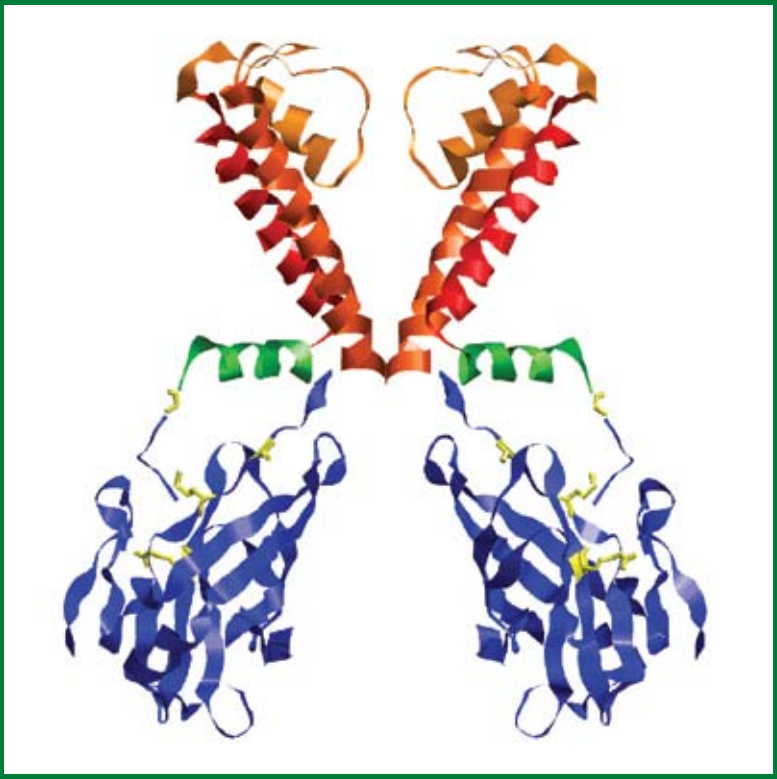

Illustration of two subunits of the Kir6.2 protein. This protein is part of a potassium ion channel that regulates the balance of potassium and calcium ions inside and outside of the beta cells of the pancreas, which in turn helps to regulate insulin secretion. As described in this chapter, mutations in the gene encoding this protein contribute to the development of permanent neonatal diabetes and type 2 diabetes. Mutations affecting the portions of the protein shown in yellow are associated with permanent neonatal diabetes.

Image provided by Dr. Andrew T. Hattersley. From Gloyn AL, et al: New Engl J Med 350: 1838 1849, 2004.

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, they affect many millions of Americans and profoundly decrease their quality of life. Many of these diseases are complex—an interplay between genetic and environmental factors contributes to disease development.

Diabetes is a debilitating disease that affects an estimated 20.8 million people in the U.S.—over 7 percent of the total population—and is the sixth leading cause of death.[1] Diabetes lowers average life expectancy by up to 15 years,[2] increases cardiovascular disease risk two- to four-fold, and is the leading cause of kidney failure, lower limb amputations, and adult onset blindness.[1] In addition to these human costs, the estimated total financial cost for diabetes in the U.S. in 2002—including costs of medical care, disability, and premature death—was $132 billion.[1] Effective therapy can prevent or delay diabetic complications, but approximately one-third of Americans with diabetes are undiagnosed.[1]

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone which 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.

Type 1 diabetes affects approximately 5 to 10 percent of individuals with diagnosed diabetes.[1] It most often develops during childhood, but may appear at any age. Type 1 diabetes is an autoimmune disease, in which the immune system launches a misguided attack and destroys the beta cells of the pancreas. These beta cells, which are found within tiny cell clusters called islets, produce the hormone insulin. If left untreated, type 1 diabetes results in death from starvation despite high levels of glucose in the bloodstream. Thus, patients require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—in order to regulate their blood glucose levels. Despite vigilance in disease management, with frequent finger sticks to test blood glucose levels and the administration of insulin, it is still impossible for patients to control blood glucose levels as well as they could if they had functional beta cells. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery, as well as working on new beta cell replacement therapies meant to cure type 1 diabetes.

Type 2 diabetes is the most common form of the disease, accounting for about 90-95 percent of diabetes cases in the U.S.[1] Type 2 diabetes is associated with several factors, including older age and a family history of diabetes. It is also strongly associated with obesity: more than 80 percent of adults with type 2 diabetes are overweight or obese.[3] Type 2 diabetes occurs more frequently among minority groups, including African Americans, Hispanic Americans, American Indians, and Native Hawaiians.[1]

In patients with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin.

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[1] *www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf*

[2] *Portuese E and Orchard T: Mortality in Insulin-Dependent Diabetes. In* Diabetes in America *(pp. 221-232). Bethesda, MD: National Diabetes Data Group, NIH, 1995.*

[3] *Eberhardt MS, et al: MMWR 53: 1066-1068, 2004.*

Gradually, the pancreatic beta cells secrete less and less insulin, and the timing of insulin secretion becomes abnormal. Treatment approaches for controlling glucose levels include diet, exercise, orally administered medications, and, in some cases, injected insulin. There are also an estimated 54 million adults in the U.S. who have a condition called "pre-diabetes," in which blood glucose levels are higher than normal, but not as high as in diabetes.[4] This population is at high risk of developing diabetes. Fortunately, the Diabetes Prevention Program (DPP) clinical trial has shown that patients with pre-diabetes can dramatically reduce their risk of developing full-blown diabetes with improvements in lifestyle or with drug treatment.

Type 2 diabetes was previously called "adult-onset" diabetes because it was predominantly diagnosed in older individuals. However, this form of diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects minority youth. Believed to be related to increasing rates of pediatric obesity, this is an alarming trend for many reasons. First, the onset and severity of disease complications correlate with the duration of diabetes; thus, those with early disease onset are at greater risk with respect to complications. Second, 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 diabetes in offspring. Thus, the rising rates of diabetes and pre-diabetes in young women could lead to a vicious cycle of ever-growing rates of diabetes. Third, diabetes often becomes more difficult to control over time. With longer duration of disease, health care providers may find it increasingly difficult to strictly control a patient's blood glucose level and thus prevent or delay the development of complications. Therefore, the advent of type 2 diabetes in youth has the potential to drastically worsen the enormous health burden that diabetes already places on the U.S.

The NIDDK is supporting research to better understand the mechanisms that lead to the development and progression of diabetes and the many other endocrine and metabolic diseases within the Institute'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 Institute is vigorously pursuing studies of prevention and treatment approaches for these diseases.

GENETICS OF DIABETES

Genes that Contribute to Developing Type 2 Diabetes and Genes that Affect Treatment Outcomes: Recent studies have dramatically increased knowledge about the complex genetic underpinnings of type 2 diabetes, in which a great many genes are each thought to play a small role in promoting or preventing the disease. Two NIDDK-supported studies took a genome-wide association approach (discussed in detail in the Cross-Cutting Science chapter) to help locate genes involved. Although the method does not generally identify the precise genetic alterations that cause these disease effects, it greatly narrows their likely location in the genome. The researchers thus newly identified at least four such type 2 diabetes-affecting genomic neighborhoods and confirmed several others that had been found previously, bringing the total known to about 10. With this information, scientists can begin to dissect the actual genetic changes that increase or decrease likelihood of type 2 diabetes, and thus provide potential new targets in the quest to prevent or treat the disease. A third study builds on previously reported genetic findings in just that way. Following a group of patients from the landmark Diabetes Prevention Program (DPP) clinical trial, researchers examined the impact of different versions of two closely linked type 2 diabetes genes both on disease progression and on the effectiveness of the lifestyle and pharmacologic interventions studied in the trial. Interestingly, one of these genes, which encodes the Kir6.2 protein, is also implicated in the rare genetic disorder neonatal diabetes, as described elsewhere in this chapter. The research indicated a genetic variant associated with increased diabetes risk did not alter progression to diabetes in people who already had pre-diabetes, suggesting the increased risk occurred earlier in the course of disease. Lifestyle changes were equally effective in preventing diabetes in those with different versions of the gene, but the drug metformin was less effective in preventing progression to diabetes in people with a particular genetic risk variant. Because metformin is one of the most widely prescribed medications for

[4] *http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm*

diabetes, it will be important to confirm this finding in those at risk for diabetes and to determine whether genetic variation affects response to metformin in those who already have diabetes. Taken together these studies illustrate the dramatic advances in the fight against diabetes that have become possible in the genomic era.

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Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjögren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, and Purcell S: Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 316: 1331-1336, 2007.

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New Gene Associated with Type 1 Diabetes Susceptibility: Scientists have discovered that variation in a region of DNA that includes the *KIAA0350* gene is associated with risk of developing type 1 diabetes. Using a genome-wide association approach, DNA from type 1 diabetes patients, unrelated controls, and family groupings including individuals with type 1 diabetes was examined to identify areas of variation potentially associated with the disease. In order to verify their results, the researchers conducted the genome-wide association study in two independent populations. Results from both populations indicate that three DNA variations, called single nucleotide polymorphisms (SNPs) in the region including the *KIAA0350* gene are associated with decreased risk of developing type 1 diabetes. With the approach used in this study, it is difficult to determine conclusively that *KIAA0350* is the gene that is influenced by these SNPs, and thus may confer protection from type 1 diabetes. However, *KIAA0350* is the only known gene in the area and the protein product of this gene is found primarily in cells that are part of the immune system. It is possible that this gene product could play a role in mediating immunity, which may have significant implications for the way the immune system reacts to the pancreatic beta cells that are eventually destroyed in type 1 diabetes. The discovery of the association of the *KIAA0350* region adds to the increasing understanding of the genetic basis of type 1 diabetes. Previously established genes associated with type 1 diabetes account for only half of the genetic risk of developing the disease; therefore, research into additional genetic markers is greatly needed. This discovery provides new avenues for exploration as researchers probe the function of this gene in the hope of establishing causes and developing new treatments for type 1 diabetes.

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TYPE 1 DIABETES RESEARCH

Recurrent Episodes of Low Blood Sugar Do Not Impact Long-Term Cognitive Function: Research has brought good news to people with type 1 diabetes: recurrent bouts of low blood sugar (hypoglycemia) do not affect long-term cognitive function. Low blood sugar is a serious and frightening

complication of type 1 diabetes. Because of its dangerous acute effects, it remains an obstacle to the practice of intensive glucose control that was proven to dramatically reduce the development of diabetic complications by the Diabetes Control and Complications Trial (DCCT) and subsequent studies.

