



Diabetes affects women, men, and children of all ages, races, and ethnic groups. For some, susceptibility to diabetes may have begun in the womb, while others may develop diabetes as a result of another disease or condition. Prevention and treatment strategies need to take into account the diverse needs of people with or at risk for diabetes. *(Photo credits: Top row, left image: ©iStockphoto.com/Yuri_Arcurs. Top row, middle image: Ian Hooton / Photo Researchers, Inc. Bottom row, left image: ©iStockphoto.com/monkeybusinessimages. Bottom row, middle image: ©Suprijono Suharjoto | Dreamstime.com)*

SPECIAL NEEDS FOR SPECIAL POPULATIONS

contents:

Introduction

Recent Research Advances

- Type 2 Diabetes Can Be Effectively Delayed or Prevented in Diverse Populations and Across the Age Spectrum in Adults
- Diagnosis and Management of Gestational Diabetes
- Long-Term Impact of Maternal Diabetes and Obesity on Offspring
- Diabetes Burden in Children and Youth
- Intensive Diabetes Treatment for Older Adults
- Increased Rates of Type 2 Diabetes and Modifiable Cardiovascular Risk Factors in People With Mental Disorders
- Psychotropic Medication As a Risk Factor for Type 2 Diabetes
- Effects of Glucose Dysregulation in Patients with Cystic Fibrosis
- Diabetes Risk is Increased and Associated with Increased Cardiovascular Risk in HIV Disease

Key Questions and Future Directions for Research

- Ethnic and Racial Disparities
- Pregnancy and the Intrauterine Environment
- Diabetes in Children and Youth
- Diabetes in Older Adults
- Diabetes and Psychiatric Disorders
- Secondary Diabetes

Importance of Research Goals and Strategies: How Translating Research Outcomes May Lead to Improvements in Health

INTRODUCTION

There is no age, ethnic, or racial group free from diabetes and its serious health complications. However, the impact of diabetes on minority groups in the United States and on children and older adults, pregnant women, and people already battling other serious diseases and conditions presents special challenges that need to be addressed by research.

Of the approximately 24 million Americans with type 2 diabetes, a disproportionate number come from racial and ethnic minorities in the U.S. population. For example, after adjusting for population age differences, 2007 to 2009 national survey data for people ages 20 years or older indicate that 7.1 percent of non-Hispanic whites, 8.4 percent of Asian Americans, 11.8 percent of Hispanics, and 12.6 percent of non-Hispanic blacks had diagnosed diabetes (primarily type 2 diabetes) (1). About 16.1 percent of the adult population served by the Indian Health Service has diagnosed diabetes (1). Prevalence is also higher in Native Hawaiians and other Pacific Islanders. This profile is also reflected in the over 79 million Americans at risk for the disease: A disproportionate number of people with pre-diabetes are from racial and ethnic minority groups—including the increasing number of children at risk for type 2 diabetes. Gestational diabetes—a form of glucose intolerance that is detected during pregnancy—places women at greatly increased risk of progressing to diabetes in the 10 to 20 years after pregnancy; this condition occurs more frequently among African American, Hispanic/Latino American, and American Indian women (1). Disparities also exist in the health complications of diabetes, with, for example, greater renal failure, cardiovascular disease, and retinopathy rates in minority populations.

Distinct issues are also associated with diabetes at different times throughout the lifespan, from the intrauterine environment, through childhood, pregnancy, and older age. For example, maternal metabolic health and its effect on the developing fetus have been drawn into sharp focus by the epidemic levels of diabetes and obesity in the United States. Not only are at least 7 percent and possibly as many as 18 percent of pregnancies in the United States affected by gestational diabetes (1,6), but an increasing number of women may already have diabetes before they become pregnant. In addition to the immediate risks to the mother's health, diabetes during pregnancy places offspring at increased risk to be large for gestational age and to have birth defects. The last decade has also been marked by a new appreciation of how maternal diabetes and obesity during pregnancy exert long-term effects on the risk of these conditions and other metabolic problems in offspring. Breaking this cycle will be important to reduce the future burden of diabetes.

Diabetes also poses special challenges for children and their families. Current therapy to prevent complications of diabetes requires keeping glucose levels as near the normal range as possible while avoiding unacceptable episodes of hypoglycemia. Diabetes management requires meticulous attention to balancing food intake, medication administration and dosing, and physical activity, while monitoring glycemia. For young children, diabetes management must be done by adults—parents, other family members, and child care and school personnel—who are trained and motivated to optimize their diabetes care. As children with diabetes grow older, they need to acquire the

knowledge, skills, and attitude towards self-care that will help them successfully transition to adulthood with the best possible short- and long-term health outcomes. Children with type 1 diabetes, some with type 2, and those with certain forms of secondary diabetes (see below) are at risk to develop diabetic ketoacidosis (DKA), a life-threatening condition. A complication of DKA unique during childhood, cerebral edema, can lead to devastating complications resulting in morbidity and death, and can incur high costs to the medical system. DKA is especially frightening for families because it can develop rapidly and be the presenting sign of diabetes. The rates of DKA at the time of diagnosis and during the course of the disease remain unacceptably high in the United States.



Research is needed to help improve diabetes self-care strategies in youth and in the transition to adulthood. (Photo credit: © iStockphoto.com/MarkHatfield)

Older Americans face a different set of challenges with diabetes and its effective management. The risk of developing type 2 diabetes increases significantly with age; moreover, advances in biomedical research have enabled more people diagnosed with type 1 diabetes in youth to live longer and reach older age. Now, among people 65 years and older, the prevalence of diabetes is 26.9 percent—nearly twice the prevalence of diabetes in middle age (1). Diabetes also disproportionately

affects older adults from minority groups. With increasing age, people with diabetes are more likely to have cardiovascular disease in addition to other health problems and are likely to be taking multiple medications (polypharmacy), increasing their chances for adverse drug reactions. Many complications of diabetes lead to physical inactivity and are associated with a higher prevalence of geriatric syndromes and functional decline. Geriatric syndromes such as injurious falls, frailty, depression, cognitive impairment, urinary incontinence, and polypharmacy are all more common among older adults with diabetes, increasing the burden of care for these individuals.

