Diabetes Research: A Perspective From the National Institute of Diabetes and Digestive and Kidney Diseases

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This is the third in a series of articles, invited by the editors of *Diabetes*, that describes the research programs and aims of organizations committed to funding and fostering diabetes-related research. The first piece, contributed by the Juvenile Diabetes Research Foundation, appeared in the January 2012 issue of *Diabetes*. The second piece that describes the American Diabetes Association's research program appeared in the June 2012 issues of *Diabetes* and *Diabetes Care*.

The growing human and economic toll of diabetes has caused consternation worldwide. Not only is the number of people affected increasing at an alarming rate, but onset of the major forms of the disease occurs at ever younger ages. We now know that the reach of diabetes extends far beyond the classic acute metabolic and chronic vascular complications to increased risk of an ever-increasing array of conditions including Alzheimer disease, cancer, liver failure, bone fractures, depression, and hearing loss. In the U.S. one in three Medicare dollars is spent on care of people with diabetes, and the proportion of cardiovascular disease (CVD) risk attributable to diabetes is rising. While complications of diabetes may develop slowly over decades, antecedents of diabetes may lay in utero or early life. Thus the breadth of meaningful research extends across the life span, ranging from studies of how the in utero environment alters diabetes risk to improved understanding of the special needs of older patients with diabetes.

Since the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) was established in 1950, we have seen huge progress in our ability to predict, classify, and treat diabetes and its complications as well as to prevent or delay type 2 diabetes. Landmark NIDDK-led clinical trials have demonstrated that glucose control can dramatically reduce diabetes complications, and lifestyle change producing modest weight loss, or the drug metformin, can substantially reduce development of type 2 diabetes. Were it not for this progress, the toll from rising rates of the major forms of diabetes would be much higher.

Despite a challenging fiscal climate, the National Institutes of Health (NIH) expends over $1 billion on diabetes research annually. NIDDK accounts for about two-thirds of this total, and we are determined that these resources will be invested wisely and balanced among competing priorities. We must address the most compelling practical questions about clinical management and prevention of diabetes and its complications while also uncovering and exploiting novel pathways that will provide new targets and approaches to combat the disorder. Last year, a new strategic plan for diabetes research (1) was issued under NIDDK's leadership with input from over 100 scientists and multiple federal agencies and components of NIH. The plan highlights progress and opportunities in 10 key areas as well as resource and infrastructure needs. Conquering diabetes will require a wide range of expertise and talent from molecular and cell biology to behavioral and social sciences. Development and empowerment of this human capital is critical to this endeavor, including facilitating multidisciplinary collaborations and the application of new technologies to diabetes research. Here we will touch on highlights of our diabetes research priorities and initiatives, referring readers to the Diabetes Research Strategic Plan (1) for a more comprehensive analysis of advances and opportunities.

ENHANCING THE DIABETES RESEARCH WORKFORCE

A well-trained and diverse scientific workforce is essential to our efforts to improve outcomes for people with or at risk for diabetes. To ensure a pipeline of new well-trained investigators in basic and clinical disciplines, NIDDK supports training grant, fellowship, and career award mechanisms to provide opportunities for investigators at all stages of the career trajectory. These are supplemented by programs targeted to specific needs, such as our medical student research program in diabetes, which allows medical students to conduct research under the direction of an established scientist at one of our seventeen NIDDK-funded Diabetes Research Centers; supplements to research and training grants to foster recruitment of underrepresented minority scientists to diabetes research; and institutional career development programs to attract pediatric endocrinologists to careers in childhood diabetes research. It is increasingly important to build multidisciplinary research teams and train multidisciplinary researchers. We are establishing interdisciplinary training grants to promote diabetes research training for bioengineers as well as career development programs in diabetes research for behavioral scientists. We will continue to foster the application of new expertise, for example in computational science and bioinformatics, to diabetes research problems. To help new investigators transition to independence, we also provide a less stringent pay line for early career investigators. We also invite new investigators with NIDDK research or career development grants to participate in NIDDK workshops designed to help them succeed as independent investigators.