To determine the effects recurrent episodes of low blood sugar may have on cognitive function, the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group examined 1,144 participants from the original DCCT trial. The DCCT compared intensive management of blood glucose to conventional control in people with type 1 diabetes. At the outset of the DCCT, which began in 1983, participants also underwent a comprehensive battery of cognitive tests. When these tests were repeated 6.5 years later, no adverse effects were observed among either the intensive or control treatment groups. Although those results were promising, additional follow-up was needed to determine the long-term effects of hypoglycemic episodes. Therefore, the researchers repeated the cognitive analysis on participants after an average follow-up time of 18 years. In general, researchers found that measures of cognition did change over the nearly two decade follow-up, which is to be expected as people age: some measures tended to improve, while others declined. However, when the researchers stratified the cohort according to whether they were in the intensive or the control group, they did not see a difference in cognition. The same was true when they stratified according to number of hypoglycemic events: hypoglycemia did not cause cognitive decline. Only when the researchers stratified according to HbA1c (a measure of general blood glucose control) did they discern a statistically significant difference: better glucose control tended to translate to better motor skills. Even though acute episodes of hypoglycemia are worrisome, this research suggests that they do not result in long-term damage to patients' brains. The results also further support the recommendation that patients should practice intensive blood glucose control to prevent long-term disease complications.

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group; Jacobson AM, Musen G, Ryan CM, Silvers N, Cleary P, Waberski B, Burwood A, Weinger K, Bayless M, Dahms W, and Harth J: Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med 356: 1842-1852, 2007.

Omega-3 Fatty Acids Reduce Children's Risk of Developing Early Markers of Type 1 Diabetes: Type 1 diabetes is a complex disease to which both genetic factors and environmental triggers contribute. Although several genes associated with type 1 diabetes have been identified, much less is known about environmental factors that increase or decrease a person's risk of developing the disease. Previous studies in mice and humans suggested that omega-3 fatty acids may be protective. These fatty acids are found in some food sources, such as fish, green leaves of plants, and some seeds, nuts, and legumes. To examine the effect of dietary omega-3 fatty acids on the risk of developing type 1 diabetes, researchers studied participants in the Diabetes Autoimmunity Study of the Young (DAISY). This longitudinal, observational study enrolled and followed children at high genetic risk of developing type 1 diabetes. At different time intervals, the researchers measured the children's levels of predictive markers of future development of type 1 diabetes (autoantibodies). The scientists examined whether there was a correlation between omega-3 fatty acid intake and the development of early risk markers of type 1 diabetes (defined by the presence of at least two different predictive autoantibodies). They collected data on omega-3 fatty acid intake from an annual questionnaire in which parents were asked about their children's food intake beginning at age 2 and by measuring a biological marker of fatty acid levels. The researchers discovered that children with higher reported dietary intake of omega-3 fatty acids were less likely to develop early markers of type 1 diabetes. However, correlations found in observational studies are not sufficient to establish a causal relationship. Such proof requires a clinical trial. Recently, Type 1 Diabetes TrialNet launched a pilot study to test whether omega-3 fatty acid supplements given to pregnant women in their third trimester, or added to babies' formula, could protect children from developing early markers of type 1 diabetes. If successful, dietary intervention to increase children's levels of omega-3 fatty acids could be a possible approach for preventing type 1 diabetes.

Norris JM, Yin X, Lamb MM, Barriga K, Seifert J, Hoffman M, Orton HD, Barón AE, Clare-Salzler M, Chase HP, Szabo NJ,

Erlich H, Eisenbarth GS, and Rewers M: Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. JAMA 298: 1420-1428, 2007.

Increasing Rates of Childhood Diabetes: Worldwide data suggest that rates of type 1 diabetes are increasing. Now, similar observations are being made in the United States. Recently, researchers participating in a study, called SEARCH for Diabetes in Youth, reported the prevalence (or total number of cases) of childhood diabetes in the U.S. One of every 523 youth had physician-diagnosed diabetes in 2001. To further characterize diabetes in children, SEARCH investigators next examined the incidence (or number of new cases) of type 1 and 2 diabetes in youth under age 20 in 10 locations across the U.S. for the 2002-2003 period. Non-Hispanic white youth had the highest rate of childhood diabetes of all racial and ethnic groups. The incidence rate was highest among 10- to 14-year-old youth and slightly higher in females than in males. While type 2 diabetes is increasing in children over 10, particularly in minority populations, type 1 diabetes accounts for most new cases, with an estimated 15,000 youths diagnosed annually. In a separate study, researchers determined that not only is the incidence of type 1 diabetes increasing, but it is occurring at younger ages and has particularly increased in children under age four. A study in Colorado found that rates of the disease doubled in these young children from the 1980s compared to 2002-2004. Overall, rates of type 1 diabetes in Colorado's youth increased by 1.6-fold over this time period. Together, these studies suggest that type 1 diabetes is increasing in the U.S., particularly in the youngest children. Further understanding of these trends can help to uncover the underlying mechanisms that are driving them.

Writing Group for the SEARCH for Diabetes in Youth Study Group, Dabelea D, Bell RA, D'Agostino RB Jr, Imperatore G, Johansen JM, Linder B, Liu LL, Loots B, Marcovina S, Mayer-Davis EJ, Pettitt DJ, and Waitzfelder B: Incidence of diabetes in youth in the United States. JAMA 297: 2716-2724, 2007.

Vehik K, Hamman RF, Lezotte D, Norris JM, Klingensmith G, Bloch C, Rewers M, and Dabelea D: Increasing incidence of type 1 diabetes in 0- to 17-year-old Colorado youth. Diabetes Care 30: 503-509, 2007.

PANCREATIC REGENERATION

Finding safe and effective ways to increase the mass of insulin-producing beta cells could greatly benefit diabetes patients. These cells, which are found in clusters called "islets" in the pancreas, are damaged in both type 1 and type 2 diabetes. It is important to understand the underlying mechanisms controlling beta cell growth and development in order to identify possible therapeutic targets and preserve or restore beta cell function.

Expanding Beta Cell Mass: Researchers have determined that in mice, a transcription factor protein called HNF-4alpha is important for expanding beta cell mass during pregnancy. Pregnancy is a period when the body becomes somewhat less sensitive to insulin and therefore needs more insulin production. The researchers generated a genetically-engineered mouse model, in which most of the animals' beta cells no longer produced this protein. Experiments using these mice demonstrated that the protein regulates the expression of several genes, many of which are involved in cell growth. Surprisingly, young adult genetically-engineered mice did not appear to have decreased beta cell mass, which would be expected if the protein regulated beta cell growth. However, the researchers found that during pregnancy the animals' beta cell mass was lower than that of controls. This research suggests that HNF-4alpha plays an important role in regulating beta cell expansion during this key period. Mutations in the gene encoding this protein were previously found to be associated with a rare and inherited form of diabetes, called MODY1. However, this research is the first to suggest that HNF-4alpha is necessary for expanding beta cell mass. Because it was particularly important during pregnancy in the animal model, it is possible that stimulation of the protein could one day be a viable approach to treat gestational diabetes. Additional research will provide greater understanding of this protein's role in diabetes, including its role in increasing beta cell mass in response to other stressors such as age and other forms of insulin resistance, and may lead to novel therapeutic approaches for increasing beta cell mass in people with the disease.

Gupta RK, Gao N, Gorski RK, White P, Hardy OT, Rafiq K, Brestelli JE, Chen G, Stoeckert CJ Jr, and Kaestner KH: Expansion of adult beta-cell mass in response to increased metabolic demand is dependent on HNF-4alpha. Genes Dev 21: 756-769, 2007.

New Mouse Model for Studying Beta Cell Regeneration: Finding a way to regenerate the beta cells of the pancreas is a possible approach for treating both type 1 and type 2 diabetes. Scientists in the NIDDK-supported Beta Cell Biology Consortium have now developed a mouse model useful for studying beta cell regeneration. When the genetically engineered mice are treated with a certain drug, a toxin is expressed in their beta cells. Expression of the toxin causes the beta cells to die, and the mice develop diabetes. Surprisingly, the researchers found that if they stopped the drug treatment after the mice developed diabetes, the animals recovered from the disease. The mice not only regained normal blood sugar levels, but also regenerated their beta cell mass. The scientists determined that the new beta cells came predominantly from preexisting beta cells, suggesting that beta cells have a significant capacity for regeneration.

Importantly, the mouse model also provides a system for testing the effects of different drugs on beta cell regeneration. For example, transplanting pancreatic islets that contain beta cells is an approach being tested for treating type 1 diabetes in people. However, the transplanted islets often lose function in the patients over time. Using the mouse model, the researchers showed that drugs commonly used to suppress the immune system after islet transplantation have an adverse affect on beta cell regeneration. This result may help to explain why the transplanted islets lose function in people. The mouse model may be useful for identifying other immunosuppressive drugs that do not have this negative effect on beta cell regeneration. This research suggests that finding ways to promote regeneration of existing beta cells may be a therapeutic approach for treating diabetes. It also provides an important model system for testing the effect of therapeutic agents on beta cell regeneration.

Nir T, Melton DA, and Dor Y: Recovery from diabetes in mice by beta cell regeneration. J Clin Invest 117: 2553-2561, 2007.

REGULATORS OF METABOLISM IN HEALTH AND DISEASE

Controlling Inflammation and Metabolism—The STAMP2 Protein: Chronic overeating can lead to obesity and type 2 diabetes, both of which are associated with excess inflammation and its damaging effects. However, normal daily fluctuations in nutrient levels do not incite inflammatory responses, and scientists recently gained insight as to why. A protein called STAMP2, made primarily by fat cells, keeps such inflammation in check. The scientists began with the hypothesis that there must be some way that the body limits inflammation, for example, when there is temporary nutrient abundance from eating. They thus designed a screen in mice for biologic factors that might play a role in this process, and uncovered STAMP2 as a likely candidate. When the researchers compared fed and fasted mice, they found that STAMP2 levels varied in response to changes in nutrient levels. In obese mice, however, this regulation of STAMP2 by nutrients was lost. The researchers then generated mice that lacked STAMP2, and observed substantial inflammation in visceral fat, the type of fat that is located around the internal abdominal organs and is most strongly associated with metabolic disease. To examine more specifically the role of STAMP2 in nutrient-rich conditions, the scientists injected mice with fat (in a form used for intravenous nutrition) and glucose, and found that these nutrients elicited more inflammation in STAMP2-deficient mice than in normal mice. Mice without STAMP2 also showed signs of insulin resistance, a condition that both precedes and characterizes type 2 diabetes, and the insulin resistance was observed even though the mice were fed a standard diet. Yet another adverse health effect observed in mice without STAMP2 was fatty liver disease. Collectively, these results illuminate a new regulatory link between nutrient metabolism and inflammation. Levels of STAMP2 in mice increase in response to nutrients and inflammatory signals, and this protective protein in turn limits inflammation under normal conditions. In obesity and diabetes, however, STAMP2 action may be disrupted or insufficient to prevent chronic inflammation. Future research will help elucidate the role of STAMP2 in human metabolism and disease.

Wellen KE, Fucho R, Gregor MF, Furuhashi M, Morgan C, Lindstad T, Vaillancourt E, Gorgun CZ, Saatcioglu F, and Hotamisligil GS: Coordinated regulation of nutrient and inflammatory responses by STAMP2 is essential for metabolic homeostasis. Cell 129: 537-548, 2007.

