National Institute of Diabetes and Digestive and Kidney Diseases
Diabetes Mellitus Interagency Coordinating Committee

Risk Factors Related to Development of Pre-Diabetes and Diabetes: Deterioration and Opportunities for Prevention in Young and Middle-Aged Adults

Natcher Conference Center, Conference Room A
National Institutes of Health
Bethesda, Maryland

September 12, 2005
Summary Minutes

WELCOME AND OPENING REMARKS

Allen Spiegel, M.D.; Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Bethesda, Maryland

Dr. Spiegel welcomed members of the Diabetes Mellitus Interagency Coordinating Committee (DMICC), guest speakers, and guest attendees. He introduced Dr. Judith Fradkin to give a progress report on the Type 1 Diabetes Initiative and the Special Funding Program.

Judith E. Fradkin, M.D.; Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK, NIH, Bethesda, Maryland

Dr. Fradkin provided an update on the implementation of recommendations from the January expert panel planning and evaluation meeting, for the Special Statutory Funding Program for Type 1 Diabetes Research. One recommendation of the expert panel was that the NIH develop a Strategic Plan to identify future opportunities for type 1 diabetes research. This Strategic Plan is being developed under the auspices of the DMICC. Major input for the plan has come from working groups that were established for five of the six overarching goals that have informed the use of the Special Funds. Because the sixth goal is cross-cutting, each of the five working groups will contribute to development of the strategic plan related to this goal. An executive committee comprised of NIH representatives and the chairs of the five working groups was established to guide the development of the Strategic Plan. Draft chapters for these five goals are being compiled and will be distributed to the executive committee in anticipation of the executive committee meeting scheduled for September 28 (slide 1).

Dr. Fradkin also noted that the Congressional appropriations report called for a report on progress toward meeting HbA1c guidelines and how best to close the disparities that exist between treatment guidelines and the care that people with diabetes receive in the first year after diagnosis (slide 2). The strategies to be used in preparing the report include defining the problem and identifying factors that contribute to the disparity between HbA1c guidelines and actual treatment; identifying barriers and challenges to implementation, adoption, and

dissemination; and suggesting possible courses of action to promote greater diffusion and adoption of the guidelines (slide 3).

Dr. Fradkin explained the role of the DMICC members in providing input for the report (slide 4). DMICC representatives will be asked to prepare material that can be incorporated into the report and to submit this by November 15, 2005. This material should include: (1) two to three sentences on the barriers and challenges to implementation, adoption, and dissemination of the guidelines, and (2) one-half page on suggested ways in which each Institute, Center or Agency can promote greater implementation, adoption, and dissemination of the HbA1c guidelines. At the next DMICC meeting on December 12, 2005, DMICC representatives will be asked to give a brief presentation on his or her agency's plans. Not every member agency of the DMICC may be involved directly in this report, if its mission does not focus on glycemic control. The December 12 meeting also will include an external speaker to help provide perspectives on opportunities to improve implementation of HbA1c guidelines within health care systems (slide 5). Dr. Fradkin is contacting New York City health officials regarding a potential initiative there that would involve collecting information on HbA1c values in New York City residents and providing feedback to the patients and their health care providers regarding HbA1c targets Dr. Spiegel commented on the rationale for the New York City program and potential involvement of DMICC member agencies. He noted that this initiative would be relevant to many of the agencies represented on the DMICC, such as the Center for Medicare and Medicaid Services, the Centers for Disease Control and Prevention (CDC), and the Agency for Healthcare Research and Quality (AHRQ), among others.

Turning to the topic of today's DMICC meeting, Dr. Fradkin commented that there is considerable interest in risk factors for diabetes, and that there is commonability among risk factors for diabetes and cardiovascular disease (CVD). Identification of risk factors is a pre-requisite for prevention. This meeting will include presentations by researchers who have collected important prospective data on the development of diabetes and CVD. A list of questions to be addressed during the meeting was presented, including the types of outcome measures that would be useful in planning for meaningful initiatives (slide 6).

Peter J. Savage, M.D., Director, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute (NHLBI)

Dr. Savage noted that there is much to be gained from delaying the onset of diabetes, including beneficial effects for CVD. He introduced Dr. Kiang Liu, who is a Principal Investigator at Northwestern University for the Coronary Artery Risk Development in Young Adults (CARDIA) study, funded by NHLBI. Dr. Savage, as NHLBI Project Officer for the CARDIA study, has seen data on the links between several risk factors, premature disease, and public health.