Diabetes also poses special challenges for people with major mental disorders. It has been estimated that depressed individuals are 60 percent more likely than non-depressed individuals to develop type 2 diabetes (14), and those with schizophrenia and bipolar disorder have similar or even higher risk. Increased risk is most likely mediated primarily by increased rates of obesity, smoking, and inactivity in these populations, as well as limitations in quality and access to general medical care. Certain drugs used to treat mental illnesses also appear to increase type 2 diabetes risk, in part by causing weight gain. Conversely, among individuals who already have type 2 diabetes—especially those suffering from diabetes complications—rates of depression are higher than they are in the general population (14,15). Depression and even subclinical depressive symptoms are associated with less participation in diabetes self-care, and higher blood glucose levels, complication rates, and mortality rates.

Finally, an ever-increasing number of people have secondary diabetes—diabetes that develops as a result of another disease or disease treatment. Diabetes is the most common comorbidity in people with cystic fibrosis

(CF), with CF-related diabetes present in 2 percent of children, 19 percent of adolescents, and 40 to 50 percent of adults with CF (16). Both the fibrotic destruction of the pancreatic islets and, possibly, insulin resistance induced by repeated inflammation and infection play a role in the development of abnormal glucose tolerance and diabetes in people with CF. The additional diagnosis of diabetes or pre-diabetes in people with CF is associated with lung function decline, underweight, and significantly greater mortality. In other people, drugs used to treat an illness can trigger diabetes. People who are HIV-infected, for example, are at increased

risk of developing diabetes when taking antiretroviral drugs. This increase has been associated with increased cardiovascular disease rates. HIV disease remains a major issue in the United States, where over 1 million people are infected, as well as in the underdeveloped world, with total estimates of about 33 million living with HIV/AIDS worldwide (17). Organ transplantation also raises risk for the development of diabetes in organ recipients, with perhaps as many as half of transplant recipients developing impaired glucose tolerance or diabetes as a side effect of the treatments used to prevent organ rejection—which, in turn, significantly increases the risk of transplanted organ failure and death. In all these cases, developing diabetes secondary to an already challenging disease or condition creates a new burden of care, complicates treatment, and may increase mortality.



One question about treatment of diabetes in older adults relates to optimizing care when diabetes is one of many medical conditions. (Photo credit: © iStockphoto.com/dscz)

RECENT RESEARCH ADVANCES

In just the past decade, researchers have made great strides in understanding the complex nature of diabetes and its effects on specific populations, including racial and ethnic minorities, women, children, older adults, people affected by psychological problems, and those with diabetes secondary to another condition. The following are some major examples of this research.

Type 2 Diabetes Can Be Effectively Delayed or Prevented in Diverse Populations and Across the Age Spectrum in Adults:

Once established, type 2 diabetes currently has no cure, which makes primary prevention a compelling priority. The Diabetes Prevention Program (DPP), a randomized, controlled clinical trial, examined the effects of lifestyle and medical interventions on the development of type 2 diabetes in adults at risk for this disease. The DPP compared intensive lifestyle modification, treatment with the medication metformin, and standard medical advice (control). Of the over 3,200 participants, 45 percent were from minority groups—African American, Alaska Native, American Indian, Asian American, Hispanic/Latino, or Pacific Islander—at increased risk of developing diabetes, and 20 percent were over the age of 60 years. Lifestyle intervention, leading to moderate weight loss through diet changes and increased physical activity levels, reduced diabetes incidence by 58 percent and treatment with metformin decreased the incidence by 31 percent, compared with placebo. The effects were similar for men and women—including women with a history of gestational diabetes—and for all ethnic and racial groups. Lifestyle changes worked particularly well for participants aged 60 and older, reducing their risk by 71 percent. Equally remarkable was the

associated finding that the same lifestyle modification was associated with reversion from pre-diabetes to normal glucose tolerance in about 36 percent of participants. Other studies have shown that type 2 diabetes can also be prevented or postponed by treatment with the medications acarbose, rosiglitazone, and pioglitazone.



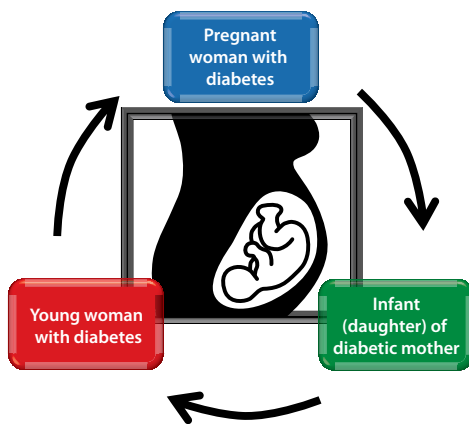
Racial and ethnic minority populations in the United States are disproportionately affected by diabetes and its complications. Research that can address these disparities is important to improving people's health and reducing the national burden of diabetes. *(Photo credit: Indian Health Service, Division of Diabetes Treatment and Prevention.)*

Diagnosis and Management of Gestational

Diabetes: The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study confirmed a linear relationship between maternal glucose levels during pregnancy and risk of perinatal morbidities, such as neonatal hyperinsulinemia and high birth weight, even at glucose levels significantly lower than those considered to be consistent with diabetes. As a result, the diagnostic criteria for gestational diabetes may be changed to include more women with glucose-associated perinatal risk (1,6). Separately, two oral antidiabetic agents, glyburide and metformin, have been shown to achieve acceptable glycemic control and perinatal outcomes

when used to treat gestational diabetes. The long-term effects of these drugs—which cross the placenta in varying degrees and do appear in the breast milk—remain unknown. Together, these advances provide the potential to revolutionize the diagnosis and management of gestational diabetes.

Long-Term Impact of Maternal Diabetes and Obesity on Offspring: Recent research has extended the finding, observed earlier among the Pima Indians in the Southwest, that a mother's diabetes and obesity can have long-lasting effects on her offspring's risk for these conditions. The SEARCH for Diabetes in Youth (SEARCH) Case-Control study found that, in a multi-ethnic cohort of youth, youth with type 2 diabetes were much more likely to have been exposed to diabetes or obesity while *in utero* than non-diabetic youth. These results indicate a universal effect of intrauterine exposure that operates, in addition to factors such as genetics and race/ethnicity, to increase lifetime risk for developing type 2 diabetes. As there are an increasing number of people developing diabetes and obesity at younger ages, it will be important to try and break this vicious cycle by preventing or mitigating the effects of diabetes and obesity during child-bearing years and pregnancy.