Discovery of a Biological Missing Link May Aid Research on Diabetes and Obesity: Researchers have identified a hormone that helps animals adapt to periods of starvation and could play a future role in treating obesity and diabetes. When food is plentiful, the body uses the energy it gets from food as its main fuel source. However, during periods of starvation, the body uses other metabolic pathways to generate energy. For example, the liver metabolizes fatty acids from fats stored in adipose tissue to produce "ketone bodies," which the body (particularly the brain) uses for energy. Mammals may also enter into hibernation-like states to conserve energy. It is important for individuals that these processes are tightly regulated in order to stay healthy. Therefore, scientists are examining the metabolic cues that regulate how the body transitions from the "fed" to the "fasting" state.

Previous research determined that a transcription factor, called PPAR-alpha, plays an important role in the body's metabolic response to starvation. Research now shows that this transcription factor increases the levels of a hormone, called FGF21, which is produced and secreted by the liver. In a mouse model, levels of the hormone increased after a fast. In addition, researchers discovered that the hormone regulates key metabolic pathways needed to adapt to starvation in mice engineered to express high levels of the hormone. For instance, it promotes the breakdown of fatty acids and increases the production of ketone bodies. It also caused the animals to go into a hibernation-like state to further conserve energy. In a complementary study, researchers studied mice that were experimentally induced to have low levels of FGF21 in their livers. When placed on a special diet that simulates nutrient availability in the fasted state and promotes lipid metabolism in the liver, the animals had severe metabolic abnormalities that included fatty liver and high levels of fats circulating in the blood. Thus, the hormone is required for the liver to fully regulate lipid metabolism under these nutritional demands. In previous research, the hormone was found to improve metabolic characteristics of diabetic and obese mice. Together, these research studies suggest that FGF21 is a missing link between diet and the regulation of lipid metabolism in the liver during fasting. They also suggest that the hormone could be a possible therapeutic target for treating diabetes and obesity.

Inagaki T, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, Li Y, Goetz R, Mohammadi M, Esser V, Elmquist JK, Gerard RD, Burgess SC, Hammer RE, Mangelsdorf DJ, and Kliewer SA: Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. Cell Metab 5: 415-425, 2007.

Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, and Maratos-Flier E: Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. Cell Metab 5: 426-437, 2007.

The Skeleton Plays More Than a Supporting Role: Researchers have shown that the skeleton—once thought to be strictly structural in purpose—is an endocrine organ that may play an important role in obesity and diabetes. In earlier studies, leptin, a hormone produced by fat cells and involved in regulating body weight, was found to send chemical signals to bone. In biology, communication is often a two-way street, so researchers hypothesized that bone might be sending its own signals back to the body. To examine this possibility, scientists generated a genetically-engineered mouse model in which bone cells lacked a protein, called OST-PTP. Unexpectedly, mice lacking this protein were protected from both diabetes and obesity. The animals also had several metabolically favorable characteristics: increased numbers of insulin-producing beta cells in the pancreas, lower blood sugar levels, increased insulin secretion, and increased insulin sensitivity. The animals expended more energy and had less visceral fat compared to their control counterparts.

How is bone causing these favorable metabolic changes? The scientists discovered that OST-PTP regulates the activity of a hormone, called osteocalcin, that is produced and secreted by bone-forming cells. Osteocalcin was found to regulate both insulin secretion and insulin sensitivity. It also increases the mass of insulin-producing beta cells. Without this hormone, animals are obese, are insulin resistant, and have decreased beta cell mass. This research is the first to demonstrate that bone has an important role in regulating metabolism and weight. It also sheds new light on the link between diabetes and obesity. Researchers have already observed that people with type 2 diabetes have low osteocalcin levels. If osteocalcin has a similar role in humans, the identification

of therapeutic agents to intervene in this signaling pathway could open new doors to therapy. Now that we know that bone is communicating with endocrine organs in the body, a closer listen could uncover other exciting findings.

Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, Zhang Z, Kim JK, Mauvais-Jarvis F, Ducy P, and Karsenty G: Endocrine regulation of energy metabolism by the skeleton. Cell 130: 456-469, 2007.

Shedding LIGHT on Regulation of Lipid Metabolism: Recent studies have shown that two chemicals in the immune system that can promote inflammation also play an important role in controlling lipid (fat) metabolism. Elevated blood levels of lipids, such as triglycerides, and cholesterol are associated with atherosclerosis (clogging of the blood vessels) and can contribute to heart disease and stroke. Previous research has elucidated how the immune system and elevated blood lipids contribute to the inflammation and plaque formation characteristic of atherosclerosis. Now, new studies have added a surprising twist to this tale by showing how the immune system also acts to directly regulate lipid metabolism. Building on previous findings from human and animal studies, researchers studied the effects on lipid metabolism of two immune-system chemicals that promote inflammation—called lymphotoxin and LIGHT. These chemicals are produced on the surface of immune cells known as T cells. Using mice genetically altered to overproduce LIGHT, researchers found that an overabundance of this chemical on the mouse T cells correlated with elevated cholesterol and triglycerides in the blood. Because the liver is an important player in lipid metabolism, the researchers next conducted a microarray analysis of 45,000 genes expressed in the liver of the LIGHT-overproducing mice. They noticed very low levels of the enzyme hepatic lipase, which usually contributes to lipid metabolism by breaking down triglycerides. Levels of this enzyme were 20 times lower in the mice with excessive LIGHT than in normal mice. Injecting the mice with a compound to neutralize the overactive LIGHT production corrected the lipid imbalances. Further studies in other animal models and in cell culture provided more evidence that, in addition to their pro-inflammatory role in the immune system, LIGHT and lymphotoxin work through the same pathway to inhibit a beneficial liver enzyme and contribute to a pathologic elevation of lipid levels. This work highlights a previously unappreciated relationship between immune cells and liver cells in controlling lipid metabolism. Furthermore, the research demonstrates the feasibility of a possible therapeutic approach for treating atherosclerosis by targeting the LIGHT-lymphotoxin pathway in the immune system.

Lo JC, Wang Y, Tumanov AV, Bamji M, Yao Z, Reardon CA, Getz GS, and Fu YX: Lymphotoxin beta receptor-dependent control of lipid homeostasis. Science 316: 285-288, 2007.

Metabolic Connection Found Between Brain Glucose and Liver Fat Processing: Recent research findings point to a previously unrecognized relationship between metabolism of glucose in the brain and the processing and distribution of lipids by the liver. Some of the defining features of metabolic syndrome—a constellation of symptoms that puts individuals at higher risk for developing diseases such as type 2 diabetes and cardiovascular disease—are a higher level of fats known as triglycerides in the blood, and overweight. The liver packages triglycerides (TGs) into particles known as very low-density lipoprotein (VLDL) for secretion into the blood. This process is regulated by such factors as nutrients and the hormone insulin. In the current study, researchers provided a new insight into this process by showing how the brain's metabolic responses to nutrient intake can communicate with the liver, affecting its processing and packaging of fats. To achieve this, the researchers first directly infused glucose into the brains of rats and observed a resulting decrease in the level of circulating TGs. Then, by using specific enzymatic inhibitors and metabolic products, they identified the major components in the pathway that leads from brain glucose metabolism to effects on liver VLDL-TG (fat) secretion. Ultimately, the researchers demonstrated the relevance of this brain-liver metabolic connection to situations such as metabolic syndrome through experiments on rats overfed a high-fat diet. When glucose was infused into the brains of these rats, the typical reduction in circulating VLDL-TG was not seen, suggesting that overfeeding disrupts the brain-liver connection, in terms of its ability to harmoniously regulate metabolism. These findings of

a new brain-liver circuit that regulates fat distribution, which could be defective in those with metabolic syndrome, provide a possible target for future approaches to controlling this complex condition.

Lam TKT, Gutierrez-Juarez R, Pocai A, Bhanot S, Tso P, Schwartz G, and Rosetti L: Brain glucose metabolism controls the hepatic secretion of triglyceride-rich lipoproteins. Nat Med 13: 171-180, 2007.

Metabolic Regulator May Also Be a Therapeutic Target for Degenerative Brain Diseases: To drive its essential activities, the body relies on mitochondria, the so-called "power-houses" of the cell. Through a series of chemical reactions, mitochondria convert nutrients from food into usable energy and heat. However, these reactions sometimes generate dangerous chemical by-products that can damage cells in the brain, heart, and other vital organs. This type of damage, called oxidative damage, is thought to play a role in degenerative brain diseases, such as Huntington's disease, Parkinson's disease, and Alzheimer's disease. Scientists now have evidence that a key regulator of mitochondrial activity also regulates cellular defenses against oxidative damage. Through experiments using cell lines and rodent models, the researchers found that the PGC-1alpha protein is necessary for cells and tissues to react normally to the threat of oxidative damage. Cells with increased levels of PGC-1alpha were more strongly protected against oxidative damage. Conversely, cells lacking the protein were unable to increase production of enzymes that "clean up" the toxic molecules and render them harmless. Most intriguingly, the researchers found that mice genetically engineered to lack PGC-1alpha had brains more vulnerable to oxidative damage than those of normal mice. PGC-1alpha has been well-studied because reduced levels are thought to play an important role in diabetes and obesity, and molecules that increase its activity are in development. While the connection between brain degeneration and PGC-1alpha activity needs further exploration, current research indicates that this protein may be a promising therapeutic target not only for metabolic disorders, but for brain diseases as well.

St-Pierre J, Drori S, Uldry M, Silvaggi JM, Rhee J, Jäger S, Handschin C, Zheng K, Lin J, Yang W, Simon DK, Bachoo R, and Spiegelman BM: Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. Cell 127: 397-408, 2006.

Type 1 Diabetes TrialNet: Study Testing Oral Insulin To Prevent Type 1 Diabetes

Researchers have begun a clinical study to test the ability of oral insulin to prevent or delay type 1 diabetes in at-risk people. NIDDK's Type 1 Diabetes TrialNet is a network of researchers dedicated to the understanding, prevention, and early treatment of type 1 diabetes. TrialNet is conducting the study in more than 100 medical centers across the U.S., Canada, Europe, and Australia.

In type 1 diabetes, a person's own immune system destroys the insulin-producing beta cells of the pancreas. Beta cells sense blood glucose and produce the hormone insulin, which is essential to regulating glucose and converting it to energy. The immune attack on beta cells begins well before a person develops type 1 diabetes and continues long after the disease is diagnosed. In the early stages of disease, up to 10 years before diabetes is diagnosed, proteins called "autoantibodies" may appear in the blood. These autoantibodies to glutamate decarboxylase (GAD), IA-2, and to insulin itself indicate a greater risk for developing type 1 diabetes.