RISK FACTOR CHANGE IN YOUNG ADULTS: THE CARDIA STUDY

Kiang Liu, Ph.D., Professor and Associate Chair for Research, Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Dr. Liu focused his presentation on data from the CARDIA study on risk factors in relation to diabetes and prediabetes. He addressed three issues (slide 2):

- Are CVD risk factors elevated prior to the development of type 2 diabetes (T2D) and Impaired Glucose Tolerance (IGT) (slide 4)?
- Is there a relationship between the Metabolic Syndrome at baseline and the presence of Coronary Artery Calcium (CAC) 15 years later?
- What is the impact of body mass index (BMI) change on CVD risk factors?

With regard to the first issue, comparisons were made in normal, IGT, and T2D groups (classified according to the oral glucose tolerance test results at year 10) of baseline data (slide 5 and slide 6) for CVD risk factors. Risk factors assessed included systolic blood pressure (SBP), high-density lipoprotein-C (HDL-C), low-density lipoprotein-C (LDL-C), triglycerides, uric acid, fasting glucose, fasting insulin, BMI, and waist circumference. In each case, the baseline CVD risk factors were graded with the highest level (lowest for HDL-C) in the diabetes group and lowest level (highest for HDL-C) in the normal group. The differences between the diabetes group or IGT group and the normal group were significant statistically. When analyses of the data were controlled for waist circumference and BMI, only triglycerides, uric acid, and fasting insulin factors appeared to be significant (slide 7). For those who developed diabetes or IGT, increases in risk factors appeared to change more over time than for those in the normal group (slides 8-12).

For the second issue, data were analyzed to determine the impact of clusters of risk factors (i.e., the Metabolic Syndrome) on coronary atherosclerosis as determined by surrogate marker CAC (slide 13). The Metabolic Syndrome is defined as those with a waist circumference of greater than 102 cm (40 in) in men and greater than 88 cm (35 in) in women; triglycerides greater than 150 mg/dl; HDL cholesterol greater than 40 mg/dl in men and 50 mg/dl in women; blood pressure greater than or equal to 130/85 mmHg or on treatment; and a fasting glucose greater than or equal to 100 mg/dl (slide 14). For each race and gender group, there is a clustering of risk factors in those with CAC evidence of early atherosclerosis (slides 15-16), even when adjusted for age, LDL-C, and cigarette smoking.

Regarding the third issue, Dr. Liu presented data on the potential impact of BMI change and CVD risk factors (slide 17). BMI was stratified according to those who increased BMI, had stable or decreased BMI, or had fluctuating BMI at year 15 (slides 18-19). Few individuals who were obese at baseline remained stable or were included in the fluctuating group; the vast majority continued to gain weight. For every risk factor over time, there was an increase in risk among those who gained weight (slides 20-24). The increase, however, was small for those who had stable or decreased BMI. In addition, increasing weight over 15 years increased the risk for Metabolic Syndrome by as much as 6 to 9 times compared to the stable weight group; those who gained weight and then lost weight (fluctuating) were able to reduce their risk as compared to those who gained but did not lose weight (slide 25). For impaired fasting glucose (IFG) and diabetes, those who were overweight at baseline had a higher risk of developing IFG or diabetes over 15 years (slides 26-27).

Dr. Liu summarized his findings by noting the following (slides 28-29):

- For young adults who developed IGT or T2D by year 10, most risk factors were elevated at baseline, and the risk factors continued to progress adversely over the 10-year period;
- Metabolic Syndrome at baseline was associated significantly with coronary calcium 15 years later;
- Young adults who maintained a stable BMI over time may have prevented the progression of other risk factors;
- An increase in BMI (weight gain), rather than the initial level of BMI, was the major contributor to the progression of risk factor levels and to the development of the Metabolic Syndrome; and
- Higher BMI and increase in BMI were the major contributors to the development of IFG and T2D.

The implications of these findings are that greater public health efforts should be aimed at weight stabilization over the long term for young and middle-aged adults (slide 30).

A participant asked why there appears to be no disparity between white and African-American men regarding CAC. Dr. Liu responded that the lower calcium levels seen in African-American men and women do not necessarily indicate a lower risk of CVD. Another participant asked whether individuals with high BMI (overweight or obese) could be physically fit. Dr. Liu described investigations of people regarded as "fit and fat," who appear to do better healthwise than "low-fit and fat" individuals; however, their risk factor levels are not as low as "fit and not fat" individuals. Another participant wondered if women in the fluctuating group appeared to be at higher risk of CVD than women in the other groups. Dr. Liu replied that this was not so and did not address whether women whose weight fluctuates because of dieting cycles are at higher risk than those whose weight remains stable.