FUNDAMENTAL RESEARCH

To uncover new approaches to prevention and therapy of diabetes and its devastating complications, NIDDK will

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Received 1 March 2012 and accepted 4 October 2012.
DOI: 10.2337/db12-0269

continue to support a robust portfolio of investigator-initiated basic research. NIDDK has recently developed data on application and funding trends to help our research community understand the application and funding dynamics over recent years. This information is available at http://www2.niddk.nih.gov/Funding/Grants/FundingTrendsandValues.htm. It shows that relative funding levels of most research categories have remained fairly stable since 2003, and demonstrates our continuing strong support of investigator-initiated research project grants or R01s and training and career development programs. Information on resources to empower researchers, such diabetes centers, human islets, mouse models, reagents, and databases, and on funding opportunities and staff to contact in specific program areas is available at http://www2.niddk.nih.gov/Research/ScientificAreas/Diabetes/.

DIABETES PREVENTION

Diabetes prevention is a major public health challenge. For type 2 diabetes, the NIDDK-led Diabetes Prevention Program (DPP) demonstrated a dramatic effect of modest weight loss or the generic drug metformin in delaying or preventing type 2 diabetes (2). Ongoing studies are examining the durability of this risk reduction, the cost effectiveness of the interventions, and their impact in reducing diabetes complications. To facilitate translation of landmark clinical research into clinical practice and public health activities, NIDDK established a program to test practical, cost-effective approaches to deliver interventions proven efficacious in clinical trials for effectiveness in community and practice settings. One such NIDDK-supported study of a lifestyle change intervention delivered by YMCA fitness trainers (3) already is being rolled out nationwide by the YMCA with coverage from insurers such as United Health Group. In another promising approach, diabetes educators trained selected patients with well-controlled diabetes to serve as community health workers delivering a lifestyle intervention based on the DPP to community members with prediabetes (4). This NIDDK-funded research provides a basis for a new congressionally established National Diabetes Prevention Program at the Centers for Disease Control and Prevention (CDC) to foster delivery of evidence-based lifestyle change programs for people at high risk for type 2 diabetes. Given the sustained effort required to achieve and maintain lifestyle change, much additional research is needed to improve, disseminate, and evaluate type 2 diabetes prevention programs in the U.S. Approaches are also needed to reduce the development of risk factors for diabetes. Of particular importance are studies to reduce environmental exposures during pregnancy or childhood that may increase diabetes and obesity risk.

The incidence of type 1 diabetes is rising worldwide and the disease is occurring at younger ages suggesting an environmental trigger is responsible. Bold new programs aimed at preventing type 1 diabetes have been undertaken with support from the Special Statutory Funding Program for Type 1 Diabetes Research, which provides $150 million per year through 2013 for type 1 diabetes research. These special funds are in addition to the regular NIH appropriation. One program established under the program, The Environmental Determinants of Diabetes in the Young (TEDDY), has screened nearly half a million neonates to establish a cohort of over 8,000 at high genetic risk for type 1 diabetes. Participants will be followed from birth through 15 years of age to identify dietary, infectious, microbiome, or other environmental triggers of autoimmunity and type 1 diabetes and to study the interaction between environmental factors and specific genetic variations associated with disease risk. Identification of an infectious agent or dietary factor that triggers or protects against the disease would have immense implications for prevention through the development of a vaccine or dietary change. Also with special program support, the Type 1 Diabetes TrialNet is identifying individuals recently diagnosed with type 1 diabetes or at high risk of developing the disease and testing interventions to prevent diabetes or to slow its progression. Selective immune modulation has been shown to preserve insulin secretion in newly diagnosed patients, and TrialNet is exploring the use of one such agent, teplizumab, to prevent type 1 diabetes in individuals at very high short-term risk of type 1 diabetes. In the future, combination therapies aimed at modulating multiple steps of the toxic immune response and restoring immunoregulation may produce a clinically significant delay in onset and ultimately the prevention of type 1 diabetes.

CLINICAL TRIALS TO INFORM DIABETES MANAGEMENT

While information on how to prevent and treat type 2 diabetes has grown rapidly, adequate data from rigorous clinical trials are not available to inform many routine decisions on care for patients with diabetes. Current guidelines are moving away from a "one size fits all" approach to incorporate factors such as diabetes duration and the presence of complications or other comorbidities. However, we lack information to individualize therapy based on demographic, physiologic, or genetic variation. Improved understanding of the genetic, physiologic, and environmental factors that underlie diabetes mellitus are necessary for more individualized diabetes treatment.

