AREA OF FOCUS #1

Diabetes Mellitus, Type 2

Diabetes mellitus is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action, or both.

Type 1 diabetes accounts for approximately 5 to 10 percent of all cases of diabetes in the United States, and type 2 diabetes for 90 to 95 percent. Gestational diabetes, a transient elevation of blood glucose during pregnancy, occurs in approximately 3 to 5 percent of pregnancies. About 1 to 2 percent of the diabetes syndrome comprises other types of diabetes that have a variety of causes, such as genetic defects in insulin action, diseases of the pancreas, or drug-induced diabetes.

Diabetes affects approximately 16 million people in the United States, with one-third of those affected being unaware that they have the disease. Minority populations do not appear to have a higher prevalence of type 1 diabetes. However, they are more frequently affected by type 2 diabetes. *Minority groups constitute 25 percent of all adult patients with diabetes in the United States and represent the majority of children and adolescents with type 2 diabetes.*

- African-Americans, Hispanic/Latino Americans, American Indians, and some Asian-Americans and Native Hawaiians and other Pacific Islanders are at particularly high risk for the development of type 2 diabetes. Diabetes prevalence rates among American Indians are two to five times those of whites. On average, African-American adults are 1.7 times as likely and Mexican-Americans and Puerto Ricans are twice as likely to have the disease as non-Hispanic whites of similar age. Cuban-Americans do not seem to have an elevated risk of diabetes. Some Asian-American and Native Hawaiian and other Pacific Islander groups, such as Japanese Americans and Samoans, also have elevated rates of diabetes.

- All patients with diabetes are at high risk for microvascular complications affecting the eyes, nerves, and kidneys; for lower extremity amputations; and for coronary heart disease. Diabetes patients from racial and ethnic minorities, however, are more likely to develop the microvascular complications of diabetes and to have lower extremity amputations compared with non-Hispanic white patients with diabetes.

- The rates of coronary heart disease in minority populations may not be greater than in non-Hispanic whites with diabetes; however, the frequency of cardiovascular complications in all patients with diabetes is two to five times that of people who do not have diabetes.

- Much of the racial and ethnic disparity in diabetes microvascular complications may be due to higher levels of risk factors for these conditions in minority patients with diabetes, such as hyperglycemia and hypertension. However, there also seems to be a genetic component that influences the development of certain of the microvascular complications of diabetes. In addition, there may be other physiologic, metabolic, behavioral, and health care differences that account for part of the disparity in the frequency of diabetes complications.

- Diabetes in pregnancy is associated with increased risk of congenital malformations and of complications during delivery and in the perinatal period.

- Due to the intrauterine environment, offspring of diabetic pregnancies have greatly increased risks of obesity and type 2 diabetes during childhood and adolescence. Women from minority groups, especially American Indian women, are much more likely to have type 2 diabetes during their childbearing years.

- In American Indian populations, maternal diabetes during pregnancy increases the risk of type 2 diabetes in childhood tenfold and is the most important risk factor for the development of type 2 diabetes in childhood.

- The mechanisms of how maternal diabetes increases the risk of diabetes and obesity in children and the knowledge of how to modify these risks are largely unknown.

- Type 2 diabetes, once considered a disease of adults only, has been increasing in children and adolescents. Childhood diabetes clinics have reported that as many as one-third of their new onset-diabetes patients have type 2 diabetes. More than three-quarters of these children are minorities.

- Rates of type 2 diabetes in adolescent Pima Indians have doubled in the past 30 years. Thirty years ago, type 2 diabetes was not found in Pima children in the age group of 5- to 9-year-olds. Now more than 1 percent of children this age have type 2 diabetes.

- Type 2 diabetes in childhood and adolescence leads to the development of serious kidney, eye, and heart disease in young adulthood in many of these children. Currently, there are no approved medications for the treatment of childhood obesity or type 2 diabetes in childhood. Low-calorie diets, behavior modification, and exercise are the mainstays of treatment but have had limited success in the past.