In the new study, researchers are testing whether an insulin capsule taken by mouth once a day can prevent or delay diabetes in a specific group of people at risk for type 1 diabetes. An earlier trial suggested that oral insulin might delay type 1 diabetes for about 4 years in some people with high levels of insulin autoantibodies. Animal studies have also suggested that insulin taken orally may prevent type 1 diabetes. Some scientists think that introducing insulin via the digestive tract induces tolerance, or a quieting of the immune system. Insulin taken orally has no side effects because the digestive system breaks it down quickly. To lower blood glucose, insulin must be injected or administered by an insulin pump.

Management of type 1 diabetes is extremely burdensome to patients and their families. People with the disease must check their blood sugar levels multiple times per day with a finger stick, administer insulin, and monitor food intake and physical activity levels. Moreover, patients are susceptible to developing long-term disease complications affecting the eyes, kidneys, nerves, and heart. Therefore, identifying ways to prevent the disease is critically important, not only to prevent these serious complications, but to spare people from the tremendous burden of daily disease management.

In addition to conducting the new oral insulin prevention trial, TrialNet also studies therapies to preserve insulin production in people recently diagnosed with type 1 diabetes. For example, one TrialNet study seeks to turn off the immune attack on beta cells with rituximab, a monoclonal antibody that binds to and temporarily destroys a specific class of immune cells.

TrialNet is currently recruiting people to participate in its studies. For more information about enrolling in TrialNet studies, please visit *www.DiabetesTrialNet.org* or call *1-800-HALT-DM1 (1-800-425-8361)*.

People with Diabetes and Sickle Cell Trait Should Have Reliable A1C Test: Campaign Informs Physicians and Patients

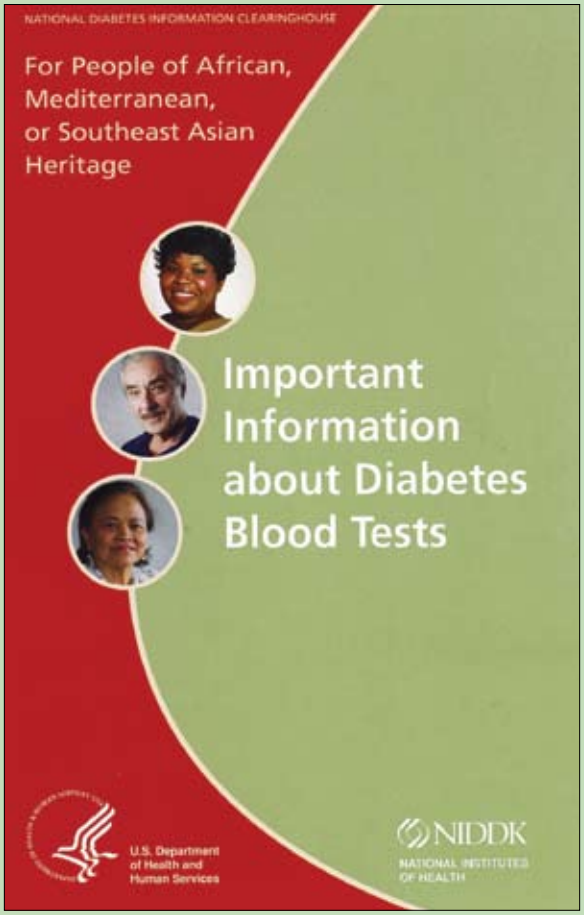
A new NIDDK information campaign highlights the importance of using accurate methods to test hemoglobin A1c in people with diabetes who have sickle cell trait or other inherited forms of variant hemoglobin. The specific needs for testing blood glucose control in these patients are explained in two booklets, "Sickle Cell Trait and Other Hemoglobinopathies and Diabetes: Important Information for Physicians" and "For People of African, Mediterranean, or Southeast Asian Heritage: Important Information about Diabetes Blood Tests" from NIDDK's National Diabetes Information Clearinghouse at *www.diabetes.niddk.nih.gov*

Studies have repeatedly shown that intensive control of blood glucose, blood pressure, and cholesterol reduces heart disease and the other complications of diabetes. The hemoglobin A1c blood test (or simply the A1C test) is an essential tool in diabetes care because it shows a patient's average level of blood glucose control in the previous 2 to 3 months. Physicians base their treatment decisions in large part on the A1C test results. Inaccurate A1C readings, whether falsely high or low, may lead to the over treatment or under treatment of diabetes.

The A1C test, though essential in diabetes management, is not recommended for diagnosing diabetes. However, if an A1C test is given to a person not known to have diabetes and the result is higher than normal, a fasting blood glucose test is needed to confirm a diabetes diagnosis.

The National Glycohemoglobin Standardization Program (NGSP) at the University of Missouri School of Medicine, supported by the NIDDK and Centers for Disease Control and Prevention, is working to improve and standardize the measurement of A1C in laboratories around the world. The NGSP website (*www.NGSP.org*) lists the test methods that accurately measure A1C in patients with hemoglobin variant S, also known as sickle cell trait, and variant C, another common variant in the United States.

In a press release announcing the new campaign, Dr. Randie Little, head of the NGSP, said, "In the United



This booklet, which was developed for people of African, Mediterranean, or southeast Asian descent, is part of a new NIDDK campaign that highlights the importance of using accurate methods to test hemoglobin A1c in people with diabetes who have sickle cell trait or other inherited forms of variant hemoglobin.

States, more than 3,000 labs rely on 20 different methods to measure A1C in people with diabetes. However, six of these methods yield unreliable results in patients with sickle cell trait. Health care professionals caring for people with diabetes should know that specific A1C tests should be used in this group of patients."

Many individuals are unaware they have a hemoglobin variant such as sickle cell trait because the condition usually

causes no symptoms. In diabetes patients of African, Mediterranean, or southeast Asian descent, several situations may suggest the presence of a hemoglobin variant:

- An A1C result does not correlate with results of self blood glucose monitoring;
- An A1C result is different than expected or radically differs from a previous test result after a change in lab A1C methods; or
- An A1C result is more than 15 percent.

In the same announcement, Dr. Griffin Rodgers, NIDDK Director, advised physicians, "If you see a significant discrepancy between a patient's A1C reading and the results of routine blood glucose monitoring, consider the possibility that your patient may have a hemoglobin variant and find out if your lab is using an accurate method to measure A1C."

Hemoglobin is the oxygen-transporting protein in red blood cells. Mutations in the genes that code for the protein, which occur more frequently in people of African, Mediterranean, and southeast Asian descent, cause variations in the structure or amount of hemoglobin. Researchers have identified hundreds of hemoglobin variants in the human population, affecting millions of people worldwide.

The most common variant is sickle cell trait in which a person inherits a gene for hemoglobin S and a gene for hemoglobin A, the usual form of hemoglobin. Sickle cell trait affects about 8 percent of African Americans.[1] Having sickle cell trait or another hemoglobin variant does not increase a person's risk for developing diabetes.

In sickle cell disease, a person inherits two genes for hemoglobin S, which causes the malformation, or sickling, of red blood cells, leading to anemia, repeated infections, and periodic episodes of pain. The A1C test is not used in diabetes patients with sickle cell anemia due to the shortened life span of red blood cells.

Diabetes afflicts nearly 21 million people in the United States, but its burden is disproportionately felt by minorities, including African Americans, Hispanic/Latino Americans, American Indians and Alaska Natives, Asian Americans, and Pacific Islanders. About 13 percent of African Americans age 20 and older suffer from diabetes, a rate that is nearly twice that of non-Hispanic whites.[2]

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[1] *www.nhlbi.nih.gov/health/dci/Diseases/Sca/SCA_WhoIsAtRisk.html*
[2] *www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf*

STORY OF DISCOVERY

Studies of Underlying Biology of Insulin Secretion Pave the Way to New Treatment for Neonatal Diabetes

In the 1950s, little did scientists know that new drugs being used to treat type 2 diabetes in adults would be used half a century later to treat a rare form of diabetes in babies.

The drugs are called "sulfonylureas." The initial observation about these drugs came in the early 1940s, when French scientists used them to treat typhoid patients. After treatment, the patients had symptoms of dangerously low blood sugar levels (hypoglycemia). Tests of the same drugs in dogs showed that they stimulate insulin secretion, leading to hypoglycemia. Insulin is a hormone released by the beta cells of the pancreas in response to elevated blood sugar levels. Its release then promotes the uptake of sugar by cells in the body. These novel findings paved the way to clinical trials to test this class of drugs in people with the form of diabetes now known as type 2. People with type 2 diabetes produce insufficient amounts of insulin to compensate for diminished responsiveness of cells to the hormone. In the mid-1950s, sulfonylureas were found to be effective for treating human type 2 diabetes. Sulfonylureas were the first diabetes pills used as an alternative to insulin injections for people with type 2 diabetes.

This result was great news, but it remained unknown exactly *how* sulfonylureas stimulated insulin secretion. Teasing out this mystery has been the subject of research for several decades. A clue came in 1985, when NIDDK-supported scientists demonstrated that sulfonylureas inhibit a potassium ion channel. This type of channel allows movement of potassium ions between the inside and outside of the beta cell, a common method the cell uses to control its processes. Although this observation shed some light on how the drugs may work, it also led to several new questions: what protein (or proteins) comprised the potassium ion channel? Were sulfonylureas binding directly to the channel or were they binding to an intermediate protein to stimulate insulin release?

A breakthrough came in 1995, when NIDDK-supported scientists cloned a gene encoding the sulfonylurea receptor, or SUR. This protein was the target to which the drugs were binding in beta cells. Interestingly, mutations in the gene encoding SUR were found to be linked to a rare genetic disease, called persistent hyperinsulinemic hypoglycemia of infancy (PHHI). People with this disease have high levels of insulin and correspondingly low blood sugar levels. These findings suggested that SUR was a critical component of cellular pathways regulating insulin secretion. Was SUR the potassium ion channel that was inhibited by sulfonylureas? Research showed that SUR alone could not function as an ion channel. However, a few months later, the same group of NIDDK-supported scientists identified SUR's partner—a protein called Kir6.2. The combination of SUR and Kir6.2 worked together as a potassium ion channel. This research demonstrated that the previously unidentified potassium ion channel was composed of SUR and Kir6.2; sulfonylureas bound directly to the SUR subunit of the channel to inhibit it.

These pioneering NIDDK-supported discoveries contributed to a model of the regulation of insulin secretion by sugar. The SUR/Kir6.2 ion channel regulates the balance of potassium and calcium ions inside and outside the beta cell, which in turn helps to regulate insulin secretion. In healthy people, when blood sugar levels are low, the channel is "open" and insulin is not secreted. When blood sugar levels are high (e.g., after a meal), sugar metabolism in the beta cell closes the ion channel, and insulin is secreted. Sulfonylureas cause the same biological effect as high

STORY OF DISCOVERY

sugar levels—they close the channel and stimulate insulin release from the beta cell. Mutations causing PHHI also result in a similar biological effect—they prevent the channel from opening and promote insulin release.