Numerous drugs are approved for the treatment of type 2 diabetes, based largely on relatively short-term efficacy in glycemic reduction. However, it is not known whether particular drugs or drug combinations will have more durable effects in the maintenance of glucose control. NIDDK is supporting a large comparative effectiveness trial to inform the choice of second agent when metformin alone is inadequate for glycemic control. This multicenter randomized trial will provide information on health benefits as well as cost effectiveness of widely used treatments.

Small studies suggest it may be possible to preserve β-cell function during prediabetes and early in the course of type 2 diabetes. Major questions include the optimal timing of interventions, whether specific treatments have maximum benefit at different stages of the disease, and what patient characteristics influence the choice of initial therapy for individuals. A newly formed consortium will examine the approaches to the initial treatment of type 2 diabetes that may reverse or slow the decline in β-cell function over time.

While major trials have established the importance of blood pressure and lipid control in reducing CVD in type 2 diabetes, much less is known about how cardiovascular risk factors should be managed in type 1 diabetes. When blood pressure and lipid lowering should begin and optimal therapeutic targets remain to be established. Although type 1 diabetes increases the risk of CVD as much as 10-fold compared to an age-matched population, testing practical approaches to mitigate this risk is challenging

due to the low incidence of CVD in the younger type 1 diabetes population. Such trials may require the development of the validated biomarkers discussed below.

Diabetes self-management training and promotion of effective self-care behaviors are vital to improving outcomes. The choices patients make daily about diet, physical activity, adherence to medications, self-monitoring, foot and dental care, and medical follow-up for early detection of complications are critical for improving diabetes outcomes. Research has established effective counseling and education strategies, including motivational interviewing, patient empowerment, and social and peer support. However, research is needed to expand the reach of such approaches to more patients and providers. NIDDK encourages research studying approaches such as group visits, telemedicine, and social media that may extend the impact of the limited workforce skilled in the provision of this care.

DIABETES IN SPECIAL POPULATIONS

Diabetes spares no age, sex, racial or ethnic group, yet each such group faces special challenges. Intensive glycemic control in youth may afford lifelong protection from complications yet infancy and adolescence pose unique challenges in attaining such control. Treatment priorities and optimal glycemic, blood pressure, and cholesterol targets to prevent complications and maintain quality of life may differ for older adults or those with limited life expectancy. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)-led Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (5) showed that perinatal harm to mother and offspring occurs in pregnancy at lower levels of glycemia than previously appreciated. To identify gestational glycemic thresholds for longer-term effects on offspring and the risk of type 2 diabetes in mothers, NIDDK will support a follow-up study of this important cohort. NIDDK has also recently launched a study to explore approaches for the prevention of gestational diabetes mellitus. It also remains to be established what treatments during pregnancy mitigate perinatal and/or long-term complications of gestational diabetes mellitus.

The biologic and environmental risk factors that contribute to underlying racial and ethnic disparities are poorly understood. The alarming emergence of type 2 diabetes in youth overwhelmingly occurs in minority populations. Ominous data on poor risk factor control portends very poor outcomes for this vulnerable population. To address this threat, NIDDK recently completed a major multicenter trial comparing three approaches to the treatment of type 2 diabetes in youth and a trial conducted in schools serving poor and minority children to prevent the development of risk factors for type 2 diabetes.

As better therapy for HIV infection, organ transplantation, cystic fibrosis, and other conditions improve survival, diabetes has emerged as an increasingly important complication. Critical questions must be addressed about optimal strategies to prevent and treat diabetes. For example, early diabetes diagnosis and treatment helped improve survival in people with cystic fibrosis–related diabetes (CFRD). An NIDDK-funded trial showed that chronic weight loss can be reversed with the institution of insulin therapy but not with repaglinide early in the course of CFRD before fasting hyperglycemia develops (6). A current initiative will support research to understand the pathogenesis of CFRD, which affects half of adults with cystic fibrosis. NIDDK will also encourage research on treatment and prevention of diabetes in HIV patients.