Current Activities

Diabetes Prevention Program Outcomes Study

Background

The Diabetes Prevention Program (DPP) was a large, NIDDK-supported, randomized clinical trial designed to determine whether individuals at high risk for developing type 2 diabetes could have their risk for developing diabetes prevented or delayed. The interventions tested were lifestyle activities or the drug metformin. A total of 3,234 individuals with impaired glucose tolerance (IGT) were randomly assigned to metformin, placebo, or a lifestyle program. The lifestyle program was aimed at a weight loss of 7 percent or greater and 150 minutes or greater physical activity per week. Participants' mean age was 51 years; 68 percent were women, and 45 percent were from minority groups. The study results indicated that metformin reduced diabetes incidence rates by 31 percent and lifestyle by 58 percent over an average intervention of 2.8 years.

The DPP was designed with the expectation that prevention or delay of diabetes would in the end prevent or delay the development of long-term, duration-dependent, diabetes-specific complications. Also, preventing or delaying cardiovascular disease (CVD), and/or CVD risk factors resulting from diabetes prevention or delay, would be of major benefit to individuals with IGT and would contribute to long-term health.

Research Goals and Scope

The DPP Outcomes Study (DPPOS) is a 5-year study that will take advantage of the unique cohort of volunteers that participated in the conduct of the DPP. The DPPOS will permit (1) an examination of the long-term effects and durability of the prior DPP interventions on DPP outcomes, including diabetes onset, CVD, atherosclerosis through measurement of intimal medical thickening, quality of life, and cost-benefit; (2) a determination of the clinical course of new onset type 2 diabetes, not possible in any other existing cohort of individuals; and (3) an examination of nos. 1 and 2 in minority populations, men vs. women, and older and aging subjects of the DPP.

Performance Measures

The DPPOS Data and Safety Monitoring Board (DSMB) has been charged by the NIDDK to oversee study performance both in terms of study conduct and in terms of participant safety. The DSMB will make recommendations to the NIDDK as to study performance and study continuation. In addition, DPPOS subcommittees will be created with the responsibility of overseeing ongoing protocol adherence and participant retention.

Outcome Measures

Of the 3,234 subjects randomized to the 3 arms of the DPP, it is estimated that 2,300 participants who have not converted to type 2 diabetes and who agree to participate will remain in the long-term followup of the DPP cohort. Participant retention will remain a focus of the followup study. The study, based on the numbers projected, will have sufficient power to continue to follow the conversion to diabetes. The study will also be powered to detect differences in the development of retinopathy between the originally randomized groups, including the converters to diabetes. For the first time it will be possible, using the DPP cohort, to follow the development of

retinopathy from its initiation and the effects of the DPP treatments on this process. In addition, the cohort will be followed using surrogate measures of cardiovascular risk and clinical CVD events. Although poorly powered to examine the latter over this 5-year phase of the DPPOS, it is hoped that participants will be followed over the long term to permit sufficient power to compare the intervention groups for clinical CVD events.

Race-Ethnic Disparities in the Incidence of Diabetes Complications

Background

Epidemiological studies have generally found a striking and large excess of diabetic microvascular disease in minority racial/ethnic groups, including Native Americans, African-Americans, Hispanic Americans, and Asian-Americans and Pacific Islanders. However, the reasons for these differences are not well understood.

The Diabetes Control and Complications Trial (DCCT), for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), for type 2 diabetes, established the importance of intensive diabetes control in dramatically reducing the devastating complications that result from poorly controlled diabetes. Both the DCCT and the UKPDS demonstrated the efficacy of intensive glucose control in reducing the risk for the microvascular complications of diabetes, such as retinopathy, neuropathy, and nephropathy. In addition, numerous studies have recently demonstrated that intensive blood pressure control is essential in preventing both microvascular and macrovascular complications of diabetes. Aggressive management of dyslipidemia has also been shown to decrease macrovascular complications. Some of the racial differences in diabetic complications may be explained by differences in the availability and quality of health services. There may also be differences in race-ethnic and socioeconomic status in self-care practices, health care provider practices, and/or access to quality health care and prevention services. These differences would directly impinge on the frequency and magnitude of risk factors for diabetes complications and on the intensity of medical care for early stages of complications to prevent progression to end-stage disease.

