1) early intensive insulin treatment with a long-acting form of insulin called “glargine,” followed by the first-line type 2 diabetes drug, metformin; 2) an injected diabetes medication called liraglutide delivered along with metformin; 3) metformin by itself; and 4) placebo. Each participant was randomly assigned to receive one of the four treatment approaches for 12 months. Just before starting treatment, as well as periodically during and afterward, the participants received a variety of tests to ascertain how well their bodies responded to insulin, and to test the ability of their bodies to produce and release their own insulin in response to glucose in a drink or delivered intravenously. The participants also received cognitive testing to determine whether any of the treatments had beneficial effects on mental function.

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In addition, the RISE studies have enabled an important substudy having to do with obstructive sleep apnea (OSA)—pauses of breathing due to closing of the airway during sleep due to relaxation of the muscles in the throat. OSA can cause excessive daytime sleepiness, and severe cases are associated with high blood pressure, a risk factor for cardiovascular disease. There is now evidence that OSA may increase the risks of type 2 diabetes, and vice versa. To improve our understanding of the relationship between apnea and diabetes, researchers enrolled a subset of RISE participants—

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including Angela—in a RISE sleep substudy. In this way, Angela learned that she has a mild case of OSA, primarily when she slept on her back. As a result, she now makes an effort to ensure that she sleeps on her side.

Angela was randomized to receive either metformin or placebo. Although she didn't know which she was taking, she didn't mind. "You know I just kind of left it up to them.... Sometimes I thought I was taking placebo, and other times I'm like, maybe I *am* taking metformin." In any case, she was pleased with the result. As she says, "maybe my mind was just playing games with me, but I lost 10 pounds during the whole treatment."

And that wasn't the only benefit of participating in the trial: Angela says the study also helped her track her own health. "They were very efficient at giving me a list of all my test results," noting they also sent the results to her doctor. "They kept me informed of what's going on, and ... I felt good about that." This meant that if a major health issue had arisen, whether or not it was related to diabetes, it might have been caught early. For example, Angela recalls, "At one point they said I had a little bit low blood count ... and I spoke to the doctor about it." Fortunately, it turned out to be nothing serious.

Angela has high praise for RISE study and its staff: "The bunch of people that I came in contact with, you know, I love them, and I would love to continue to be a participant, because I feel I could trust them. They showed me a great amount of kindness, and it's very supportive as well."

Angela speaks glowingly of her experience in the trial, especially of the staff with whom she worked. "It's just amazing the amount of testing they were doing, and they were very safe—I felt safe.... Everybody was friendly—super friendly—and I felt like I can trust them."

Regarding the metabolic testing, she notes, "I was totally feeling good when they were doing all that." She has more mixed feelings about the cognitive testing: "Every time I went in and did a cognitive test ... that was hard, but it was a great challenge!"

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TAKING CHARGE OF HER HEALTH

After she was diagnosed with prediabetes, Angela worked on improving her diet and exercising more. She joined a gym, which she confesses she doesn't like, but she enjoys going out walking. She even participated in a 3-day, 60-mile walk for breast cancer research and prevention, which not only reaped rewards for the breast cancer community but also personal ones for Angela. "I forced myself to go to the gym and get in shape for it, and it was awesome! I got to meet a lot of ladies that had had breast cancer and victory over it, and there were some that were ... [still] in the midst of it all. And I heard a lot of testimonies, which was awesome.... It was fun, too!"

Angela credits participating in the RISE Adult Medication Study with helping change her outlook. "It has definitely shown me the importance of taking care of yourself," she shares. She also has high praise for RISE and its staff: "The bunch of people that I came in contact with ... I love them, and I would love to continue to be a participant, because I feel I could trust them. They showed me a great amount of kindness, and it's very supportive as well.... A lot of care and love," she says, was put into the RISE study.

Of the RISE staff who worked with her, Angela continues, "they're wonderful. And I wouldn't mind

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doing another study again so I can see them again, and just be willing to do something for the good of others. Or even for myself to benefit from it.” She adds that “I’ve learned more, come to appreciate my health more. I’m realizing that the more you know, the more you take care of yourself!”

“I thought that the RISE Study is a great study,” Angela says, and she adds “they are doing a tremendous good.”

At the end of the intervention period of the trial, the staff went over Angela’s test results with her, giving her and her health care provider information to help keep Angela as healthy as possible. “They said I’m

doing really good.... They said my results turned out to be really good, and they also gave me a rundown on my good cholesterol and my bad cholesterol, and they said that it’s normal,” although “the bad is a little bit high.” In view of this, they reminded her of the importance of keeping a healthy diet.

Angela can’t say enough good things about her experience with RISE. “I thought that the RISE Study is a great study, and ... they are doing a tremendous good,” she says. She notes that she is looking forward to finding out about results, as well: “When everybody that has participated [has] completed the study, they’re going to have a big party, and then all the participants will get the inside scoop: the results of what we were taking, and so forth, and it’s going to be exciting!”