Exceptional contributions to understanding diabetes in special populations have emerged from NIDDK's intramural research program. Spanning decades and generations, longitudinal studies of Pima Indians have uncovered physiologic, environmental, and genetic determinants of diabetes in the U.S. population with highest rates of type 2 diabetes. These studies have foreshadowed findings in the broader population, such as the contribution of intrauterine factors to childhood obesity and type 2 diabetes and the prognosis for these youth. Collaborations between intramural and extramural researchers studying individuals with severe insulin resistance and lipodystrophy have yielded important physiologic information and the emergence of leptin replacement therapy for lipodystrophy.

EPIDEMIOLOGY AND SURVEILLANCE IN DIABETES

Population health data are essential to inform prevention strategies for diabetes and its complications, to identify trends in the development of diabetes and diabetes complications in the general population and in subpopulations, and to measure gaps in the translation of proven therapies into practice. NIDDK has partnered with CDC to support the SEARCH for Diabetes in Youth study. This multicenter study identifies cases of diabetes in people below 20 years of age in five geographically dispersed populations that encompass the ethnic diversity of the U.S.

SEARCH has found that 1 out of every 523 persons under 20 years of age has diabetes, and 15,000 children are diagnosed with type 1 diabetes and 3,700 diagnosed with type 2 diabetes annually (7). SEARCH also provides data on trends in incidence and risk factor control in the pediatric diabetes population.

So that information on diabetes can be obtained at lower cost than if an independent study were initiated, NIDDK provides substantial support for the diabetes components of major CDC-led efforts including the National Health and Nutrition Evaluation Survey and the National Health Information Survey; partners with other components of NIH to enhance diabetes measures in ongoing studies; and offers support for investigator-initiated ancillary studies focused on diabetes. Of particular importance are collaborations with the National Heart, Lung, and Blood Institute (NHLBI) to address the increasing proportion of CVD attributable to diabetes and issues such as balancing the cardiometabolic risks and benefits associated with statin use.

A third edition of the NIDDK publication *Diabetes in America* is currently in preparation. *Diabetes in America* provides a compilation and assessment of epidemiologic, public health, and clinical data on diabetes and its complications in the U.S.

RESEARCH TO PRACTICE TRANSLATION

There is a substantial gap between the results achieved in clinical trials and the outcomes in real-world settings. This is particularly true for the minority racial and ethnic groups and low socioeconomic status populations that suffer a disproportionate diabetes burden. Addressing this disparity is a major focus of our multipronged translation research program. Newly established Centers for Diabetes Translation Research will serve as a key component of our program to translate efficacious research findings into practice and the community to improve the health

of Americans with—or at risk for—diabetes. In addition, R34 planning grants and R18 translational clinical trial grants offer a targeted mechanism to test strategies to improve the delivery of evidence-based therapies to improve diabetes management or prevention. These programs test innovative methods to improve clinical care and translate research findings into cost-effective and sustainable clinical treatment strategies, including community-based approaches to make preventive measures as widely accessible and practical as possible. NIDDK has also partnered with CDC to support the Natural Experiments for Translation in Diabetes (NEXT-D) Study, a research network designed to test the effectiveness and sustainability of population-targeted diabetes prevention and control policies emerging from health care systems, business and community organizations, and health care legislation. It includes large-scale natural experiments or effectiveness studies and rigorously designed prospective studies of diabetes prevention and control interventions. The National Diabetes Education Program, jointly sponsored by NIH and CDC, plays an important role in dissemination and translation of NIDDK-supported clinical research.

GENETICS OF TYPE 1 AND TYPE 2 DIABETES

Because knowledge of genetic risk factors has the potential for disease prediction, patient stratification, and insights into pathogenesis that can generate new approaches to prevention and treatment, NIDDK has expended considerable resources to apply state-of-the-art molecular and computational science to identify diabetes risk genes. Perhaps the most profound impact of these genetic discoveries has been in children with neonatal diabetes, who were often wrongly diagnosed with type 1 diabetes and treated with insulin. Now children with mutations in the genes encoding the SUR1 and Kir6.2 subunits of the potassium ion channel that regulates insulin secretion are treated more safely and effectively with sulfonylurea drugs rather than insulin (8). Genetic testing for type 1 diabetes risk has made possible the TEDDY study and TrialNet prevention studies described above. The NIDDK-led international Type 1 Diabetes Genetics Consortium helped increase the number of identified risk genes and gene regions from 3 only a decade ago to over 50 today. The challenge now is to understand how this variation contributes to disease pathogenesis opening up new therapeutic targets.