Building on this research foundation, researchers in Europe hypothesized that SUR/Kir6.2 may be involved in monogenic diabetes. These forms of diabetes result from mutations in a single gene; in contrast, type 1 and type 2 diabetes involve variations in multiple genes. The two main forms of monogenic diabetes are neonatal diabetes mellitus and maturity-onset diabetes of the young (MODY). Neonatal diabetes is a rare condition, usually occurring within the first 6 months of life, and may either be permanent, or transient—with the possibility of relapse later in life. While a number of genes had been found that each could cause MODY—the monogenic form of diabetes that is usually diagnosed later in childhood or young adults—the genetic cause of permanent neonatal diabetes was unknown.

In 2004, the European researchers examined the gene encoding Kir6.2 in patients with permanent neonatal diabetes. Several people with the disease had mutations in this gene. Upon examination of the underlying biology of the mutant channels, researchers found that the mutations caused the channels to be "open" all the time, even in the presence of high levels of sugar. Thus, these mutations appeared to prevent insulin release. These findings helped to explain why children with these mutations produce insufficient amounts of insulin and require insulin administration. They also suggested that, if there were another way to close down the channels—such as through treatment with sulfonylureas—perhaps insulin secretion could be restored.

These observations laid the foundation for a recent clinical trial by the same group of scientists to test the effect of switching neonatal diabetes patients from insulin to oral sulfonylurea treatment. People in the trial had mutations in their gene encoding Kir6.2. Strikingly, 90 percent of patients successfully discontinued insulin after receiving the oral drugs. Average blood sugar control improved in all patients who switched treatment strategies. These results are extremely exciting because oral therapy is a much less burdensome treatment strategy than insulin administration, which requires daily injections or use of a pump. It is of particular benefit for babies and young children to be able to take oral medication for their neonatal diabetes, rather than experience an arduous regimen of daily insulin administration.

NIDDK-supported scientists have also recently shown that some people with permanent and transient neonatal diabetes have mutations in their gene encoding SUR. People with these mutations who were switched from insulin to sulfonylurea therapy appeared to respond favorably. Together, these studies demonstrate that mutations in the gene encoding Kir6.2 are the most common cause of permanent neonatal diabetes; mutations in the gene encoding SUR account for fewer cases of permanent and some cases of transient neonatal diabetes.

How do people with PHHI and neonatal diabetes have mutations in the same ion channel, but PHHI patients have too much insulin and patients with neonatal diabetes have insufficient amounts? It turns out that mutations causing PHHI have the opposite effect on the function of the ion channel than mutations causing neonatal diabetes. The mutations causing PHHI prevent the channel from opening, which causes beta cells to secrete insulin continually. The mutations causing neonatal diabetes cause the channels to always remain open, which prevents insulin release. Thus, even though the same ion channel is involved in both diseases, the effects of the different mutations lead to completely opposite biological responses.

These studies identify a novel mechanism for the development of a significant fraction of permanent and transient neonatal diabetes mellitus and identify

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a less burdensome treatment strategy for some patients. They also pave the way for genetic testing to inform personalized treatments for people with the disease. Importantly, this research elegantly demonstrates how long-term studies of underlying biological mechanisms directly led to an improved treatment option for patients. Incremental studies of how sulfonylureas worked in the beta cell culminated with the NIDDK-supported discovery of the SUR/Kir6.2 potassium ion channel. This discovery not only informed key genetic studies, but also provided a much greater understanding of the basic biology of insulin secretion. Recently, using a whole genome association study, NIH-supported investigators have confirmed that the gene for Kir6.2 can contribute to type 2 diabetes. These studies now serve as the foundation for additional research on the role of this ion channel in diabetes, with the potential to improve and personalize therapies by targeting specific treatments to patients with specific genetic changes underlying their diabetes.

Genetic testing could be helpful in selecting the most appropriate treatment for people with monogenic diabetes. If you think that you or a family member has a monogenic form of diabetes, you should seek help from a healthcare provider. For more information on monogenic forms of diabetes, please see an NIDDK fact sheet available at: *http://diabetes.niddk.nih.gov/dm/pubs/mody/mody.pdf*

The Intersection of Drug Metabolism and Diabetes

Dr. David Moore

Dr. David D. Moore is a professor in the departments of Molecular and Cellular Biology and Molecular and Human Genetics at Baylor College of Medicine in Houston, Texas. He received his Ph.D. in Molecular Biology from the University of Wisconsin, Madison. He trained as a post-doctoral fellow in the laboratory of Dr. Howard Goodman at the University of California, San Francisco. He has received numerous awards for his teaching and research, including the Edmund B. Astwood Award from the Endocrine Society. The following are highlights from the scientific presentation that Dr. Moore gave to the NIDDK's National Advisory Council in May 2007.

Dr. Moore's presentation focused on nuclear hormone receptors, which are proteins that help certain chemicals, such as vitamin D or the sex hormones estrogen and testosterone, exert some of their effects. Typically, when one of these chemicals enters a cell it binds to its receptor, and the hormone-receptor complex then interacts with both specific DNA sites and other proteins to turn some genes in the nucleus "on" and others "off." Most of the 48 nuclear hormone receptors encoded by the human genome actually bind—not to true hormones—but to other chemicals coming from outside the body. Through support from NIDDK, the National Heart, Lung, and Blood Institute and the National Institute of Environmental Health Sciences, the Nuclear Receptor Signaling Atlas project is cataloging the diverse and extremely important physiological effects of these proteins. An important subset of these receptors plays a vital role in triggering the process by which the body eliminates certain drugs or toxins, a process called drug metabolism.

Dr. Moore first discussed recent research from his laboratory that has shed light on the way that type 1 diabetes influences drug metabolism via CAR, a member of the nuclear hormone receptor family originally cloned in his laboratory. Dr. Moore then presented work showing that drug metabolism mediated by CAR may be helpful in achieving healthier blood glucose levels in patients with type 2 diabetes. Thus, not only can diabetes influence drug metabolism, but also drug metabolism can affect diabetes.

Diabetes Impacts Drug Metabolism

The experiments Dr. Moore highlighted were inspired by observations from other researchers that type 1 diabetes accelerates metabolism of certain drugs, both in humans and in rodent models. Dr. Moore's lab looked at drug metabolism genes that are turned on by CAR. The researchers found that these genes were turned on in a mouse model of type 1 diabetes. Controlling the diabetes reversed the effect: when insulin was given to the mice, the CAR-induced genes turned off.

In fact, type 1 diabetes not only leads to activation of drug metabolic genes, but also has a profound effect on the metabolism of certain drugs. Mice with induced type 1 diabetes rapidly clear their systems of a compound that induces temporary paralysis, while normal mice cannot. These experiments also underline the central importance of the CAR nuclear receptor in affecting drug metabolism: mice without CAR take much longer to clear the drug, whether or not they have diabetes.

How does CAR promote speedier drug metabolism in animals or people with diabetes? The answer may have to do with an unusual property of CAR compared to other nuclear hormone receptors. In addition to its response to binding to a hormone or other activating molecule from outside the cell, CAR can move into the

nucleus and turn on its target genes when it is activated by an enzyme within the cell called AMP kinase. Not surprisingly, AMP kinase is activated by certain drugs. In addition, the Moore lab found it to be modestly activated in the livers of mice with uncontrolled type 1 diabetes. Further research will be required to extend these suggestive results and determine the actual mechanism underlying the impact of type 1 diabetes on drug metabolism.

Drug Metabolism Impacts Diabetes

Early in the course of type 2 diabetes, the pancreas reacts to elevated blood glucose by producing more insulin to try to compensate. However, because the disease is characterized by insulin resistance, the result is that both blood sugar and insulin are elevated in these patients if they do not have proper treatment. Gradually, during the course of the disease, years of elevated blood glucose take their toll on insulin-producing cells, diminishing their ability to produce the vital hormone. Thus, without proper treatment, glucose control often goes from bad to worse.

Surprisingly, researchers have found that phenobarbital, a medication formerly used to treat epilepsy, also has the effect of reducing blood glucose levels in people with type 2 diabetes. The effect is only observed in patients whose disease is in its early stages and whose ability to produce insulin is not yet seriously diminished or lost. Phenobarbital has no impact on blood glucose or insulin levels either in those whose type 2 diabetes has progressed to the point where insulin production falls, or in people who do not have the disease.

Phenobarbital is an effective treatment for epilepsy, but it is no longer widely used because it has two serious side effects: it is a potent sedative, and it is such a powerful activator of drug metabolism (via CAR) that it can adversely affect the way a patient's other medications are handled by the body. The effect on blood glucose can also be thought of as a side effect, albeit a potentially beneficial one in some patients due to its theoretical benefit for some people with type 2 diabetes. However, because of its serious side effects and the availability of safer medications that improve insulin sensitivity, phenobarbital is not a recommended treatment for the disease.

Nevertheless, understanding the way phenobarbital exerts its effects might point the way to other avenues of diabetes treatment. The lower blood glucose levels observed in type 2 diabetes patients taking phenobarbital might result from an overall improvement in insulin sensitivity among the body's cells that allows them to absorb more glucose, or they might come from a more subtle metabolic effect.

To distinguish between these possibilities, the Moore lab examined a strain of mice that are obese because they lack a key hormonal mediator of appetite control. Invariably, the uncontrolled appetite of these mice leads them to become obese and to develop type 2 diabetes at a very young age. As in humans, a drug treatment that stimulates CAR helped normalize the otherwise sharply elevated blood glucose levels typically observed in these animals. When the obese mouse strain was modified by deleting the gene for CAR, the drug treatment had no effect on blood glucose, indicating that CAR is necessary for the effect.

If CAR has a general effect on insulin sensitivity, CAR stimulation would be expected to improve the ability of all tissues in the animal to absorb glucose. However, when the Moore group looked more carefully at how specific tissues in these mice respond to a sudden surge of injected glucose, they discovered this was not the case. CAR stimulation did not improve glucose clearance in peripheral tissues. Rather, the effect was confined to the liver.

One possible explanation for the importance of the liver in mediating CAR's glucose-modulating effects relates to the liver's vital metabolic role in keeping blood glucose sufficiently high to facilitate brain function during periods of fasting. The liver does this

by liberating glucose from energy stores. One of the important messages insulin sends to the body is to tell the liver that it should stop producing glucose when blood levels of the molecule begin to rise after a meal, and to signal to the body that it should instead switch to replenishing energy stores. Because of the insulin resistance observed in type 2 diabetes, however, the liver continues to produce glucose even when its concentration in the blood is already too high. Interestingly, CAR seems to reduce the activities of several proteins with a key function in liver glucose production, while stimulating proteins that direct blood glucose into energy stores.

Conclusion

Dr. Moore's presentation made the surprising case for two distinct intersections between the physiology of drug metabolism and that of diabetes. First, he recounted research that has shown the profound effect that type 1 diabetes can have on the metabolism of certain drugs by stimulating the CAR nuclear receptor. These data may ultimately bear not only on the way type 1 diabetes is treated, but also on the way people with the disease are treated for other conditions. Second, he showed that drug treatments that trigger CAR signaling can impact blood glucose levels in a mouse model of type 2 diabetes, probably by modulating glucose metabolism in the liver. These observations suggest that inhibiting glucose production and/or stimulating glucose storage by the liver is a potentially valuable approach to treating type 2 diabetes, perhaps in conjunction with other therapies.