In addition to differences in blood glucose, lipid, and blood pressure control, which may be modified by improved medical care, genetic susceptibility and other biological risk factors may contribute in unknown ways to complications. This idea is suggested by the clustering of complications (especially nephropathy) within families and by the excess risk of retinopathy in Hispanics versus non-Hispanics, which continues even when the degree of hyperglycemic exposure is taken into account.

Finally, lifestyle, psychosocial factors, stress, family structure, social support, diet and culture, and socioeconomic status vary among racial/ethnic minorities and may contribute to the differential risk of developing diabetes complications and the progression of complications. Little is known about how these behavioral factors influence the risk of complications and the effectiveness of interventions designed to prevent or reduce diabetes complications in racial/ethnic minority groups.

The identification of these divergent etiologies and the quantification of their correlation to risk have important implications for the prevention and amelioration of microvascular complications. Such information might improve the effectiveness of treatment to reduce the disparities in the incidence of diabetes complications among racial/ethnic groups.

In contrast to microvascular complications, racial/ethnic minorities with diabetes often have lower rates of macrovascular disease than Caucasian population groups. Angina, myocardial infarction, and other forms of coronary heart disease appear to be less common in African-Americans, Mexican-Americans, and Native Americans than in non-Hispanic whites. This difference is particularly striking given the higher incidence of diabetes in these populations. The factors that account for the differing macrovascular disease rates are unknown. For example, the relative contribution of glycemia (versus other risk factors) to cardiovascular risk in these minority populations has not been studied.

Research Goals and Scope

The overall objective of this Program Announcement (PA) is to understand racial/ethnic disparities in the development of the microvascular and macrovascular complications of diabetes. It is recognized that both biologic and nonbiologic factors may be operating in these populations.

Approaches may include metabolic, genetic, and/or epidemiological studies in representative populations. Researchers may be able to take advantage of extant cohort studies that have been established for the investigation of diabetes or other diseases. Collaboration among investigators of these established cohorts would be desirable so that these studies might jointly develop protocols and evaluate findings. Alternatively, investigators may propose to start a new cohort, appropriately powered, to capture the current risks and outcomes in the era of new medications for glucose, blood pressure, and lipid control. Such studies of current risks might be appropriately based in large health maintenance organizations or in clinical practices with structure and data management practices conducive to efficient and cost-effective analyses.

Investigators are encouraged to incorporate appropriate surrogate markers for complications into study designs to shorten the duration of studies. Such surrogate markers might include early indicators of end-stage complications (e.g., background retinopathy, albuminuria, serum creatinine, basement membrane thickening, EKG, carotid ultrasound).

Appropriate topics for investigation would include, but are not limited to, the following:

- Epidemiological studies to determine the rates of microvascular and macrovascular diabetic complications in appropriate representative samples of contemporary populations
- Studies to identify genes that might affect the development and progression of microvascular and macrovascular complications in different populations
- State-of-the-art, hypothesis-driven metabolic studies to determine whether there are differences in metabolism, insulin sensitivity, energy expenditure, beta-cell function, and body composition that might influence glycemic control and the risk of complications in different populations
- Studies to compare the contribution of glycemia versus other risk factors (e.g., smoking, hyperlipidemia, body composition, blood pressure) in the development of microvascular and macrovascular disease in patients with diabetes and to study how treatment of these factors may influence the development rates of complications in different racial/ethnic groups.