Diabetes in pregnancy can lead to a cycle of diabetes affecting future generations.

Diabetes Burden in Children and Youth: The first population-based study to assess the burden of diabetes in youth of all major racial and ethnic groups in the United States, the SEARCH study, has found that about 1 out of every 523 persons under 20 years of age has diabetes. Annually, approximately 15,000 children and adolescents are diagnosed with type 1 diabetes, and about 3,700 are diagnosed with type 2 diabetes. Type 2 diabetes is still rare in children under 10 years, but the diagnosis increases with age, especially in minority youth. In older adolescents (15 to 19 years), type 2 diabetes occurs more frequently than type 1 diabetes in Hispanic, African American, Asian/Pacific Islander, and American Indian youth. SEARCH found a higher estimate of type 1 diabetes incidence than previous reports, suggesting that type 1 diabetes may be on the rise. Information on the rates of diabetes in children and youth is crucial to design and implement prevention strategies and to find ways to reduce risk of diabetes complications in this population.

Intensive Diabetes Treatment for Older Adults: In three recent large clinical trials, stringent glycemic control did not demonstrate cardiovascular benefit for middle-aged and older adults with well-established type 2 diabetes who were at high risk for cardiovascular complications and who were also receiving good control of lipids and blood pressure. One of the studies suggested that intensive glucose therapy to near-normal levels is associated with higher mortality. This important finding from the ACCORD study highlights the need to identify the optimal glycemic targets in the context of prioritizing control of other critically important risk factors, such as blood pressure and cholesterol levels, among older adults. This group will soon constitute the majority of persons with type 2 diabetes. Also, the intensive lifestyle modification proven highly effective at preventing or delaying the

onset of type 2 diabetes among older adults has also been shown to reduce cardiovascular risk factors among older adults with type 2 diabetes. These important findings indicate that, to stem the epidemic of type 2 diabetes and associated cardiovascular disease, it will be critical to develop, evaluate, and disseminate the most cost effective strategies to support lifestyle modification in this special population.

Increased Rates of Type 2 Diabetes and Modifiable Cardiovascular Risk Factors in People With Mental Disorders:

Recent studies have found increased rates of diabetes and significant reductions in life expectancy, primarily due to premature coronary heart disease, in large population-based samples of persons diagnosed with major mental disorders. Recent evidence indicates high prevalence of all key modifiable risk factors in the mentally ill population, including obesity, hyperglycemia, dyslipidemia, hypertension, and smoking, along with low levels of screening and treatment interventions. These findings are important for understanding the burden of diabetes in this population.

Psychotropic Medication As a Risk Factor for Type 2 Diabetes:

Some psychiatric medications, especially antipsychotic agents associated with substantial weight gain risk, can significantly increase risk for obesity, diabetes, and dyslipidemia, with a growing literature quantifying these effects for individual medications. Treatment strategies to avoid these effects are a topic of active study. In addition, individuals with pre-diabetes in the control and intensive lifestyle arms of the DPP who were taking antidepressant medication were 2 to 3 times more likely than those not taking antidepressants to develop diabetes during the study. Recent analyses from the United Kingdom General Practice Research

Database similarly suggested that some, but not all, antidepressant medications, when taken at moderate to higher doses for prolonged periods, can increase risk for incident diabetes.

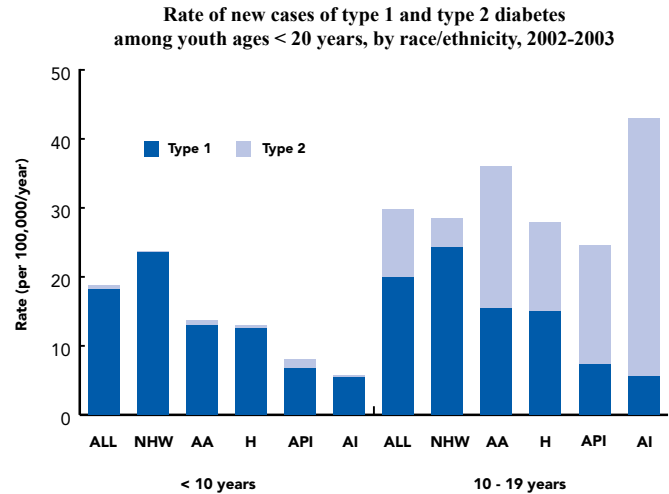
Effects of Glucose Dysregulation in People with Cystic Fibrosis:

In people with CF, impaired glucose tolerance and diabetes are associated with increased protein catabolism and nutritional failure, more rapid decline in lung function, and earlier death from pulmonary disease. Recent statistics suggest that this mortality gap has narrowed as early diagnosis and treatment of diabetes have helped improve survival in people with CF-related diabetes (CFRD). Recently, a multi-center, randomized, controlled study (CFRDT Trial) showed that chronic weight loss can be reversed with institution of insulin therapy (but not the oral medication repaglinide) early in the course of CF-related diabetes before fasting hyperglycemia develops. These findings emphasize the importance of screening for hyperglycemia in people with CF and treating insulin deficiency early, as it might extend and promote improved quality of life for these individuals.

Diabetes Risk Is Increased and Associated with Increased Cardiovascular Risk in HIV Disease:

Insulin resistance was initially recognized as common among people with HIV infection, and recent research has found diabetes among 14 percent of HIV-infected individuals receiving antiretroviral therapy. When adjusted for body mass index (BMI) and age, this means there is more than a 3-fold increase in the rate of diabetes in people infected with HIV compared to people without HIV. Diabetes has been associated with a 2.4-fold increase in coronary heart disease among HIV-infected persons. The increased prevalence of secondary diabetes in the HIV-infected population is likely due to specific effects of antiretroviral therapy (e.g., protease

inhibitors affecting GLUT-4, and nucleoside reverse transcriptase inhibitors affecting mitochondrial function), as well as changes in fat distribution among HIV-infected persons—including loss of protective subcutaneous fat and accumulation of excess fat in the liver, muscle, and viscera. Insulin sensitizers have been shown to improve diabetes and CVD risk in the HIV-infected population; whether lifestyle intervention can help prevent development of type 2 diabetes in this population is not yet known.