PATIENT PROFILE

Casey Burkhalter

Using Advanced Technology To Help Control Glucose Levels

It's the middle of the night, and the Burkhalter family of Jacksonville, Florida, is sleeping more soundly and peacefully than they have in a long time because of a newly-developed technology called a continuous glucose monitoring system, or CGMS. This promising device is being tested by their 14-year-old daughter, Casey, as part of a research network, called the Diabetes Research in Children Network (DirecNet), sponsored by the National Institute of Child Health and Human Development, the NIDDK, and the Special Statutory Funding Program for Type 1 Diabetes Research.

Casey has type 1 diabetes. The device she is testing monitors her blood glucose levels almost constantly throughout the day. It's when Casey is asleep at night, however, that the CGMS is a lifesaver for her and her family. Should Casey's glucose levels become too high or too low, the CGMS sets off an alarm that alerts her parents to take action. If her glucose level is too low, the Burkhalters give Casey orange juice to raise her blood glucose levels; if it's too high, they administer insulin through Casey's insulin pump.

Caring for children with diabetes requires great diligence, and CGMS technology has the potential to ease some of that burden. "Prior to Casey using the CGMS," says Casey's mother, Leslie Burkhalter, "my husband and I would wake up every 2 hours to prick Casey's finger and check her glucose levels." Their nightly vigil was part of an all-out effort to keep their daughter's blood glucose levels as close to the normal range as possible to prevent diabetes-related seizures and other complications.

NIDDK-supported research—including the landmark Diabetes Control and Complications Trial (DCCT) and a follow-up study, the Epidemiology of Diabetes Interventions and Complications Study (EDIC)—demonstrated that intensive blood glucose control offers remarkable long-term benefits when it comes to preventing or delaying the damage diabetes can have on a patient's eyes, kidneys, and nerves, as well as the harm the disease can inflict on large blood vessels that can lead to heart attacks and strokes.

Casey and Leslie Burkhalter

"I want to tell the world about this device," says Mrs. Burkhalter.

Most people with diabetes report checking their glucose levels every couple of hours, at best. The CGMS device Casey is testing is designed to provide, among other valuable information, glucose readings every minute—without a finger prick. The hope is that this technology will enable people of all ages with diabetes to better gain control over their blood glucose levels and reduce their risk of diabetes complications.

PATIENT PROFILE

"I want to tell the world about this device," says Mrs. Burkhalter, who works in sales and is also actively involved in the Juvenile Diabetes Research Foundation (JDRF).

About the Continuous Glucose Monitoring System
In 2006, new continuous glucose monitoring devices were approved for use in adults. In 2007, a device was approved for use in children. However, Casey wears her monitor because of her participation in the DirecNet study, which is investigating the potential use of CGMS technology and its impact on the management of type 1 diabetes in children. She received her CGMS when she enrolled in the study in December 2005.

Casey's CGMS comes with a 5-day sensor, a transmitter, and a wireless receiver with a built-in glucose monitoring system. The tiny glucose sensor is placed just under the skin of Casey's abdomen. This procedure is similar to inserting the catheter of an insulin pump, is quick, and usually is not very painful. Tape is used to hold it in place. When used during the day, the wireless receiver allows Casey to attach the monitor to a belt or the waistline of her pants. When she goes to bed, she leaves it on her night table. The system automatically records an average glucose value every minute for up to 5 days, at which time the sensor needs to be replaced and repositioned on Casey's abdomen.

Casey's CGMS, when connected to a computer, also provides charts and graphs that indicate trends in her glucose levels over time and how often her glucose levels may be out of range. Although Casey's blood glucose control was excellent when she entered the trial, while wearing the CGMS, she was able to further improve her blood glucose control, without causing hypoglycemia. The family had great comfort knowing Casey's blood glucose level all the time and in real time.

"This technology is unbelievably helpful in controlling glucose levels. It's a huge step toward an artificial pancreas," says Mrs. Burkhalter. She is referring to the day when glucose monitoring and insulin delivery technologies merge, allowing insulin pumps to not only recommend proper insulin dosages, but automatically deliver them as well.

The Burkhalters' Vigil Before the CGMS
Casey was diagnosed with diabetes at about age 10 and a half. Her 18-year-old brother, Tyler, was diagnosed with the disease in November 1999. "Both came as a surprise," says Mrs. Burkhalter. "There is no other history of diabetes in our family."

Night after night of awaking every 2 hours to check Casey's levels was taking its toll on the family. "It created a lot of wear and tear on my husband and me," says Mrs. Burkhalter. "Lack of sleep was making us both irritable and cranky. However, we didn't want Casey to go into a diabetic seizure in her sleep, and fortunately, she never has."

The CGMS has provided the Burkhalters with more than just a good night's sleep. It has provided their daughter with a new attitude toward managing her diabetes.

Casey, whom her mother describes as outgoing and determined, is also an athlete who plays basketball, rides horses, and is a member of a crew team—all rigorous physical activities that can make controlling glucose levels even more difficult than normal.

"I hate having my fingers pricked (to check glucose levels), and the calluses they make aren't very attractive," says Casey. "With the CGMS, I only need to prick my finger, on average, once instead of 7 to 12 times a day." Casey adds that her CGMS is easy to wear "because it's not technically connected to me." At night, she keeps the transmitter on her nightstand. Should its alarm beep, "my parents don't even need to wake me."

As helpful as it may be, the technology is not perfect. There can be as much as a 10 minute delay between

sensing and reading out glucose levels, and every 5 days, when the sensor needs replacing, it takes 10 hours to recalibrate, both of which timeframes users would like to see shortened, says Mrs. Burkhalter. Making the device smaller would also make it more convenient, she adds.

Participating in DirecNet

The Burkhalters learned about the DirecNet CGMS study when, in the fall of 2005, Mrs. Burkhalter read an article in *Countdown*, a publication of the JDRF, entitled, "Artificial Pancreas: How Close Are We to Closing the Loop?" It piqued her interest, and shortly thereafter she spoke with Casey's endocrinologist, Dr. Nelly Mauras at the Nemours Children's Clinic, one of the five participating centers, who recruited Casey into the study and started the ball rolling. Casey was one of the first 30 children in the U.S. to participate in this DirecNet study. Today there are about 100. "One reason Casey is a good candidate for the study is that she recognizes when her blood glucose level is low during the day but, unlike Tyler, not at night," says Mrs. Burkhalter.

The Burkhalters have been extremely pleased with their participation in the DirecNet study. "We believe in the potential of this technology and very much appreciate how those running the study have provided information to us, as well as taken information from us," says Mrs. Burkhalter. "We've recommended the study to many of our friends, and several of their children are now participants." Tyler, the Burkhalters' son, is not a study participant. "He's averse to wearing anything, including an insulin pump, and unlike, Casey, he doesn't seem to mind the finger pricks as much. But he's beginning to change his mind [about using a CGMS]," says Mrs. Burkhalter.

Five clinical centers participate in DirecNet, including Yale University, The Barbara Davis Diabetes Center (Denver), Nemours Children's Clinic-Jacksonville, University of Iowa, and Stanford University. For more information on participating in DirecNet, please visit: *http://public.direc.net*

PATIENT PROFILE

Modesta Solorzano

Gestational Diabetes Study Focuses on Hispanic Women

Modesta Solorzano was nearly eight months pregnant with her third child when she was recruited for the Gestational Diabetes Mellitus (GDM) Cohort Study. This NIDDK-supported observational study is focused on relatively young Hispanic women who have had gestational, or pregnancy-related, diabetes. The study is helping to identify potential causes of type 2 diabetes in these women, who are at greatly increased risk for the disease because of their history of gestational diabetes.

Modesta Solorzano

At the time she entered the study in 1994, Modesta, like all the original GDM Cohort Study participants, had been diagnosed with GDM. This means that, during her pregnancy, she showed higher than normal levels of glucose (sugar) in her blood after drinking a special high-sugar test drink. Fourteen years later, at age 52, Modesta continues to manifest slightly higher than normal glucose levels when tested, such that she is considered to have "pre-diabetes." However, aided by the study's emphasis on providing information on exercise and healthy diet to participants, she remains free of type 2 diabetes. Also free of diabetes is her son, Anthony, who she proudly says is a "very healthy boy" and straight-A student in school.

About Gestational Diabetes Mellitus (GDM)

GDM is a form of diabetes that is first detected during pregnancy. Like other forms of diabetes, it is characterized by high blood glucose levels and can have serious consequences. Left untreated or uncontrolled, gestational diabetes can result in babies being born very large and with extra fat, which can make delivery difficult and more dangerous for both mother and child. It also can lead to babies with breathing problems and low blood glucose right after birth. Moreover, some studies show that when these babies reach adolescence, they have higher glucose and blood pressure levels and are more likely to be obese than children of women who never had gestational diabetes.

GDM affects about seven percent of all pregnancies in the United States and occurs more frequently among African American, Hispanic/Latina, and American Indian and Alaska Native women, as well as obese women and women with a family history of diabetes. Recent studies also suggest that many or most women diagnosed with GDM already have higher than normal (although not yet diabetic) blood glucose levels before pregnancy, but simply are not tested for this health problem until they become pregnant.

The good news for most women with GDM is that only about 10 percent of them will still have diabetes shortly after their baby is born. The down side is that 20 to 50 percent of them will develop diabetes outside of pregnancy sometime in their life, usually within the next 10 years. Also, they are very likely to have GDM during subsequent pregnancies.

PATIENT PROFILE

GDM affects about seven percent of all pregnancies in the United States and occurs more frequently among African American, Hispanic/Latina, and American Indian and Alaska Native women, as well as obese women and women with a family history of diabetes. Recent studies also suggest that many or most women diagnosed with GDM already have higher than normal (although not yet diabetic) blood glucose levels before pregnancy, but simply are not tested for this health problem until they become pregnant.

Modesta Solorzano came to the United States from El Salvador in 1976. Her family has a long history of type 2 diabetes. Her father died at age 84 of a stroke related to type 2 diabetes. In addition, Modesta's 85-year-old mother suffers from the disease, as do four of her six sisters.

Often, women with gestational diabetes have no symptoms. They also may not know about the link between GDM and the development of type 2 diabetes. Modesta, for example, says that she was unaware of her elevated risk for type 2 diabetes before entering the GDM Cohort Study.