For type 2 diabetes, we are encouraged by the DPP finding that relative risk reduction with lifestyle change was as great in those carrying the high-risk TCF7L2 mutation as in other participants, despite higher rates of progression to diabetes. DPP also provided important pharmacogenetic data showing participants with a specific *KCNJ11* variant or alterations in metformin transport genes were less protected by metformin. These observations offer the possibility of individualizing therapy based on genotype (9). However, despite substantial progress in identifying genetic variation contributing to type 2 diabetes risk in populations of European origin, there is a critical lack of information about genetic variation contributing to type 2 diabetes in disproportionately affected minority populations. NIDDK has established a consortium of investigators to identify genetic variation contributing to type 2 diabetes in minorities. With known risk genes explaining only a small fraction of the genetic risk for type 2 diabetes, the identification of epigenetic changes that may play a role in the transmission of diabetes risk across generations is assuming increasing importance.

DIABETES COMPLICATIONS

Research has identified many pathways contributing to glucose-induced damage to endothelial cells including elevated flux through polyol and hexosamine pathways, accumulation of advanced glycation end products, activation of proinflammatory pathways, and inactivation of protein kinase C. Yet many questions remain about how these pathways may interact and converge to increase production of reactive oxygen species (ROS) in the mitochondria and how we can build on this new knowledge to develop therapies that can reduce ROS, reverse glycation, and lessen inflammation. Pathogenetic mechanisms, therapeutic targets, and biomarkers must be identified in specific tissues, including mechanisms of injury to specialized cells such as podocytes and pericytes. The relative importance of hyperglycemia and insulin resistance is of particular interest in understanding the link between diabetes and Alzheimer disease.

A finite period of glycemic control has profound and long-lasting effects on the development of complications, a phenomenon termed metabolic memory (10). It has been proposed that the interaction of epigenetic changes with other persistent effects of hyperglycemia, such as glycation and oxidation of long-lived macromolecules, may explain this finding. Understanding pathways that contribute to metabolic memory may yield therapies targeted at the underlying molecular mechanisms. It may also help us learn about whether treatments that prevent the development of complications also prevent progression.

The course and development of long-term complications cannot be solely explained by the extent and duration of exposure to hyperglycemia. Genetic variation may explain why some people develop complications despite good control and others with poor control are protected. This information could yield undiscovered disease pathways and therapeutic targets, improve disease prediction over currently available clinical markers, and identify individuals for whom intensive therapy would be more or less beneficial. However, we know relatively little about genetic variation that may contribute to or protect from complications, and this is an important area for investigation.

We are also elucidating mechanisms that impair tissue repair and regeneration in diabetes, including dysfunction of endothelial and other stem cell populations. Identification of specific populations of stem or progenitor cells affected by diabetes and the extent to which damage is reversible is vital for understanding how complications of diabetes might be reversed by stimulating formation of normal new vessels and regrowth of nerves. Differentiation of induced pluripotent stem cells also holds promise for the repair of damaged tissues.

While rates of blindness, kidney failure, amputation, and CVD have fallen substantially in those with diabetes, population-wide lowering of CVD has outpaced that in people with diabetes and the share of CVD in the U.S. attributable to diabetes is rising. To address this challenge, NIDDK and NHLBI have collaborated in a number of major multicenter trials to establish effective approaches to reducing CVD in those with type 2 diabetes, including Action for Health in Diabetes (Look AHEAD), Action to Control Cardiovascular Risk in Diabetes (ACCORD), and Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D). Results from ACCORD and other recent large clinical trials attempting to prevent CVD did not demonstrate a benefit of intensified near-normal glucose

control on clinical CVD events in people with moderate to long-term diabetes duration and moderate to high CVD risk. More information is needed on the impact of diabetes duration and preexisting tissue damage on the ability to respond to therapies. Beyond the practical management questions addressed in clinical trials, new approaches to uncouple diabetes and CVD must be based on a mechanistic understanding of factors linking these conditions, including obesity, inflammation, insulin resistance, metabolic perturbations, altered coagulation, neuropathy, and nephropathy, and how the pathophysiology of atherosclerosis differs between people with type 1 and type 2 diabetes.