- Studies that investigate environmental factors, such as medical care, behavior and lifestyle, and socioeconomic status, which may contribute to the risk for the development and progression of complications, and that could incorporate culturally specific lifestyle factors into treatment and prevention strategies to reduce risk across racial/ethnic groups

- Studies to determine whether different pathophysiologic mechanisms or risk factors are operative among subgroups within racial/ethnic minorities (e.g., different subgroups of Hispanic Americans, such as Mexican-Americans, Puerto Ricans, Caribbean Hispanics, and Cuban-Americans).

Understanding the basis for differing susceptibilities could provide information that would lead to specific therapies likely to be useful in various subpopulations at high risk for the development of diabetes complications.

Performance Measures

The performance measures that the Institute will use to demonstrate that the objectives have been met will include the number of grants funded, the quality of proposals, the number of patients enrolled in the study, and the funding level.

Outcome Measures

The outcome measures will include the extent to which the results accurately define the rates of diabetic complications; differences in the genes; metabolic differences; and the effect of social, economic, and behavioral factors in the different race-ethnic populations.

Racial/Ethnic Differences in the Etiology of Type 2 Diabetes in the United States

Background

There are major differences in the prevalence of type 2 diabetes among race-ethnic groups in the United States. Substantial progress has been made toward identifying population-based risk factors in the development of type 2 diabetes that might lead to these race-ethnic disparities. Such established risk factors include, for example, genetic predisposition, total and central obesity, duration of obesity, high caloric intake, and physical inactivity. Factors such as socioeconomic status, acculturation, and stress may also be important. Individuals who have progressed along the pathogenic course toward diabetes are at higher risk of developing overt disease, and these individuals include those with insulin resistance, IGT, gestational diabetes, and reduced beta-cell function.

Although these diabetes risk factors appear to operate in all race-ethnic groups, it is not known whether specific groups are inherently different in the ways they respond to risk factors, which may lead to their differential susceptibility to diabetes. Environmental, genetic, and metabolic differences may underlie the disparity in diabetes rates, and physiological outcomes of risk factors may arise from a complex interplay of genetic and nongenetic (e.g., behavioral, lifestyle, environmental) factors.

Epidemiological studies have documented the differing risk for diabetes among race-ethnic groups and have established the identity of diabetes risk factors. However, with few exceptions, these studies have not been designed to examine in depth the metabolic and physiologic effects of diabetes risk factors in specific race-ethnic populations. Consequently, there is an important need for carefully designed clinical studies to investigate these issues in representative samples of the various U.S. race-ethnic groups.

Research Goals and Scope

The overall objective of this PA is to determine the metabolic and physiologic reasons for disparities in the incidence of type 2 diabetes in minority race-ethnic populations. Such information could lead to new prevention and treatment strategies, especially for high-risk groups. Additionally, information from these studies would be important for devising cost-effective approaches to phenotyping patients with type 2 diabetes and individuals at risk for developing diabetes. The ability to characterize and identify discrete subgroups of type 2 diabetes would be essential in genetic studies of this disease.

Studies to investigate the behavioral, socioeconomic, psychosocial, cultural, family, and community factors that influence the individual's risk for developing type 2 diabetes and the process of how these factors can lead to racial/ethnic disparities in incidence rates are important. Understanding these issues is vital to the development of culturally appropriate prevention strategies to reduce risk across racial/ethnic groups. However, studies to investigate nonbiologic factors should not be submitted under this PA, which will focus on biologic factors responsible for race-ethnic disparities in the incidence of type 2 diabetes.

Appropriate topics for investigation would include, but are not limited to, the following:

- State-of-the-art, hypothesis-driven metabolic studies in which fat metabolism, glucose levels, insulin secretion, and energy expenditure are measured in individuals from U.S. race-ethnic groups. Such studies might determine, for example, whether some groups are at greater risk for type 2 diabetes from insulin resistance or from reduced beta-cell reserve, whether fat content and distribution differ among race-ethnic groups, and what metabolic or physiologic processes are responsible in the pathogenetic pathway leading to type 2 diabetes.