GDM Cohort Study

Specifically targeted to Hispanic women, the University of Southern California (USC) GDM Cohort Study began in 1993. Conducted by a team of researchers led by Dr. Tom Buchanan, it is an observational rather than interventional study—that is, no treatment is involved. During its first several years, the study focused on potential physiological and hormonal factors or problems present in women with GDM that may predict development of type 2 diabetes post-pregnancy. To help identify these factors, the researchers gathered a variety of metabolic and other information from participants. Upon enrollment in the study, women with GDM had three metabolic tests. These tests provided baseline information about factors important in the development of diabetes, such as insulin resistance. Within 6 months after delivery, the participants began a series of regular follow-up visits. Every 15 months, participants had their blood glucose checked, underwent metabolic tests, were given a thorough physical examination, and were asked to fill out a questionnaire related to diet and exercise. They also routinely received advice on diet and exercise that could help them take steps to improve their health and delay or prevent diabetes. These visits have continued into the current, long-term follow up phase of the study. From the beginning, participants have been followed by study investigators until they develop blood sugar levels high enough to require clinical intervention. Women have been followed for as long as 12 to 14 years after their GDM pregnancy.

Fortunately for Modesta, her blood sugar has remained at levels that are relatively easy for her to control through diet and exercise. "I walk a lot," says Modesta, "and I no longer eat a lot of greasy foods." Instead, she has purchased kitchen utensils that enable her to steam vegetables and other foods, and she has reduced her intake of candy and other sweets. "I've lost 12 pounds since being in the study," she says.

Modesta is the mother of three children. Her first child was born in El Salvador 32 years ago. Modesta does not recall having been checked for high glucose levels during that pregnancy. Her second child was born in California 28 years ago. Modesta did not develop GDM as a result of the pregnancy. During her third and final pregnancy, however, Modesta manifested higher than normal glucose levels during a test, and she was therefore recruited to take part in the GDM Cohort Study. She decided to participate in the study because, "I was told that it would help me control my glucose levels and possibly help prevent me from getting type 2 diabetes in the future," she says.

Shortly after enrolling, Modesta gave birth to her third child, Anthony, delivered by Caesarian section. Like many babies of mothers with GDM, Anthony was heavier than normal at time of delivery, weighing just over 9 pounds, but otherwise very healthy.

PATIENT PROFILE

Today, at nearly 14 years of age, Anthony remains free of type 2 diabetes even though he is at higher risk for the disease because Modesta experienced GDM during the pregnancy. Modesta makes sure he exercises and eats properly. As a result, Anthony recently lost 15 pounds, going from 140 to 125 pounds. He's a straight-A student, is taking part in his 7th grade decathlon, and has been selected to take special college preparatory classes. "We are very proud of him," says Modesta.

As for the study, Modesta says that she was very happy to be a part of it, was treated very well by the USC study team and learned a lot about her body. For example, she says that she now knows that losing five to seven percent of her normal body weight—even if it means being above ideal weight—is enough to reduce her chances of getting type 2 diabetes. She also learned that she needs to continue to be tested for type 2 diabetes every 1 to 2 years, to help prevent complications—such as heart disease later in life—that could result from progression to type 2 diabetes.

The NIDDK-sponsored GDM Cohort Study ultimately achieved its initial goal of identifying metabolic factors or problems present in Hispanic women during and after a GDM pregnancy that may predict future development of type 2 diabetes. The study team has found that a key predictor of later type 2 diabetes in these women is whether their pancreatic beta cells have difficulty secreting enough insulin to compensate for increased insulin resistance during pregnancy. Importantly, data from this study helped to form the basis for a separate set of studies that have tested interventions to prevent type 2 diabetes in Hispanic women with recent GDM, using medications that can increase sensitivity to insulin and thus reduce stress on the insulin-producing beta cells. Now in a long-term follow-up phase, the GDM Cohort Study is contributing to a better understanding of the chain of events leading to type 2 diabetes in these women who, as a group, are at very high disease risk. This information could also help in designing strategies to identify those individuals at highest risk and reduce their likelihood of developing type 2 diabetes.

"It would be better for members of the Hispanic community if they got more involved in these sorts of programs so that they could learn more about their health," Modesta says.

Modesta says she knows lots of Hispanic women with type 2 diabetes, and has talked about the study to many of her friends. "It would be better for members of the Hispanic community if they got more involved in these sorts of programs so that they could learn more about their health," Modesta says. She adds that studies such as the GDM Cohort Study would "help more Hispanic women take better care of themselves, especially during pregnancy."

Modesta plans to stay in the follow-up portion of the GDM Cohort Study for as long as possible. If there were another study, she'd like to be involved in it, as well. "It's been very helpful to me and my family," she says.

For health information on diabetes, please visit:
http://diabetes.niddk.nih.gov/

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Modesta Solórzano

Estudio de Diabetes Gestacional Centrado en las Mujeres Hispanas

Modesta Solórzano estaba casi en el octavo mes de su tercer embarazo cuando se incorporó al estudio de cohortes sobre la diabetes gestacional. Este estudio de observación está respaldado por el Instituto Nacional de la Diabetes y las Enfermedades Digestivas y del Riñón (NIDDK, por su sigla en inglés) y se centra en mujeres hispanas relativamente jóvenes que han tenido diabetes gestacional, que es la diabetes relacionada con el embarazo. El estudio está ayudando a identificar las posibles causas de diabetes de tipo 2 en estas mujeres, que corren un riesgo mucho mayor de sufrir la enfermedad debido a sus antecedentes de diabetes gestacional.

Modesta Solórzano

Al igual que todas las participantes originales del estudio de cohortes sobre la diabetes gestacional, a Modesta ya le habían diagnosticado diabetes gestacional cuando ingresó en el estudio en 1994. Esto significa que durante su embarazo tuvo concentraciones de glucosa (azúcar) en la sangre más altas que las normales. Esto se descubrió después de una prueba donde tomó una bebida especial con alto contenido de azúcar. Catorce años más tarde, a los 52 años de edad, Modesta sigue teniendo concentraciones de glucosa más altas que las normales cuando se le hacen esta prueba, por lo que se considera que tiene "prediabetes." Sin embargo, gracias al énfasis que hace el estudio en proporcionar a las participantes información sobre el ejercicio y la alimentación saludable, ella aún no ha desarrollado diabetes de tipo 2. Su hijo Anthony tampoco tiene diabetes y Modesta dice con orgullo que "es un chico muy sano" y muy buen estudiante.

Diabetes Gestacional

La diabetes gestacional es una forma de diabetes que se detecta por primera vez durante el embarazo.

En los Estados Unidos la diabetes gestacional afecta a cerca del siete por ciento de todos los embarazos y ocurre con más frecuencia entre las mujeres afroamericanas, hispanas, indígenas americanas y mujeres nativas de Alaska, así como en mujeres obesas y en mujeres con antecedentes familiares de diabetes. Estudios recientes también indican que muchas o la mayoría de las mujeres con diagnóstico de diabetes gestacional ya tienen concentraciones de glucosa en la sangre más altas que las normales antes del embarazo (aunque todavía no sean diabéticas), sino que simplemente no se habían hecho pruebas para este problema de salud hasta que quedaron embarazadas.

Al igual que otras formas de diabetes, se caracteriza por concentraciones altas de glucosa en la sangre y puede tener consecuencias graves. Si no se trata o no se controla, la mujer con diabetes gestacional puede tener un bebé muy grande y con exceso de grasa, lo cual puede dificultar el parto y hacer que

sea más peligroso tanto para la madre como para el hijo. Además, los bebés pueden tener problemas respiratorios y concentraciones bajas de glucosa en la sangre inmediatamente después de nacer. Por otra parte, algunos estudios demuestran que cuando estos bebés llegan a la adolescencia tienen concentraciones más altas de glucosa y tensión arterial más elevada, y son más propensos a la obesidad que los niños de las mujeres que nunca tuvieron diabetes gestacional.

Lo bueno es que sólo un 10 por ciento de las mujeres con diabetes gestacional seguirá teniendo diabetes poco después del parto. Lo malo es que entre un 20 y un 50 por ciento de ellas desarrollará diabetes en algún momento de la vida cuando no estén embarazadas, por lo general en los diez años siguientes. Además, es muy probable que también tengan diabetes gestacional en los embarazos siguientes.

En los Estados Unidos la diabetes gestacional afecta a cerca del siete por ciento de todos los embarazos y ocurre con más frecuencia entre las mujeres afroamericanas, hispanas, indígenas americanas y mujeres nativas de Alaska, así como en mujeres obesas y en mujeres con antecedentes familiares de diabetes. Estudios recientes también indican que muchas o la mayoría de las mujeres con diagnóstico de diabetes gestacional ya tienen concentraciones de glucosa en la sangre más altas que las normales antes del embarazo (aunque todavía no sean diabéticas), sino que simplemente no se habían hecho pruebas para este problema de salud hasta que quedaron embarazadas.

Modesta Solórzano llegó a los Estados Unidos proveniente de El Salvador en 1976 y tiene antecedentes familiares de diabetes de tipo 2. Su padre murió a los 84 años de edad por un derrame cerebral relacionado con la diabetes de tipo 2. Además, la madre de Modesta, que tiene 85 años de edad, es diabética. También son diabéticas cuatro de sus seis hermanas.

A menudo las mujeres con diabetes gestacional no tienen síntomas. Muchas de ellas no saben de la relación que existe entre la diabetes gestacional y la diabetes de tipo 2. Modesta, por ejemplo, dice que antes de ingresar al estudio de cohortes sobre la diabetes gestacional no sabía que corría un riesgo alto de sufrir diabetes de tipo 2.

Estudio de Cohortes sobre la Diabetes Gestacional
La Universidad de Sur de California (USC) estudio de cohortes sobre la diabetes gestacional, dirigido específicamente a mujeres hispanas, comenzó en 1993. Conducida por un equipo de investigadores liderado por el Dr. Tom Buchanan es un estudio de observación más que de intervención; es decir, no se da ningún tratamiento. Durante los primeros años, el estudio se centró en los posibles factores fisiológicos y hormonales o en los problemas presentes en mujeres con diabetes gestacional que pueden predecir la aparición de la diabetes de tipo 2 después del embarazo. Para identificar esos factores los investigadores reunieron muchos datos, tanto metabólicos como de otro tipo, a partir de las participantes. Al ingresar al estudio, se les hicieron tres pruebas metabólicas a las mujeres con diabetes gestacional. Estas pruebas proporcionaron información inicial sobre factores importantes en la aparición de la diabetes, tales como la resistencia a la insulina. Las participantes comenzaron una serie de consultas periódicas de seguimiento dentro de los seis meses siguientes al parto. Cada 15 meses se les determinó la concentración de glucosa en la sangre, se les hicieron pruebas metabólicas, se les hizo una exploración física completa y se les pidió que llenaran un cuestionario relacionado con la alimentación y el ejercicio. Además, periódicamente se les dio consejos sobre la alimentación y el ejercicio, de modo que pudieran tomar medidas para mejorar su salud y así retrasar o prevenir la diabetes. Estas consultas han continuado hasta la fase actual del estudio de seguimiento a largo plazo. Desde el comienzo, a las participantes se les ha hecho seguimiento por investigadores del estudio hasta que presentan

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concentraciones de azúcar en la sangre lo suficientemente altas como para requerir intervención médica. A algunas mujeres se les ha hecho seguimiento hasta 12 a 14 años después de la diabetes gestacional.