THE β-CELL

Impaired insulin production is key to all forms of diabetes. The extent to which it is possible to preserve and/or restore β-cell function early in the course of diabetes and whether β-cell recovery is possible later in the disease remains to be established. Both the nature and optimal timing of interventions to preserve β-cell function and the impact on clinical care and outcomes must be addressed. NIDDK has recently established the Restore Insulin SEcretion (RISE) consortium to explore approaches to remission of insulin secretory function early in type 2 diabetes. Investigators will study both pharmacologic interventions and bariatric surgery. The Type 1 Diabetes TrialNet studies approaches to slow β-cell loss early in the course of type 1 diabetes. Specific immunomodulatory therapies have been shown to preserve C-peptide, and additional strategies including intense metabolic control with continuous glucose monitoring and pump therapy at onset of disease are being investigated.

Mechanistic studies are necessary to understand why β-cells lose their ability to secrete insulin as well as the physiology underlying recovery and preservation of endogenous insulin secretion. Particularly encouraging is the finding of some residual C-peptide production in a substantial proportion of patients with long-established type 1 diabetes. Such individuals might be amenable to novel strategies under development to stimulate islet neogenesis with the potential to improve β-cell mass and function. The intriguing observation of diabetes remission after some forms of bariatric surgery must be investigated to establish durability of the effect and the characteristics of patients and procedures associated with remission. Elucidation of mechanisms underlying improved β-cell function after bariatric surgery is being pursued in both human studies and animal models potentially generating new approaches to restore β-cell function. Moreover, the recent identification of platelet-derived growth factor as a factor involved in the replication of β-cells in early life that are lost over time offers a potential pathway to β-cell regeneration (11).

Clinical studies of approaches to mitigate β-cell loss and/or restore function could be accomplished much more efficiently if more reliable biomarkers or methods to image β-cell mass or function were available. The development of such tools has been and continues to be a high priority of NIDDK. It may be facilitated by the identification of proteins expressed in β-cells and β-cell surface markers and antibodies through the Beta Cell Biology Consortium (http://www.betacell.org). This consortium is pursuing a multifaceted approach to correct the loss of β-cell mass in diabetes, including cell reprogramming, regeneration, and replacement. It is also supporting research to develop mouse models in which development and function of human islets can be studied. Also, because of differences between murine and human islets, NIDDK has established a resource, the Integrated Islet Distribution Program (http://iidp.coh.org), to make human cadaveric islets available to the research community.

The Clinical Islet Transplantation Consortium, a joint effort of NIDDK and the National Institute of Allergy and Infectious Diseases (NIAID), is fostering development of islet transplantation as a cure for type 1 diabetic patients whose disease cannot be effectively managed with current methods of insulin administration or who have received a successful kidney transplant. Its ongoing trials aim to improve the methods of isolating and administering islets and minimizing the toxic effects of immunosuppressive drugs required for transplantation. NIDDK also supports collection, analysis, and communication of comprehensive and current data on all islet/β-cell transplants performed in North America, as well as some European and Australian centers through the Collaborative Islet Transplant Registry. This clinical islet transplantation research is entirely supported through the special appropriation for type 1 diabetes research.

OBESITY

A trans-NIH Task Force cochaired by NIDDK, NHLBI, and NICHD coordinates NIH efforts to identify genetic, behavioral, and environmental causes of obesity to understand how obesity leads to type 2 diabetes, CVD, and other serious health problems and to build on basic and clinical research findings to develop and study innovative prevention and treatment strategies. One key goal is to understand how biologic, cognitive, behavioral, social, and physical environmental factors interact to influence the development of obesity. For example, how do diet, exercise, and other factors influence reprogramming of neural circuits involved in regulating food intake and thermogenesis. Another goal is to identify distinct strategies that may be needed for achieving weight loss, maintaining weight loss, and preventing weight gain. Understanding responses to weight change that contribute to the very high recidivism to obesity may lead to effective strategies for maintenance of reduced body weight. These therapies might be quite different from those used to induce weight loss per se.