- The temporal relationship of changes in body weight and body composition, glucose tolerance, and insulin resistance in the etiology of type 2 diabetes. Clinical studies could unravel the sequence of events leading to type 2 diabetes, especially the timing of weight gain with regard to glucose tolerance and insulin resistance. A critical question is whether individuals who develop diabetes first gain weight and then develop diabetes, with the same genes leading to both conditions, or whether individuals gain weight and then proceed to diabetes because of beta-cell defects.

- Beta-cell function. There is a growing appreciation that substantial beta-cell defects occur prior to the onset of type 2 diabetes. Little is known about the types of defects that actually predict or attend diabetes. Most studies that have examined complex aspects of beta-cell function *in vivo* have been cross-sectional comparisons of high- vs. low-risk individuals. A combination of detailed beta-cell assessments with longitudinal followup would likely yield important information about the pathogenesis of the beta-cell defects. Other phenotypic traits may also be useful in such studies, such as beta-cell responses to fatty acids, hyperglycemia, amino acids, and insulin resistance. Studies are needed to better understand whether there are racial/ethnic

differences in the incidence and prevalence of impaired fasting glucose and IGT and whether there are differences among groups in the rates of progression to type 2 diabetes.

- Fat metabolism and insulin resistance. There is mounting evidence that altered fat metabolism in the whole body and, possibly, in skeletal muscle or adipocytes in muscle is an important determinant of insulin resistance. Longitudinal studies employing detailed assessments of fatty acid turnover and/or muscle fat metabolism could yield important information about the relationship between fat metabolism and insulin resistance as people change their physical activity, weight, and so forth.

- The temporal relationships among the components of the metabolic syndrome (Syndrome X). The clustering of hypertension, hyperglycemia, obesity, and insulin resistance is well documented; however, the temporal development of the individual components of the metabolic syndrome remain to be determined. In particular, the etiologic relationship among these components and their relationship to type 2 diabetes need further investigation. Studies should examine the racial/ethnic differences in the constellation of metabolic abnormalities in this syndrome.

- The role of the *in utero* environment on the subsequent development of IGT or type 2 diabetes. Extensive epidemiological evidence suggests that intrauterine growth retardation is associated with numerous metabolic abnormalities in adults, including hypertension, CVD, IGT, hyperinsulinemia, and type 2 diabetes. However, little is known about the pathophysiologic mechanisms by which the intrauterine environment programs fetal metabolism to predispose individuals to chronic disease later in life. Studies are needed to assess whether abnormalities in the uterine environment contribute to racial/ethnic disparities in the incidence of type 2 diabetes and, conversely, whether there are racial/ethnic differences in the response to a given *in utero* milieu.

Research scientists may be able to take advantage of extant cohort studies that may have been established for the investigation of diabetes or other diseases. Collaboration among investigators of these established cohorts would be desirable so that these studies might jointly develop protocols and evaluate findings. Alternatively, investigators may propose to start new cohorts, appropriately powered, to capture the current risks for development of type 2 diabetes.

Performance Measures

The performance measures that the Institute will use include the number of grants funded, the quality of proposals, the number of patients enrolled in the study, and the level of funding.

Outcome Measures

The outcome measures will include the definition of the incident rate of type 2 diabetes; differences in the genes; metabolic differences; and the effect of social, economic, and behavioral factors in the different racial/ethnic populations.

Prevention and Treatment of Type 2 Diabetes in Children and Adolescents—Clinical Centers and Coordinating Center

Background

Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion, although its precise etiology and pathogenesis are only incompletely understood. The public health impact of type 2 diabetes is enormous.