Source: SEARCH for Diabetes in Youth Study.
 NHW=Non-Hispanic Whites; AA=African Americans;
 H=Hispanics; API=Asians/Pacific Islanders;
 AI=American Indians

KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, recognized the disproportionate burden, unique impact, and special needs diabetes confers on certain populations in the United States, particularly women, children, older adults, and racial and ethnic minority groups. In the intervening years, the additional issues of diabetes risk in individuals with major mental disorders, such as major depressive disorder, schizophrenia, and bipolar disorder, and of diabetes secondary to other diseases, have simultaneously become better recognized and increasingly urgent. The research challenges posed by these special diabetes problems cut across many fields and disciplines. Described below are research questions and opportunities to pursue in the next several years to reach the goal of meeting clinical challenges in these important, cross-cutting areas.

Ethnic and Racial Disparities

Because certain ethnic and racial populations have significantly higher risks of developing type 2 diabetes and subsequent end-organ complications, a broad-based research effort to understand potential genetic and biologic factors that contribute to disease development is required. In addition, further study of environmental factors, including the intrauterine environment, psychosocial triggers, beliefs, self-management skills, community support for lifestyle modification, economics, access to health care, and gene/environment interactions among different ethnic and racial populations, is urgently needed.

Key Questions

- **What are non-traditional biologic risk factors that contribute to underlying race/ethnic disparities in the development of diabetes and its complications?**
- **What are the “non-biologic” (i.e., environmental, social, cultural, and economic) factors across the lifespan that affect diabetes prevalence and progression to complications in different ethnic and racial groups?**
- **What are the most important genes associated with type 2 diabetes in different ethnic/racial groups?**
- **What novel interventions can be developed that address the racial/ethnic disparities in diabetes incidence, complication rates, and mortality, and that take into account pharmacogenomics, environmental, social, cultural, and economic factors?**

Future Directions

- **Determine what behavioral strategies work well to promote and sustain effective lifestyle change in minority individuals at high risk for developing diabetes.**

The DPP demonstrated that lifestyle change is an effective strategy for preventing type 2 diabetes in high-risk minority individuals. More research is

needed to understand the behavioral and psychosocial factors that lead to poor nutrition and a sedentary lifestyle and the barriers to change. Community- or work-based programs need to be tested that can target and reach large numbers of high-risk individuals. The cost effectiveness of such programs will also need to be considered. The role of social marketing and new information technologies should be explored.

- ▶ **Determine what behavioral strategies are effective in promoting and sustaining adherence to diabetes treatment regimens in individuals belonging to racial and ethnic minority groups, to improve health outcomes.**

Studies demonstrate that access to care alone does not explain racial and ethnic disparities in the outcomes of individuals with diabetes. Research is needed to better understand the attitudes and values at the individual, family, and community levels that affect adherence to treatment regimens. The roles of different behavioral techniques, such as motivational interviewing and peer support, should be studied. For example, CMS is currently working with organizations on diabetes self-management training, with a focus on minority populations, as a part of its overall focus on health disparities in the Medicare population.

- ▶ **Identify biological mechanisms underlying ethnic and racial differences in susceptibility to diabetic complications.**

Although many risk factors for diabetes and its complications have been identified for the general population, important racial and ethnic differences remain unexplained. For example, African Americans, especially those with diabetes, appear to have higher susceptibility to cardiovascular disease even at blood lipid levels that confer relative cardioprotection in other

racial and ethnic groups. Moreover, higher rates of kidney complications persist in African Americans and American Indians with diabetes even when glycemia is normalized. To understand these disparities in cardiovascular and kidney risks, research is needed to develop novel biomarkers and methodologies for analyzing the contributions to risk of established factors, such as lipoproteins, and of other, novel risk factors.

- ▶ **Identify racial and ethnic differences in the interactions among antenatal care, diet, gestational glycemic burden, and other aspects of the intrauterine environment, and the risk of diabetes and obesity in childhood, adolescence, and adulthood.**

There is an emerging understanding that the intrauterine fetal environment exerts profound effects on future health outcomes in adulthood. Excess risk is associated with both maternal undernutrition and overnutrition. Maternal undernutrition and intrauterine growth retardation (evidenced by low birth weight) expose the fetus to increased risks of obesity, diabetes, hypertension, metabolic syndrome, and cardiovascular disease in later adult life. On the other hand, maternal diabetes also predisposes the fetus to increased risk of obesity and for developing diabetes in later life. Several conditions associated with low birth weight, including poor antenatal care, undernutrition, and pre-eclampsia, are more prevalent in ethnic minority populations, as are gestational and type 2 diabetes. Moreover, gestational diabetes exacerbates rates of pre-eclampsia. Thus, ample opportunity exists for a “vicious cycle” of interactions among several obstetrical risk factors that may contribute to the current epidemic of obesity and diabetes in minority racial and ethnic populations.

- **Identify genes for type 2 diabetes and their mechanisms of action in different racial and ethnic groups to facilitate disease prevention and treatment strategies.**

Recent advances in genetics research and technology, such as genome-wide association (GWA) studies, have accelerated the identification of genes that influence the susceptibility to type 2 diabetes. To date much of this work has been done among populations of European descent. Extending this research effort to find diabetes-related genes in non-European groups is necessary to determine how type 2 diabetes differs among ethnic and racial groups. Other studies can be pursued to determine whether diabetes susceptibility genes already identified in European populations extend to other ethnic and racial groups. Studies of gene mechanisms that include intermediate phenotypes, as well as research on gene-environment interactions in specific racial and ethnic populations, should also be pursued. Once causative genes have been identified, further pharmacogenetic studies should be pursued as they may help tailor therapy for prevention and treatment of diabetes in high-risk racial and ethnic groups.

Pregnancy and the Intrauterine Environment

Understanding of the immediate and long-term health consequences of diabetes and obesity during pregnancy, for both mother and child, has expanded greatly over the past decade. Recently, researchers have found that maternal blood glucose levels lower than previously regarded as abnormal can adversely affect the newborn and have long-lasting effects on the offspring. Coupled with better means of monitoring maternal glucose and fetal growth, this observation has opened up new areas of research. Several small studies have suggested that oral hypoglycemic agents, previously thought to be

potentially detrimental to the fetus, may be safe in the treatment of gestational diabetes. However, further studies are needed to vigorously evaluate the safety and efficacy of these therapies, particularly over the long-term. Finally, gestational diabetes in the mother and exposure of the fetus to diabetes can be used to identify individuals at high risk for developing diabetes. Research into optimal strategies for monitoring such individuals to determine if they are moving toward diabetes and for intervening to delay or prevent diabetes, even before glucose levels become impaired, are important future directions for research.