RISK FACTOR CHANGE IN MIDDLE AGES: THE ARIC STUDY

Frederick Brancati, M.D., M.H.S., Professor of Medicine and Epidemiology, Director, Division of General Internal Medicine, Johns Hopkins University, Baltimore, Maryland

Dr. Brancati provided an historical perspective on the causes of T2D and results from the Nurses' Health Study (NHS) and Physicians' Health Study (PHS) that indicated that BMI and physical activity are associated strongly with T2D (slides 2-4). His presentation focused on emerging risk factors and the Atherosclerosis Risk in Communities Study (ARIC) (slides 5-7). Dr. Brancati noted that BMI or adiposity are key risk factors for T2D, although other risk factors also are important.

Data on food constituents and lifestyle choices indicate that some may modify T2D risk. For example, high intake of cereal fiber and coffee, high levels of serum magnesium, alcohol use among women, and low caloric intake in general may lower the risk of T2D; high intake of saturated fat, monounsaturated fat, alcohol use in men, smoking tobacco, high C-reactive protein (CRP) levels, and a high inflammation score may increase the risk of T2D (slides 8-17). In the

NHS, the odds ratio (OR) of incident diabetes among women with high CRP levels and aspirin use was lower than among women with high CRP levels and nonaspirin use (slide 18). Lower risk also is indicated by higher adiponectin levels, as seen in the European Prospective Investigation into Cancer and Nutrition (EPIC) study (slide 20).

Dr. Brancati commented that, in the Diabetes Prevention Program, the screening eligibility committee eliminated participants who were taking medications that might lead to a T2D phenotype. This included those on HIV retroviral therapy, oral or inhaled steroids, and certain antipsychotic medications (slides 21-23). In addition, possible participants on antihypertension medication (i.e., beta-blockers) also were eliminated (slides 24-25). Another lesser known risk factor for T2D may be unexplained aminotransferase elevation, which has been shown in National Health and Nutrition Examination Survey (NHANES) data to be a strong predictor of risk of T2D (slides 26-28).

Intriguing associations between anthropomorphic measures and diabetes have been reported. To illustrate, although the lung generally is not considered an organ that is involved in diabetes complications, a study of fasting and 2-hour insulin levels and an Apnea-Hypopnea Index (AHI) in overweight adults found that insulin levels increased with elevated AHI (slide 29). In addition, a recent analysis of ARIC data found that middle-aged women in the lowest quartile of forced vital capacity had double the risk of incident diabetes compared to those in the highest quartile (slide 30). An analysis of NHANES III data also found a possible association between IGT and T2D and upper leg length (slide 31). Finally, the Barker hypothesis, which asserts an association between various medical conditions and birth weight, appears to suggest that low birth weight is associated with incident diabetes in middle age, even in leaner Chinese adults (slides 32-33).

Dr. Brancati completed his presentation by showing retinal photographs in ARIC in year 6 that indicated that, the smaller the artery diameter compared to the vein in the retina, the higher the risk of diabetes and coronary heart disease and stroke (slides 34-35). In addition, analysis of ARIC data on whole blood viscosity (WBV) indicated that higher viscosity is associated with the risk of diabetes (slide 36).

In conclusion, Dr. Brancati cautioned that the data presented came primarily from prospective studies and would need to be tested in intervention studies to determine if they are associated with diabetes or the risk of diabetes.

A participant commented that, when he speaks to the media after a study shows a new association of dietary or anthropomorphic measures and diabetes, he likes to emphasize that there are long-known risks for diabetes that are more powerful than what is being reported in the media. Dr. Brancati responded that it is important to keep to the public health message of risks that are well known, but we should not disregard strategies that may work for some individuals. Another participant asked Dr. Brancati to comment on the impact of weight change on diabetes. Dr. Brancati responded that weight loss, on the order of 5 to 7 percent of body weight, is achievable and has been proven to have a significant impact on diabetes prevention. There are,

however, bariatric surgery studies in which some individuals lost 30 to 40 kilograms and glucose normalized or dropped precipitously.