Clearly associated with aging and obesity, type 2 diabetes has traditionally been considered a disease of adults. Children are assumed to have type 1 diabetes, an autoimmune disease. However, recent epidemiological data reveal an increasing number of cases of type 2 diabetes in the pediatric population, especially among adolescents and in certain minority populations. In general, population-based screening data are not available. Data culled from diabetes clinics in several locations suggest that the percentage of children diagnosed with diabetes who are classified as having type 2 diabetes has risen from less than 5 percent (prior to 1994) to 20 to 30 percent (after 1994). The increase in type 2 diabetes in children is presumed to be a consequence of widespread obesity and decreased physical activity.

Data from the Third National Health and Nutrition Examination Survey suggest that up to one-third of adults who have type 2 diabetes may go undiagnosed. A similar situation may exist with children. In fact, the diagnosis of type 2 diabetes in children is often made because of routine laboratory screening being conducted as part of a school physical and not because the child presents to a health care provider with specific complaints. Thus, many children who do not receive such screening may go undiagnosed until they become symptomatic, at which time they may have been hyperglycemic for many years and are at high risk of developing diabetic microvascular and macrovascular complications. In addition, significant numbers of children may not have frank diabetes but may be at high risk of developing diabetes based on the presence of insulin resistance, impaired fasting glucose, or IGT. It is, therefore, imperative to establish appropriate screening criteria and effective primary prevention programs to avoid a potential major public health burden.

The majority of children with type 2 diabetes are in the preadolescent or adolescent age range. The adolescent period presents special challenges to health care providers and families when attempting to promote behavior and lifestyle changes. Prevention and treatment programs must also consider cultural differences among racial/ethnic groups that may influence the acceptance of medical regimens. This is especially important for type 2 diabetes in children, which disproportionately affects minority groups.

When children develop diabetes, efficacious therapy is needed to maintain euglycemia to prevent the development of complications. Diabetes is currently estimated to cost the U.S. health care system approximately $98 billion annually. Much of the cost is related to the microvascular and macrovascular complications of diabetes. Because the development of complications is related, in part, to the duration of diabetes, children represent a population at high risk. Unfortunately, the drugs currently approved for use in adults with type 2 diabetes have not been systematically studied in children. Thus, treatment options for those children diagnosed with type 2 diabetes are restricted by the lack of data on the use of such pharmacological agents. Optimal treatment of type 2 diabetes in children, as well as in adults, should go beyond merely achieving euglycemia. Preserving beta-cell function in children with IGT or type 2 diabetes is of critical importance. Thus, clinical trials are needed to establish appropriate and effective treatment regimens for children with type 2 diabetes.

Research Goals and Scope

NIDDK has funded a cooperative agreement to plan and conduct trials for the prevention and treatment of type 2 diabetes in the pediatric population. Previously, two cooperative agreement Request for Applications were issued—(1) to solicit applications from potential study sites to perform clinical trials for the prevention and treatment of type 2 diabetes in children and (2) to solicit applications for a coordinating center to provide clinical center coordination and analytical and statistical support for the clinical trials. Based on peer review, awards were made to seven clinical sites and the coordinating center.

The cooperative agreement is funded for 7 years, anticipating three phases: (1) planning, (2) recruitment and study, and (3) analysis. Currently, a steering committee—composed of the Principal Investigators from the clinical sites, the Principal Investigator from the Coordinating Center, an NIDDK representative, and several outside experts—is beginning protocol development for these trials. The treatment trial will likely include lifestyle changes, as well as pharmacological therapy, and will assess beta-cell function and glucose control. The primary prevention trial will focus on a cost-effective, school-based intervention, with the potential for a broad, populationwide study. The trials will be conducted at multiple sites to ensure an adequate sample size and geographic and racial/ethnic diversity.

Performance Measures

The performance measures will include the number of centers funded and the quality of research proposals.

Outcome Measure

The outcome measure will be the extent to which the results will alter clinical practice, including the diagnosis, prevention, and treatment of type 2 diabetes in children and adolescents.