Childhood obesity has fueled the rise of type 2 diabetes in teens and young adults. An NIDDK-led randomized trial testing an intervention to improve nutrition and physical activity in middle schools serving high-risk children demonstrated efficacy in secondary outcomes, reducing BMI *z*-score and other indices of adiposity. However, the primary outcome of the combined prevalence of overweight and obesity decreased in both the intervention and control schools perhaps due to information about the participating children's health, which was sent to all families (12). Family-based interventions have been successful for childhood weight control, but strategies for translation and widespread implementation of such interventions in high-risk populations remain to be developed. The roles of technologies such as smartphones and social networking and of community organizations must be evaluated for their potential to support individualized and tailored delivery of interventions outside of the clinical setting.

At the molecular level, there has been an explosion of knowledge about the mechanisms linking obesity to insulin resistance and excitement about potential therapeutic manipulation of adipose tissues based on the understanding of

white adipose tissue heterogeneity, persistence of brown adipose tissue into adulthood, and metabolic flexibility of adipocytes. Tools and techniques have enabled researchers not only to define adipose anatomy and morphology but also to examine its dynamic function. Yet key questions remain about the mechanisms that determine adipocyte number and size, govern development and distribution, and link variation in body fat deposition to metabolic sequelae and macrophage recruitment and activation.

Particularly challenging but of utmost importance are studies to understand mechanisms by which obesity, hyperglycemia, or other metabolic factors in pregnant women may predispose their offspring to obesity or diabetes. Research is needed on how placental biology and the intrauterine environment shape neural circuits, adipose tissue, and islet development in the fetus. Studies relating differences in energy homeostasis and body composition to genetic variation and defining the critical developmental periods for imprinting maladaptive metabolic changes will contribute to understanding how metabolic fate may be programmed early in development.

The finding that Roux-en-Y gastric bypass not only causes profound weight loss but can also restore euglycemia through mechanisms that appear independent of weight loss makes identification of these mechanisms a very high priority with the potential to uncover new therapeutic pathways to treat and possibly reverse type 2 diabetes. NIDDK is pursuing this through clinical research on the response to various bariatric surgical procedures and through murine studies in which examination of defined procedures in genetically altered mice enables examination of the roles of specific pathways in the metabolic outcomes of these surgeries. Understanding the hormonal and neural controllers of energy balance will be key to designing potential drug combinations targeting multiple components of the regulatory system with additive or synergistic effects.

DIABETES RESOURCES

NIDDK supports numerous resources to improve the quality and multidisciplinary nature of research on diabetes by providing shared access to specialized resources. The NIDDK-supported Diabetes Research Centers, formerly known as Diabetes Endocrinology Research Centers and Diabetes Research and Training Centers, provide increased and cost-effective collaboration among multidisciplinary groups of investigators at institutions with an established, comprehensive research base in diabetes and related areas of endocrinology and metabolism. The National Mouse Metabolic Phenotyping Centers (http://www.mmpc.org) provide a range of complex exams used to characterize mouse metabolism, hormones, energy balance, eating and exercise, organ function and morphology, physiology, and histology. NIDDK supported research consortia, such as the Beta Cell Biology Consortium (http://www.betacell.org/) and the Nuclear Receptor Signaling Atlas (http://www.nursa.org/), provide data and reagents to the broader scientific community. Other important diabetes resources supported by NIDDK include a type 1 diabetes mouse repository at The Jackson Laboratory (http://www.jax.org/t1dr/) and Islet Cell Resource Centers (http://icr.coh.org/) that provide human islets for research.

Samples and data from the limited number of cohorts from large diabetes studies with well-characterized phenotypes at baseline and with longitudinal measurement of characteristics of interest are highly prized. To expand the usefulness of these major clinical studies by allowing the wider research community to access study materials beyond the end of the study or after a limited proprietary interval for ongoing studies, NIDDK has established biosample, genetics, and data repositories. Recently NIDDK has gone beyond the repository concept to create a living biobank, which provides investigators with the opportunity to obtain "on-demand" biological samples from selected individuals. This effort builds on the unique population of individuals at risk for the development of type 1 diabetes ascertained and monitored through TrialNet. The unprecedented availability of such samples and data may allow immunologists to understand early inciting events in type 1 pathogenesis.