Afortunadamente para Modesta, su azúcar en la sangre se ha mantenido en concentraciones que para ella son relativamente fáciles de controlar con la alimentación y el ejercicio. "Camino mucho," dice Modesta, "y ya no como muchos alimentos grasosos." En vez de ello, ha comprado utensilios de cocina que le permiten cocinar al vapor las verduras y otros alimentos, y ha dejado de comer tantos caramelos y otros dulces. Dice que ha bajado 12 libras desde que entró al estudio.

Modesta tiene tres hijos. Tuvo el primero en El Salvador hace 32 años y no recuerda que durante el embarazo le hubieran hecho pruebas de sangre para saber si tenía la glucosa alta. Su segundo hijo nació en California hace 28 años y Modesta no tuvo diabetes gestacional como resultado de ese embarazo. Sin embargo, durante su tercer y último embarazo, Modesta tuvo concentraciones de glucosa en la sangre más altas que las normales durante una prueba y por eso la invitaron a participar en el estudio de cohortes sobre la diabetes gestacional. Dice que decidió participar en el estudio, porque "me dijeron que me ayudaría a controlar las concentraciones de glucosa y que tal vez me ayudaría a prevenir la diabetes de tipo 2 en el futuro."

Poco después de ingresar en el estudio tuvo a su tercer hijo, Anthony, por cesárea. Al igual que muchos bebés de madres con diabetes gestacional, Anthony pesó más de lo normal—un poco más de 9 libras—en el momento del parto, pero aparte de eso era muy sano. Actualmente Anthony tiene casi 14 años de edad y no tiene diabetes de tipo 2, aunque corre un riesgo mayor de sufrir esta enfermedad porque Modesta tuvo diabetes gestacional durante el embarazo. Modesta se asegura de que él haga ejercicio y coma bien. Como resultado, hace poco Anthony también bajó 15 libras: pesaba 140 libras y ahora pesa 125 libras. Es un estudiante sobresaliente de séptimo grado, está participando en el decatlón de su curso y ha sido seleccionado para tomar clases preparatorias especiales para entrar a la universidad. "Estamos muy orgullosos de él," dice Modesta.

En cuanto al estudio, Modesta dice que estaba muy contenta de participar, que el equipo de USC la trataron muy bien y que aprendió mucho sobre su cuerpo. Dice, por ejemplo, que ahora sabe que bajar entre un cinco y un siete por ciento de su peso normal—incluso si esto significa estar por arriba del peso ideal—es suficiente para reducir sus probabilidades de presentar diabetes de tipo 2. También aprendió que necesita seguir haciéndose pruebas para la diabetes de tipo 2 cada año o cada dos años con el fin de prevenir complicaciones en el futuro (por ejemplo, enfermedades del corazón) que podrían presentarse a causa de la progresión a diabetes de tipo 2.

Modesta dice que "sería mejor para los miembros de la comunidad hispana si participaran más en este tipo de programas para que pudieran aprender más sobre su salud."

El estudio de cohortes sobre la diabetes gestacional patrocinado por el NIDDK finalmente logró su objetivo inicial de identificar los factores o problemas metabólicos presentes en las mujeres hispanas durante y después de un embarazo con diabetes gestacional que pueden predecir la aparición de diabetes de tipo 2. El equipo del estudio descubrió en el estudio que un factor pronóstico de la aparición futura de diabetes de tipo 2 en estas mujeres es si las células beta del páncreas no pueden secretar suficiente insulina para compensar el aumento de resistencia a la insulina durante el embarazo. Es importante anotar que los datos de este estudio sirvieron de base para un conjunto distinto de estudios que han evaluado

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intervenciones para prevenir la diabetes de tipo 2 en mujeres hispanas con diabetes gestacional reciente, utilizando medicamentos que pueden aumentar la sensibilidad a la insulina y así reducir el estrés sobre las células beta productoras de insulina. El estudio de cohortes sobre la diabetes gestacional, que ahora se encuentra en una etapa de seguimiento a largo plazo, está contribuyendo a que se entienda mejor la cadena de acontecimientos que causan la diabetes de tipo 2 en estas mujeres que, como grupo, corren un riesgo muy alto de sufrir la enfermedad. Esta información también podría servir para diseñar estrategias con el fin de identificar a las personas que corren el mayor riesgo y reducir sus probabilidades de presentar diabetes de tipo 2.

Modesta dice que conoce a muchas mujeres hispanas con diabetes de tipo 2 y que ha hablado del estudio con muchos de sus amigos. También dice que "sería mejor para los miembros de la comunidad hispana si participaran más en este tipo de programas para que pudieran aprender más sobre su salud." Agrega que estudios tales como el estudio de cohortes sobre la diabetes gestacional "ayudarían a más mujeres hispanas a cuidarse mejor, especialmente durante el embarazo."

Modesta piensa permanecer el mayor tiempo posible en la parte de seguimiento del estudio de cohortes. Si hubiera otro estudio, también le gustaría participar. Dice que "ha sido muy útil para mí y para mi familia."

Para más información acerca de diabetes, vea: *www.diabetes-espanol.niddk.nih.gov*

The National Diabetes Education Program: It's Never Too Early To Prevent Diabetes

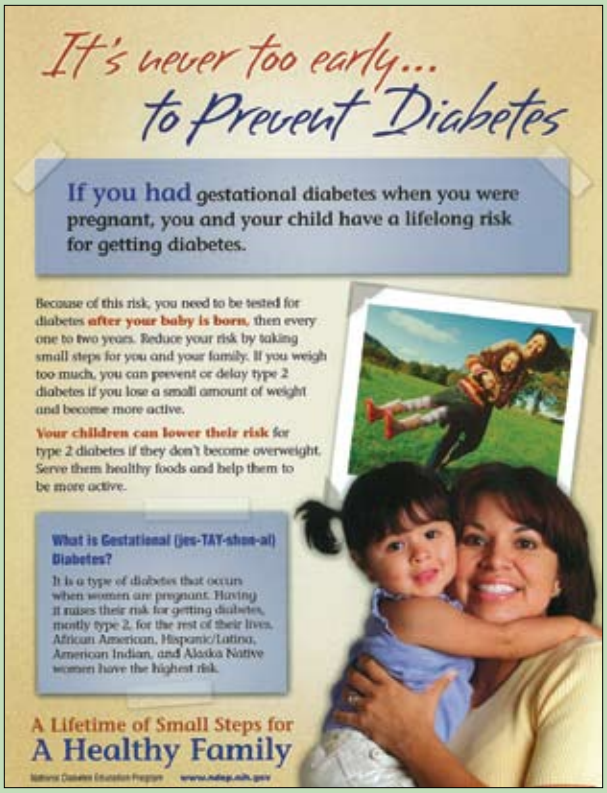
Gestational diabetes mellitus (GDM) is a form of glucose intolerance that is diagnosed during pregnancy. GDM affects about 7 percent of all U.S. pregnancies annually, resulting in approximately 200,000 cases a year.[1] Women diagnosed with GDM not only face an increased risk of complications during pregnancy and delivery, but they and their children bear an elevated risk of developing type 2 diabetes in the future. An information campaign developed by the National Diabetes Education Program is raising awareness of this risk and of ways to reduce its impact.

Who is at risk? Gestational diabetes occurs more frequently among obese women and women with a family history of diabetes, and among African American, Hispanic/Latina, and American Indian and Alaska Native women. Women who have had GDM have an increased risk of GDM in a subsequent pregnancy.

After pregnancy, 5 to 10 percent of women who had GDM are found to have type 2 diabetes. Women who have had GDM have a 20 to 50 percent chance of developing diabetes in the next 5 to 10 years following pregnancy. The children of women with a history of GDM are at an increased risk for obesity and diabetes compared to other children.

Recent reports have shown high or increasing rates for GDM in various parts of the country, including:[1]

- Washington, D.C, where, in 2003, the GDM prevalence rate in Hispanic women was 12 percent —close to the highest rate of 14 percent seen in some American Indian women.
- New York City, where the GDM prevalence rate increased 46 percent from 1990 to 2002—with the highest increase found among Asian women.
- Colorado, where the GDM prevalence rate increased 95 percent from 1994 to 2002— with the highest increase among Hispanic women.
- Northern California, where the number of new cases each year increased 35 percent from 1991 to 2000.



The educational campaign, "It's Never too Early To Prevent Diabetes," is spreading the word about the risk for type 2 diabetes faced by women with a history of gestational diabetes mellitus and their children.

These regional GDM prevalence rates raise concern that the increase may reflect the ongoing pattern of increasing obesity and contribute to the upsurge in cases of diabetes in the U.S.

The latest diabetes prevention campaign message by the National Diabetes Education Program (NDEP) is: *It's Never Too Early To Prevent Diabetes: A Lifetime of Small Steps for a Healthy Family.* This campaign, which was launched by Dr. Griffin Rodgers, Director, NIDDK, together with then-Deputy Surgeon General Kenneth Moritsugu, is spreading the word about the risk for type 2 diabetes faced by women with a history of gestational diabetes mellitus and their offspring. The message, *It's Never Too*

Early To Prevent Diabetes, is the latest addition to NDEP's campaign, *Small Steps. Big Rewards*. *Prevent Type 2 Diabetes*, the nation's first comprehensive multicultural type 2 diabetes prevention campaign. The campaign offers materials that can help women with a history of gestational diabetes take steps to prevent or delay type 2 diabetes and help their children lower their risk for the disease.

To ensure that the campaign effectively reaches the broad audience of women and children at risk, materials include a tip sheet in both English and Spanish for women who have had GDM, a tip sheet in English and Spanish for children at risk for type 2 diabetes, and a booklet for adults to help women and their families make healthy food choices and be more physically active to prevent or delay type 2 diabetes.

The campaign is based in large part on results from the Diabetes Prevention Program (DPP) clinical trial. This NIDDK-funded study found that people at increased risk for type 2 diabetes can prevent or delay the onset of the disease by losing 5 to 7 percent of their body weight through increased physical activity and a low-fat, low-calorie eating plan. The DPP included several hundred women with a history of gestational diabetes, and the powerful reduction in risk of diabetes demonstrated in the study—up to 58 percent—was found in all subgroups, including this group of women.

The U.S. Department of Health and Human Services' National Diabetes Education Program is jointly sponsored by the National Institutes of Health and the Centers for Disease Control and Prevention with the support of more than 200 partner organizations. The NDEP has materials for health care professionals and people at risk for diabetes—including older adults, American Indians and Alaska Natives, Hispanics/Latinos, African Americans, and Asian Americans and Pacific Islanders. For more information about the NDEP or to obtain a copy of the new It's Never Too Early To Prevent Diabetes *and* Nunca es muy temprano para prevenir la diabetes *tip sheets and other* Small Steps. Big Rewards. *diabetes prevention materials, visit www.ndep.nih.gov*

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[1] *www.nih.gov/news/pr/apr2006/niddk-25.htm*