International Type 2 Diabetes Genetics Linkage Analysis Consortium

Background

In 1997 a group of investigators studying type 2 diabetes decided to form the International Type 2 Diabetes Genetics Linkage Analysis Consortium to combine the data from multiple genome scans. The group started with an analysis of chromosome 20. This analysis suggested that there was more than one locus on chromosome 20 linked to type 2 diabetes in the Caucasian population. This study was used as the preliminary data for an NIH Research Project Grant (R01) application submitted in 1998 to study the remaining chromosomes. The grant consisted of 11 research groups, with 3 of these groups from Europe. In addition, GlaxoSmithKline and the NIDDK Phoenix Epidemiology and Clinical Research Branch continue to participate but do not receive compensation from the grant. The application was converted to a Cooperative Agreement (U01) to allow for staff involvement and for more flexibility in funding. The grant was awarded in August 1999.

Research Goals and Scope

The transmission of complex phenotypes, such as type 2 diabetes, is likely to reflect the actions and interactions of multiple genetic and environmental factors. Linkage studies designed to localize genes for type 2 diabetes have yield few regions with highly significant evidence for linkage and fewer still that have been replicated in additional studies. Although increasing the size of the sample included in linkage studies will provide the power to detect and localize susceptibility loci with modest or moderate effects, the collection of family data is the most expensive and time-consuming aspect of linkage studies. In an effort to maximize the utility of data already collected to map genes for type 2 diabetes, the International Type 2 Diabetes Genetics Linkage Analysis Consortium has been formed to combine existing data sets for linkage analysis. In addition, the availability of a large number of samples allows for the analysis of individual ethnic groups for predominant diabetes susceptibility genes. Although the consortium data sets provide data to analyze most ethnic groups, there is a deficiency of African-American samples. Two additional sets of DNA samples from African-Americans with diabetes have been genotyped by the Center for Inherited Disease Research. These data will be combined with the Genetics of NIDdm sample and will be analyzed to identify diabetes genes in the African-American population.

Combining data from 26 groups have shown that several data sets demonstrate evidence for a diabetes susceptibility gene on chromosome 1q. The populations that showed evidence for linkage are the Pima Indians, Utah Caucasians, Amish, United Kingdom Caucasians, and French Caucasians. To further study this region, a subcommittee consisting of these groups has been formed. Its goal is to fine-map the putative type 2 diabetes susceptibility gene on chromosome 1q by linkage disequilibrium mapping using single nucleotide polymorphoses. Linkage disequilibrium would provide further evidence of a diabetes susceptibility gene.

Performance Measures

The performance measures will include the number of African-Americans enrolled and the level of success in obtaining appropriate samples for genetic linkage studies.

Outcome Measure

The outcome measure will be the extent to which the research results from the consortium will aid in the diagnosis of genetic diseases in minority populations and will increase the number of and improve the quality of publications resulting from these studies.

Diabetes-Focused Science Education in Tribal Middle and High Schools

Background

The overall objective of this trans-NIDDK initiative is to support faculty at Tribal Colleges and Universities (TCUs) to develop science education programs working with Tribal community middle and high schools. The intent of this initiative is to increase the presence of American Indians in the biomedical science research community by exposing American Indian students to the biomedical sciences and by motivating them through the prism of diabetes.

The 33 existing TCUs are fully engaged in serving and strengthening local communities. They routinely provide assistance to Indian communities on various programs and projects and are deeply integrated into Tribal culture and institutional life. The colleges serve as culturally supportive role models for future success in communities with historically low levels of educational attainment. An association between TCUs and local schools already exists through the Tribal College Rural Systemic Initiative. This program is part of the Rural Systemic Initiatives in Science, Mathematics and Technology Education Program, funded by the National Science Foundation and designed to promote excellence in the teaching of the sciences. The Diabetes-Focused Science Education in Tribal Middle and High Schools program would use these existing collaborations to design, test, and implement a biomedical science education program around diabetes. The outcome of the initiative would be an increased awareness of diabetes and its risk factors and of the role of science in the attainment of health and a healthy lifestyle in a population overburdened with diabetes and its devastating health outcomes. This awareness would be used as the motivational focus for students selecting their future career paths.