APPLYING NEW TOOLS AND TECHNOLOGIES TO DIABETES RESEARCH AND PATIENT CARE

Large clinical trials have established the long-term benefits of intensive blood glucose control in lowing the risk of diabetes complications. However, insulin therapy is burdensome and limited by hypoglycemia. NIDDK has devoted considerable resources to develop technologies for accurate and rapid detection of glucose levels and appropriate adjustment of insulin delivery to create an artificial pancreas that simulates the functions of β-cells. Achieving this goal will require more accurate and robust glucose-sensing devices; more effective and rapidly acting insulin preparations; algorithms that align real-time glucose measurements with adjustment in insulin delivery; infusion devices that deliver insulin more effectively, conveniently, and physiologically; and fail-safe mechanisms to avoid hyper- or hypoglycemia. It will also be important to determine the benefit of combining insulin delivery with the delivery of the counterbalancing hormone glucagon to reduce hyperglycemia, and how timely transmission and remote interpretation of patient data may contribute to safety and efficacy. Research is ongoing to assess the capacity of current artificial pancreas technology to improve overall metabolism, increase patient well-being, restore hypoglycemia awareness, and preserve existing pancreatic β-cell function, as well as to understand the factors affecting its use and acceptance in different age-groups.

Advances in sensors, processors, memory storage, wireless communication, and Web-based data transport, processing, and sharing have applications not only to new therapies but also to many facets of diabetes research in free-living populations. These range from instruments that measure energy intake and physical activity to the application of continuous monitoring of blood glucose to enable exploration of questions about the impact on human health of glycemic excursions, which may not be captured by HbA_{1c} measurement. Such studies could address the question of whether and how hypoglycemia may contribute to CVD events. Studies of energy balance would benefit from tools to define the neural circuits and molecular mediators that regulate energy balance by sensing and responding to signals of energy status and tools to quantitate mitochondrial biogenesis and turnover and assess mitochondrial function. To assess the progression of diabetes, measures that directly measure β-cell mass are particularly important because current methods are all linked to β-cell function, which may have both reversible and irreversible components. Complications research could benefit from tools for the study of extracellular matrix proteins and their interactions with growth factors and circulating stem cells or for

the study of epigenetic change or glycation and lipoxidation of proteins. Appropriate systems biology and computational tools are needed to facilitate the integration of sequencing, expression, proteome, and metabolome profiles to identify key biologic processes and their interactions. NIDDK seeks to foster development of paradigm-shifting technology and truly transformative tools through workshops, targeted funding opportunity announcements, and interdisciplinary research grants.

DIABETES AS A GLOBAL HEALTH ISSUE

Diabetes is a universal problem. The impact of diabetes is rapidly growing among populations in developing and middle-income countries; without action, deaths and disability due to diabetes will continue to increase substantially. NIDDK promotes international collaboration between investigators in the U.S. and scientists in other countries to develop and test strategies to stem the epidemic of diabetes at home and globally. Many other countries have health care and medical records systems that are particularly useful for clinical research on diabetes. NIDDK has collaborated globally on type 1 diabetes research through networks such as TEDDY and TrialNet to expand access to research participants and gain insight from research collaborators. Genetic research on diabetes also knows no boundaries and our research efforts have benefited from combined analysis of international cohorts. Global collaboration on type 2 diabetes is particularly relevant to understanding diabetes in immigrant and minority populations in the U.S. International collaborations offer unique opportunities to compare effects of different environmental exposures and understand why specific populations may be particularly vulnerable to diabetes.

CONCLUSION

Daunting as the challenge of diabetes appears, research has tremendously improved outcomes for people with the disorder. Were it not for declining rates of kidney disease, amputation, and CVD in people with diabetes, the burden associated with increased diabetes prevalence would be much greater. NIDDK recognizes the importance of collaboration with other components of NIH, other government agencies, and the diabetes voluntary organizations to realize the research progress. Our challenge is to stem the growing tide of diabetes through research ranging from understanding the fundamental processes underlying diabetes and its complications to studies of practical approaches to combat diabetes in medical and community settings.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

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