RISK FACTORS IN PIMA INDIANS: LESSONS FROM THE PIMA INDIANS
Jonathan Krakoff, M.D., Phoenix Epidemiology and Clinical Research Branch, NIDDK, Phoenix, Arizona

Dr. Krakoff described the Pima Indian population in the Gila River Indian Community and diabetes risk factors in those under 20 years of age. Diabetes in Pima Indians exclusively is T2D, and all data shown reflected this status. The prevalence of diabetes in Pima youth increased dramatically in all age groups from 1965 until 2002 (slide 4). In those exposed to diabetes *in utero*, the prevalence of diabetes among 15- to 19-year-olds was extremely high, approaching one in four, with an OR of approximately 3.5 calculated for offspring exposed to diabetes *in utero* compared to their siblings born prior to the mother having developed diabetes. (slides 5-7).

Dr. Krakoff presented unpublished data on risk factors for developing T2D in more recent cohorts of children in a longitudinal study. The cohorts were first examined at ages 5 to 9, 10 to 14, and 15 to 19 years (slides 7-11). In the younger cohort (age 5-9 years), waist circumference was the most powerful predictor of T2D; in the 10 to 14 and 15 to 19 year age groups, 2-hour glucose and fasting insulin appeared to be the most powerful predictors. It is interesting that fasting glucose did not appear to be a powerful predictor in any group. Receiver Operating Characteristic (ROC) curves of this data confirmed these findings (slide 12).

Studies of IGT and conversion to diabetes suggest that age is the predominant indicator of risk; populations with a high diabetes prevalence risk tend to form a "U" shaped curve, whereas populations with a lower diabetes prevalence risk tend to undergo conversion to IGT at a steady increased rate with age (slides 14-15). Comparing the progression from IGT to diabetes between adults and youth (age less than 20 years) showed that progression in youth is approximately one-half that of young adults (slide 16). This remained valid in the data for 2-hour glucose and BMI, even when adjusted for multiple variables (slides 17-19). The one variable that equalized the risk of progression from IGT to diabetes among adults and youth was accounting for their *in utero* exposure to diabetes (slide 20-21).

Dr. Krakoff presented data on risk factors for diabetes in young adults with normal glucose regulation, defined as individuals with both a 2-hour glucose measure of less than 140 mg/dl and a fasting glucose of less than 100 mg/dl (slide 22). Analysis in this cohort of Pima Indians who were euglycemic at baseline and underwent extensive physiologic testing indicated that the most important diabetes risk factor predictors were insulin resistance and acute insulin response (slides 23-24).

A possibly important surrogate for assessing the risk of diabetes is adiponectin (slide 25). Adiponectin is secreted by adipocytes, but lower levels are seen in obese individuals and in those with insulin resistance. In a cohort of individuals from the longitudinal study with normal

glucose regulation and matched for BMI, age and sex, adiponectin was a better predictor of the development of diabetes (slides 26-27) than traditional risk factors or other inflammatory markers.

Dr. Krakoff summarized the results of the investigations presented on youth and diabetes risk factors. The best early predictor of T2D is waist circumference among youth age 5 to 9 years and the 2-hour glucose test for those age 10 to 19 years. Among euglycemic young adults, insulin resistance and acute insulin response are key predictors, and hyperinsulinemia and adiponectin also are important (slide 29). For targeting prevention efforts among youth, these early risk factors are important for reducing the burden of disease among Pima youth and young adults (slide 30).

Dr. Spiegel asked if there is a mechanistic basis for the impact of *in utero* exposure and diabetes risk. Dr. Krakoff said it is a complicated issue that is in the early stages of investigation, and no clear etiology has been determined. He added that the data on acute insulin response indicate that an early beta-cell defect may influence this process. He also clarified that the definition of diabetes in these studies did not include gestational diabetes.

THE INDIAN HEALTH SERVICE: PERSPECTIVE ON RISK MANAGEMENT

Charlton Wilson, M.D., F.A.C.P., Associate Director, Phoenix Indian Medical Center, Indian Health Service, Phoenix, Arizona

Dr. Wilson presented information on diabetes risk management from the perspective of American Indian and Alaska Native (AI/AN) populations (slide 1). The AI/AN population is very young; approximately 11 percent of the AI population is older than 55 years of age, which is one-half of the proportion of the general U.S. population that is age 55 years or older (slide 4). Between 1990 and 2001, the prevalence of T2D increased 106 percent in those 15 to 19 years of age and 79 percent among those 25 to 34 years of age (slide 5). During this time period, data from ARIC and the Strong Heart Study (SHS) indicated that the incidence of heart disease increased in the AI/AN populations to become more common than the incidence of heart disease in the general U.S. population (slide 6). This is a troubling statistic given that, in the past, heart disease was not found in the AI population. Much of the increase in CVD seems to have come from the increase in diabetes. SHS data indicate that coronary heart disease is attributable to diabetes in approximately 76 percent of women and 61 percent of men (slide 7). Thus, managing risk factors for diabetes and cardiovascular disease (CVD) is of great importance to the U.S. Indian Health Service (IHS).