Key Questions

- **What are the immediate- and long-term health outcomes for offspring of women treated for diabetes or placed on weight maintenance or weight loss regimens during pregnancy?**
- **What noninvasive fetal measurements can be used to quantify diabetic “fetopathy” *in utero*? How can such measurement(s) be applied clinically to identify pregnancies in need of intensified maternal glucose control?**
- **Which anti-diabetic treatments work to mitigate perinatal and/or long-term complications in such pregnancies?**
- **By what mechanisms does the intrauterine environment increase the risk of the offspring developing obesity and diabetes?**
- **What biomarkers can be used to monitor women who have had gestational diabetes to determine if their glucose homeostasis is deteriorating, even before glucose levels become impaired? What interventions can actually stop progression to diabetes?**

Future Directions

- **Identify the safest and most effective approaches to achieve optimal glycemic control during pregnancy.**

Studies are needed to determine the most effective approaches for achieving optimal glycemic control during pregnancy in different populations of women. More research is needed to determine the optimal time to intervene, what agents should be used, the contribution of lifestyle, and recommendations for monitoring.

- **Determine the effects that different interventions for diabetes and/or obesity in mothers have on the long-term health outcomes for offspring.**

Epidemiologic data have shown that diabetes or obesity during pregnancy predisposes offspring to obesity, type 2 diabetes, and other metabolic abnormalities. It is not known whether glucose control per se in the mother is sufficient to decrease risk, or whether different types of treatment will be more efficacious in decreasing metabolic abnormalities in the offspring. For example, the long-term effects of oral diabetes drugs administered during fetal development remain unknown. Before being recommended as an alternative to insulin for routine use, their long-term effects should be determined. Long-term follow-up of offspring (20 years or more) will be required, because the metabolic abnormalities are not always evident until the second decade of life or later. Suitable cohorts need to be identified, in which mothers on either insulin or oral anti-diabetic agents have detailed obstetric histories, including the timing, dosage, and duration of drug use. Weight maintenance and weight loss interventions are approaches to managing diabetes and obesity during pregnancy whose long-term impact on offspring should

also be explored. A significant barrier to this line of research is that weight loss or maintenance is always difficult to achieve, particularly during pregnancy. Also, taboos still exist against having “inadequate” weight gain during pregnancy, and exercise during pregnancy is not universally accepted as safe. The Institute of Medicine’s recently-updated guidelines for healthy weight gain during pregnancy, which include targets for underweight, normal weight, overweight, and obese women, should help in this regard. Prenatal and neonatal metabolic information kept as part of individual medical records would be a useful research resource for these studies; health information technology should be applied to establish safe strategies to obtain this information while protecting personal information.

- **Develop new approaches to antepartum monitoring and management of gestational diabetes.**

To find new ways of managing gestational diabetes, researchers need to look beyond glucose as the only important parameter to monitor in women with this condition. The development of noninvasive methods (e.g., ultrasound, magnetic resonance imaging) to detect and quantify disease or abnormalities *in utero*, such as excessive fetal fat, will accelerate research in this field. Clinical trials could then utilize such fetal monitoring technologies to determine optimal maternal treatments and correlate fetal conditions with perinatal and longer-term outcomes.

- **Develop effective clinical approaches to prevent birth defects in diabetic pregnancies.**

Preconception glycemic control is known to dramatically reduce birth defects, but many women with known diabetes become pregnant without first instituting such control. In addition, substantial numbers of women may

have undiagnosed type 2 diabetes that is only recognized during the course of prenatal care. New approaches are needed to effectively translate research showing that it is possible to prevent birth defects in the offspring of diabetic mothers. One approach would be to test health care delivery strategies that combine diabetes testing and preconception diabetes self-management training with more common aspects of women's health, such as family planning or gynecologic care. Other studies are needed to identify strategies to improve information and outcomes for women at high risk of diabetes during pregnancy who may not have access to prenatal health care.

- ▶ **Investigate the progression to type 2 diabetes and its mitigation in women with prior gestational diabetes.**

Diabetes is a relatively late outcome of a long-term loss of beta cell function. Ideally, clinicians should be able to determine if a person's beta cell function is declining long before diabetes, or even impaired glucose tolerance, develops, so they can intervene to arrest the decline and prevent diabetes. A major research focus should be on identification of biomarkers for declining beta cell function. Such markers could then be used to test interventions for their ability to preserve beta cell function, starting relatively early in the natural history of development of diabetes. This approach could be particularly useful for monitoring and intervening in women with previous gestational diabetes at risk for type 2 diabetes, as well as to other forms of progressive loss of beta cell function, including glucose intolerance associated with HIV and CF.

Diabetes in Children and Youth

The alarming new statistics on diabetes prevalence in youth uncovered by SEARCH and other efforts makes it

even more urgent to understand the factors contributing to this disease and its morbidity in young people. Type 1 diabetes is an autoimmune disease that usually strikes early in life; major efforts to prevent and treat disease are described elsewhere in this research plan (see the chapter on "Type 1 Diabetes and Autoimmunity").

Type 2 diabetes in youth is almost universally associated with overweight or obesity, particularly in minority children. Interestingly, SEARCH found that children with type 1 diabetes also have a higher rate of overweight than youth without diabetes, as well as very high rates of obesity, especially in Hispanic and African American youth. While some children with type 1 diabetes may gain weight as a result of insulin treatment, increasing numbers of youth with type 1 diabetes are overweight/obese at diagnosis. While this may simply mirror the obesity epidemic in the general population, the high rates of overweight/obesity in youth with type 1 may reflect an added inflammatory burden on the pancreas in individuals genetically at risk for the disease. Some children seem to have a form of "hybrid diabetes," with features of both type 1 diabetes (auto-antibodies) and type 2 diabetes (insulin resistance). The role of obesity in the etiology of each of these forms of diabetes is not clear. Understanding the connection is crucial to improving approaches to prevent and treat diabetes in youth.