Research Goals and Scope

This trans-NIDDK initiative aims to increase the interest and competitiveness of American Indian students in elementary, middle, and high schools in the pursuit of biomedical careers.

Performance Measures

The performance measures will include the number of centers funded, the quality of proposals, and level of funding.

Outcome Measure

The outcome measure will be the extent to which the results of this initiative alters health behavior, increases recruitment of Native American youth to biomedical research careers, and increases awareness of diabetes in the Native American youth population.

Translational Research for the Prevention and Control of Diabetes

Background

The Diabetes Control and Complications Trial, for type 1 diabetes, and the United Kingdom Prospective Diabetes Study, for type 2 diabetes, established the importance of intensified diabetes control in dramatically reducing the devastating complications that result from poorly controlled diabetes. Both the DCCT and the UKPDS demonstrated the efficacy of intensified glucose control in reducing the risk for microvascular complications of diabetes, such as retinopathy, neuropathy, and nephropathy. In addition, results from the UKPDS suggested that strokes might be reduced in patients with type 2 diabetes through a combined regimen of intensive blood pressure and glycemic control. Unfortunately, the advances of these studies have not been successfully incorporated into general health care practice. This underuse of current knowledge was highlighted in a recent study of diabetic individuals, which demonstrated a low frequency of self-monitoring of blood glucose, good glycemic control, regular foot care, and ophthalmic examinations, all of which markedly reduce the incidence and progression of diabetic complications. Alarmingly, less than 2 percent of adults with diabetes receive the level of care that has been recommended by the American Diabetes Association (ADA), with self-monitoring of blood glucose following the ADA guidelines performed by only one in five adults with diabetes. Thus, it is clear that effective mechanisms for diabetes treatment, shown by the DCCT and the UKPDS to reduce the burden of diabetes, are not being implemented.

Ongoing clinical trials are under way that address the prevention of type 1 or type 2 diabetes (e.g., Diabetes Prevention Trial-Type 1 and DPP). The DPP has concluded its randomized intervention phase early, and the results demonstrate that both lifestyle and pharmacological treatments can significantly reduce the onset of type 2 diabetes in a high-risk population. This important finding will make it even more crucial that effective translation strategies be developed and adopted to improve adherence to accepted standards of diabetes care and to overcome barriers to the translation of scientific advances into clinical practice.

This PA solicits research in the translation of recent advances in the prevention and treatment of type 1 or type 2 diabetes into clinical practice for individuals and communities at risk. This PA establishes a diabetes prevention and control program, and it seeks applications for clinical and behavioral studies to develop and test strategies for (1) achieving objectives that have already been proven beneficial, such as control of glycemia and other risk factors for diabetic complications, or (2) enhancing behaviors expected to improve health outcomes for individuals with type 1 or type 2 diabetes. Of particular interest are interventions that focus on translating new advances into practice in underserved and minority populations.

Research Goals and Scope

This PA solicits applications furthering research in diabetes translation research. Trials proposed under this program should test (1) improved methods of health care delivery to patients with or at risk of diabetes; (2) improved methods of diabetes self-management; and (3) cost-effective, community-based strategies to promote healthy lifestyles that will reduce the risk of diabetes and obesity. Generally, these studies will take interventions that have been demonstrated to be beneficial by controlled laboratory or clinical investigations (e.g., intensive glycemic control) and extend or adapt these interventions to larger populations or other settings. Alternatively, trials may focus on enhancing behaviors (e.g., increased physical activity in individuals at risk for diabetes) generally accepted as likely to improve health outcomes for patients with or at risk of diabetes.

Performance Measures

The performance measures will include the number of grants funded, the quality of proposals, and the level of funding.

Outcome Measure

The outcome measure will be the level of success in the translation of the results into policy regarding the diagnosis, prevention, and treatment of type 1 and type 2 diabetics.