While there is an appreciation of the importance of diabetes management in children, many gaps remain. Research is needed on the interplay between developing autonomy and patient self-management behaviors, as well as on factors that influence the transition of patient care in early adulthood. Improving diabetes care across the age spectrum is imperative as data exist that microvascular and macrovascular risk factors and complications may develop in childhood. The long-term course of these early complications, and strategies to

reduce risk, including lifestyle and pharmacotherapy, need to be studied. The effects of race/ethnicity; genetics; culture; socioeconomic status/parental education; puberty and growth; access to care; family dynamics and family health; and qualities of the school, child care center, and community play key roles in determining if diabetes management is successful across the age spectrum. In addition, the problem of DKA in young children needs to be addressed. DKA has virtually been eliminated in certain areas of Italy as the result of provider and public education efforts. Strategies to reduce DKA in the United States must be developed.

Key Questions

- **What is the role of overweight and obesity in the development of diabetes—including hybrid diabetes—in children and youth? Are there racial and ethnic differences?**
- **How does the development of overweight/obesity in children or youth affect diabetes management and outcomes, and contribute to patterns of disordered eating?**
- **Do children with hybrid diabetes have the same genetic, environmental, and cultural risk factors as those with type 1 diabetes?**
- **How can children and youth be more successfully transitioned to adult management of diabetes? What are the most effective and affordable ways for parents, caregivers, and individuals with diabetes to become motivated and competent to manage diabetes?**
- **How can children and youth with diabetes obtain optimal support for their diabetes care from environments outside the home (e.g., day care, schools, colleges, community organizations)?**
- **What complications and risk factors for complications are present in youth with diabetes?**
- **Can DKA rates be significantly reduced in the United States, at presentation and over the course of childhood diabetes?**
- **How can the interactions between the four main modifiable parameters influencing glucose control (insulin administration, diet, physical activity, and stress) be better understood? What types of interventions would be successful and cost effective at achieving optimal glycemic control and improving quality of life?**
- **Can pre-diabetes be identified (by a cost effective strategy) and the development of type 2 diabetes in children and adolescents be delayed or prevented?**

Future Directions

- **Determine whether the increase in type 1 diabetes in younger children is due to increases in obesity/overweight.**

Studies in both the United States and Europe (Eurodiab) have shown an increase in type 1 diabetes in the pediatric population, particularly in very young children. It has been suggested that the shift downward in age is due to higher weights and rates of weight gain in babies and infants, referred to as the accelerator hypothesis. Overall, how obesity and overweight interact with race/ethnicity, genetics, and environmental factors to contribute to the islet autoimmune process of type 1 diabetes needs to be investigated.

- **Characterize the role of obesity in contributing to inflammation and insulin resistance in all forms of childhood diabetes.**

Multiple small studies have shown that obesity contributes to inflammation, insulin resistance, impaired glucose tolerance, and progression to type 2 diabetes in youth. In addition, puberty appears to be a major risk factor for the metabolic complications of obesity. Mechanistic studies should be conducted to understand how overweight/obesity affects islet autoimmunity, insulin resistance, beta cell function, inflammation, and other diabetes triggers. Further investigation is also required to determine how to best assess adiposity and fat compartmentalization in youth; how to characterize patterns for the trajectory of weight throughout childhood; and how environmental, social, cultural, and genetic factors interplay to cause obesity-related metabolic disturbances.

- **Develop effective weight loss strategies, in the context of the growing and developing child, for children with all forms of diabetes who are overweight.**

Data from the SEARCH study revealed that children and youth with diabetes—including type 1 diabetes—are more overweight/obese than children without diabetes. Because all children with type 1 diabetes and many with type 2 diabetes are treated with insulin, the role of insulin administration in inducing weight gain should be evaluated. Studies to address weight loss that might include behavioral, pharmacological, and surgical interventions in children with diabetes should be conducted to help reduce the risk for disease progression and complications early in life. These studies will need to take into account that girls with type 1 diabetes are at especially increased risk for disordered eating patterns, including withholding insulin, which accelerates diabetes complications.

- **Develop cost effective methods for assessing and tracking diabetes complications and risk factors for complications in children and youth with diabetes.**

Studies should be pursued to determine if the early course of diabetes; environmental, social, and behavioral factors; or biological/genetic characteristics explain differences in glycemic control and the risk for diabetes complications.

- **Study behavioral methods to improve treatment adherence in the context of a chronic disease, including a better understanding of the way treatment approaches need to evolve with the maturation of the child.**

For diabetes management to be successful, children must have the support of their family, other caregivers, and school/child care personnel. It needs to be determined how diabetes education is best delivered to those caring for these children, how the child with diabetes should receive ongoing diabetes education that is developmentally staged, and how information is transferred amongst caregivers and health care professionals. As youth transition to adulthood and become increasingly autonomous, there is the need to determine what systems of care facilitate the transfer of individuals with diabetes from pediatric to adult providers while optimizing adherence, access, and outcomes overall. Better methods to assess adherence to treatment regimens and healthy lifestyle need to be developed.

- **Determine risk factors for the development of DKA and establish approaches to reduce rates of DKA in the United States.**

The development of DKA remains the major source of morbidity and mortality in childhood diabetes. Because diabetes incidence is increasing in young children, efforts should be directed toward increasing public and professional awareness about diabetes symptoms, particularly in infants and toddlers. Methodologies should be investigated to reduce DKA rates at diagnosis taking into account a public health approach, as well as evaluating strategies that cut across the varied systems of medical care for children.

Diabetes in Older Adults

The care of the large number of older adults with or at risk for diabetes is associated with very high personal and societal costs. In particular, macrovascular complications are highly associated with disability and death for persons with diabetes. Moreover, as both type 2 diabetes and Alzheimer's disease increase in the older population, and having diabetes significantly increases the risk of developing Alzheimer's disease, there is the need to determine how a variety of potential mechanisms might interplay and account for the association of these two processes (see the "Diabetes Complications" chapter for further discussion of this association). The public health and health economic implications of identifying the best prevention and treatment strategies for older adults with diabetes are enormous, and should be considered especially as the Federal government works to simultaneously contain costs in the Medicare program and maximize the quality of care delivered to persons with prevalent and morbid chronic conditions such as diabetes.

Key Questions

- **What are the optimal strategies for motivating older people to improve and sustain lifestyle changes that can help prevent or control diabetes?**
- **What are the appropriate (optimal) glycemic, blood pressure, and cholesterol targets across the spectrum of health for older adults to help prevent diabetes complications (and maintain quality of life)?**
- **If it is not feasible to reach targets for all three risk factors (glycemia, blood pressure, and cholesterol) due to therapeutic complexity, polypharmacy, costs, and/or competing medical conditions, how should risk factor control be prioritized to limit morbidity and mortality in older adults?**
- **How does diabetes and its treatment affect other health issues faced during aging, such as falling, osteoporosis, incontinence, polypharmacy, and declines in functional status?**
- **For the frail, older adult with diabetes and limited life expectancy, what are the most important treatment priorities if the goal is to maintain quality of life and decrease the risk of the geriatric syndromes?**

Future Directions

- **Determine how to activate older adults with or at risk for diabetes to improve and sustain lifestyle modification.**

The lifestyle arm of the DPP was highly effective among older participants. However, many older adults are sedentary. Studies are needed to understand the best behavioral approaches for helping older individuals initiate and/or sustain a regular program of physical activity and to safely implement weight loss if their BMI is placing them at increased risk for complications.

- **Determine the optimal strategy to manage hyperglycemia and minimize cardiovascular risk in older adults with diabetes.**

Studies are needed to identify the optimal glycemic targets among older adults, especially in those with multiple comorbidities. In addition, many of the approaches for caring for older adults with diabetes are based on extrapolations from clinical trial results collected among younger persons. It is not known whether controlling specific risk factors leads to better outcomes in older individuals with or without multiple comorbidities. Studies are needed to determine the relative benefit of glycemic control, and treatment of high blood pressure and abnormal lipids, in older individuals who may have difficulty affording or complying with complex treatment regimens. In addition, these studies need to evaluate the prioritization of treatment goals in the context of maintaining functional status and quality of life, while limiting the risk of geriatric syndromes (e.g., falls, cognitive impairment).

- **Study differential drug clearance in older adults, as well as across the lifespan and across different races and ethnicities.**

A variety of drugs are available or under development for treatment of diabetes and its complications. However, research suggests that people may vary widely in how quickly they clear (metabolize and excrete) drugs from their bodies, depending upon factors such as

age, ethnicity, pregnancy, or developmental stage (e.g., puberty)—which, in turn, could have critical ramifications for dosing and lead to potentially deleterious drug interactions. Puberty and pregnancy could have an effect not only on drug clearance, but also drug distribution. Studies should be pursued to address these questions both in older adults, who are more likely to be taking multiple medications for diabetes and other conditions, and in ethnically and racially diverse populations across the lifespan.

Diabetes and Psychiatric Disorders

A greater understanding of the association between diabetes and psychiatric disorders and treatments has been achieved in the past several years as researchers have looked at this problem in different populations. New challenges include uncovering the mechanisms responsible for this association and identifying strategies to reduce the impact of diabetes in individuals with mental disorders. Study of this problem will be helped by application of a variety of approaches, from basic mechanistic studies to clinical trials and population-based studies.

Key Questions

- **How do depression and certain antidepressant medications increase the risk of developing type 2 diabetes?**
- **Does drug naïve schizophrenia or bipolar disorder increase the risk of developing type 2 diabetes, and if so, how?**
- **How do certain antipsychotic medications and certain “mood stabilizers” for bipolar disorder increase the risk of developing type 2 diabetes?**

- **Are there depression treatments that can reduce diabetes risk or improve outcomes in people who already have diabetes?**
- **Are there genetic risk factors that explain the increased prevalence of diabetes in the mentally ill, or is increased prevalence simply a function of increased rates of established risk factors such as obesity, dyslipidemia, smoking, sedentary lifestyle, and poor medical care? Do risks vary across the lifespan?**
- **What are optimal strategies to increase rates of screening, risk reduction, and treatment for pre-diabetes and diabetes in the systems of care responsible for mentally ill populations?**

Future Directions

- **Identify the mechanisms by which depression, schizophrenia, and bipolar disorder, and the medications used to treat them, increase diabetes risk. Identify the individuals who are susceptible to those risks.**

Research studies should be conducted to determine whether the association between antidepressant use and diabetes risk represents a direct effect of the medication, or if instead antidepressant use is a marker for more severe or chronic depression (itself a risk factor for diabetes). Similarly, research studies should be conducted in drug naïve patient groups with a range of known diabetes risk factors (e.g., a range of baseline adiposity and insulin resistance) to determine whether the association between mental disorders (such as schizophrenia and bipolar disorder) and risk of diabetes represents an effect of the mental disorder, an effect of the high prevalence of unaddressed risk factors in people with these disorders, or a direct effect of medications.

Such studies should also assess the effect of individual medications on known diabetes risk factors such as adiposity, insulin sensitivity and secretion, and lipid metabolism.

- **Evaluate the effect of depression treatment on diabetes risk or improved outcomes in people with diabetes.**

Depression treatment has been associated with some positive metabolic outcomes, including improved glucose control in individuals with high hemoglobin A1c (HbA1c) levels before depression treatment. Larger studies are needed in individuals at risk for and with diabetes to compare the effects of depression counseling with one or more widely used antidepressant agents on outcomes. Comparing depression treatments (medication versus counseling) will be challenging for many reasons: medications might not carry similar diabetes risk, the effects of antidepressants on diabetes risk might take years to be seen, and the ideal study should involve individuals who are not taking antidepressants or receiving depression counseling on entry.

- **Develop strategies to improve diabetes screening and treatment rates in the mentally ill.**

A major barrier to this line of research is the fragmented system of care for mentally ill persons who are at risk for diabetes. Improvements in cross-talk between system administrators and researchers would facilitate research, as would dissemination of results from successful programs. A variety of approaches should be tested to better integrate diabetes screening and treatment into psychiatric care.

Secondary Diabetes

The double burden of disease and accompanying complexity in management and treatment in people who develop diabetes secondary to a chronic condition raises critical challenges. For persons with CF, new knowledge about treatment for the most severely affected (e.g., people with CF who also have diabetes are best treated with insulin to help preserve nutritional status and lung function) has led to new questions about when treatment should begin. In HIV, some specific mechanisms contributing to secondary diabetes among the HIV-infected population have been uncovered, but critical questions remain as to optimal treatment strategies and methods to prevent the development of diabetes in this patient population. People who have undergone organ transplantation develop diabetes at high rates, particularly in association with certain immunosuppressive regimens. However, the risk profile for diabetes is unknown, and questions remain as to how diabetes should be best treated in this situation, and how diabetes adversely affects transplantation and survival.

Key Questions

- **Should people with CF who also have pre-diabetes receive diabetes therapy, and what is the best method of treatment? What is the mechanism behind the relationship between glucose tolerance abnormalities and excessive pulmonary morbidity and mortality in persons with CF?**
- **What are the mechanisms of diabetes development in HIV-infected persons? What is the cardiovascular risk associated with the development of diabetes in this population?**

- **What are the effects of insulin sensitizers and lifestyle modification on hard cardiovascular end points in people with HIV infection?**
- **What is the risk profile for diabetes in people undergoing organ transplantation, how should diabetes be best treated, and how does diabetes adversely affect organ and patient survival?**

Future Directions

- **Identify the best approach to treating early glucose tolerance abnormalities in CF to prevent excess mortality.**

The CFRDT Trial successfully used pre-meal rapid acting insulin to reverse chronic weight loss in participants with CFRD, but small pilot studies suggest that a single daily dose of insulin glargine (a long-acting form of insulin) may improve weight and/or pulmonary function. It is not known whether diabetes therapy affects morbidity and mortality in people with CF who have pre-diabetes. Randomized clinical trials are needed to determine the best treatment strategies. A major challenge to conducting randomized, controlled multi-center trials in CF is the recruitment of a sufficient number of participants.

- **Identify the etiology of diabetes-related morbidity and mortality in CF.**

While insulin deficiency and protein catabolism have been implicated in CF-related diabetes morbidity and mortality, the impact of intermittent hyperglycemia on inflammation and infection needs to be explored. A small pilot study demonstrated that airway fluid

glucose concentrations acutely rise in CF in response to blood glucose elevation, and that this promotes bacterial growth. Studies exploring whether increased inflammation and oxidative stress are associated with diabetes and its impact on CF lung disease are needed and should likely take place both in the laboratory and the clinical setting.

➤ **Characterize the role played by specific antiviral drugs on the pathogenesis of diabetes in people with HIV.**

Insulin resistance was one of the first metabolic abnormalities observed among HIV-infected individuals, and researchers have shown that antiretroviral drugs used to treat infection can result directly in insulin resistance. Preliminary studies suggest an important mechanism by which protease inhibitors may reduce insulin sensitivity, via GLUT-4. Nucleoside reverse transcriptase inhibitors, another major class of antiretroviral drugs, have been shown to perturb mitochondrial function *in vitro* and contribute to insulin resistance *in vivo* via a different pathway from protease inhibitors. Studies are critically needed to determine additional cellular mechanisms by which antiretroviral drugs may contribute directly and indirectly to the development of insulin resistance and diabetes mellitus. Data derived from these studies may shed light on the pathogenesis of diabetes in general, as the drugs used to treat HIV infection affect critical cellular pathways in the development of insulin resistance.

➤ **Determine the effects of lifestyle modification and insulin sensitizing strategies to prevent diabetes and reduce CVD risk in the HIV-infected population.**

Preliminary studies suggest that metformin improves insulin resistance and CVD risk markers among HIV-infected persons. Similarly, small studies have shown improvement in some CVD risk factors and HbA1c in response to lifestyle modification among HIV-infected people. However, studies to date have not assessed whether these strategies will prevent the development of diabetes and reduce hard CVD end points. Moreover, differences in racial demographics, age, and fat distribution may contribute to unique responses in the HIV-infected population. Large, multi-center, randomized, controlled studies to assess the optimal strategies to prevent the development of diabetes and reduce hard CVD end points in the HIV-infected population are critically needed.

➤ **Investigate strategies to reduce the development of diabetes and improve survival when diabetes occurs in organ transplantation.**

Data from multiple sources have shown high conversion rates to diabetes after organ transplantation and generally poorer outcomes once diabetes develops. To improve graft and patient survival, studies are needed to develop risk profiles of patient characteristics including adiposity, race/ethnicity, genetics, and environmental triggers; understand the role of aggressive monitoring of glucose during the procedure and post-transplant course, and the benefit of early initiation of treatment for dysglycemia; and develop strategies to assess how to individualize anti-rejection regimens to improve glucose metabolism.

IMPORTANCE OF RESEARCH GOALS AND STRATEGIES: HOW TRANSLATING RESEARCH OUTCOMES MAY LEAD TO IMPROVEMENTS IN HEALTH

Further research on many of the unique challenges posed by diabetes will be key to tailoring diabetes prevention, treatment, and management strategies to the diverse needs of the U.S. population at risk for or living with this disease. As demographics change, a better understanding of the influence of genetic and environmental factors on diabetes in many different racial and ethnic groups becomes critically important. Through research on diabetes during pregnancy and its consequences, there is hope that the cycle of diabetes in mothers and their offspring can be broken, helping to preserve the health of current and future generations. To decrease the burden of diabetes in children, research should focus on decreasing DKA, type 2 diabetes in youth, and childhood overweight/obesity, in addition to vigorously pursuing ways to prevent, slow, or reverse type 1 diabetes and improve its management (as described in the “Type 1 Diabetes and Autoimmunity” and “Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia” chapters). Strategies that improve glycemia

in all age groups need to be evaluated in the context of multiple factors, such as environment, culture, race/ethnicity, and family context/structure, to identify those approaches that are most effective. Older Americans should benefit from research to develop improved diabetes prevention and control strategies that take into account critical biological and health changes accompanying aging, while efforts to understand specific risk factors, complications, and the transition to adult life with diabetes hold promise to help children and youth now and in the future. A better understanding of the relationships between psychiatric disorders, their treatment, and diabetes can yield new strategies to cope with and potentially prevent diabetes in affected individuals. Finally, research on ways to reduce the impact of diabetes on people already affected by diseases such as CF and HIV infection, or by conditions requiring organ transplantation, should help to sustain and improve the health of these particularly vulnerable populations.