For many years, the U.S. Indian Health Service (IHS) has defined Standards of Care for people with diabetes and has conducted Diabetes Care and Outcome Audits to evaluate the care provided and outcomes attained in IHS programs (slides 8-10). In April 2005, a panel of experts was convened to gather the best available evidence on standards of care (IHS Guidelines for Care of Adults with Prediabetes and/or Metabolic Syndrome in Clinical Settings) that can be used to address the issues of prediabetes and management of people at risk for diabetes. A full

PDF version of the report is available at: http://www.ihs.gov/medicalPrograms/diabetes/resources/2005NDPPreDMMetsynGuidelines042605.pdf#search='IHS%20Guidelines%20for%20Care%20of%20Adults%20with%20Prediabetes%20and%2For%20Metabolic%20Syndrome%20in%20Clinical%20Settings'. One of the main controversies in establishing Standards of Care involved how to address people who had the Metabolic Syndrome. Data from the SHS indicated that insulin resistance and the Metabolic Syndrome are comparable risk factors for the development of diabetes (slide 12). The data also indicated that these risk factors are poor predictors of CVD independently of diabetes. Combined with the strong attributable risk conveyed by diabetes on the development of CVD, this suggests that prediabetes and the Metabolic Syndrome are strong predictors of diabetes and that, in turn, diabetes predicts the development of CVD (slide 13). Thus, a major focus of the Prediabetes and/or Metabolic Syndrome standards of care is the prevention of diabetes.

Dr. Wilson presented a list of factors included in the IHS guidelines for testing for prediabetes (slides 14-15). In the absence of risk factors in the AI population, the guidelines also suggest testing every 3 years in those over age 45 years. A Letter to the Editor will appear in an upcoming issue of *Diabetes Research and Clinical Practice* and will outline the approach for developing these guidelines (slide 15).

The IHS has assessed the use of screening programs to identify those with diabetes. Dr. Wilson presented data from a survey that asked clinical programs if they screen for diabetes and prediabetes and if they keep a registry of individuals in each category (slide 18). In 2004, much of the screening occurred in community programs and involved glucose meter tests. Paper and pencil checklists of risk factors were used less frequently (slide 19). Data also show that children and youth are being screened, but not at the same rate as older adults (slide 20). The IHS Competitive Grant Program is applying a model of the Diabetes Prevention Program in 33 AI/AN communities and is applying a model of case management in addressing the goal of lowering blood pressure and lipid values in people with known diabetes (slide 21). An evaluation will be conducted to ascertain how well research findings are being translated into clinical practice.

As in many communities, important unanswered questions about diabetes exist in the AI/AN community. These include (slides 22-23):

- Is CVD always preceded by diabetes, and will those factors that affect diabetes (e.g., weight reduction) result in changes in CVD?
- Can risk factors be assessed easily in community settings?
- Are there critical intervention periods?
- What is the value of risk factor modification vs. early case detection?

THE MINNESOTA PROJECT ON RISK FACTORS

Rudolph Valdez, Ph.D., Epidemiologist, Division of Diabetes Translation, Centers for Disease Control and Prevention, Atlanta, Georgia

Via teleconference, Dr. Valdez presented information on the study design and data management of the Collaborative Study of Obesity and Diabetes in Adults (CODA) (slides 1-5). Study selection was made by CODA investigators for meta-analyses of relevant studies; 34 studies were identified for CODA-1, a meta-analysis of studies containing data on obesity and diabetes. The CODA data management team at the University of Minnesota received original data sets from investigators for the 34 relevant studies. Dr. Valdez provided a list of population-based cross-sectional studies and cohort studies that comprised the CODA-1 meta-analyses (slides 6-7). A total population of approximately 270,000 study participants was available for these analyses.

Dr. Valdez presented results of the CODA-1 meta-analysis for the OR of patients with newly diagnosed diabetes using American Diabetes Association (ADA) criteria by risk factor. For BMI and waist circumference, all but one of 31 studies reported an OR greater than 1.0 (slides 8-9). There was significant heterogeneity among the studies. For incident cases of diabetes among individuals who attended a screening, did not report that they had been diagnosed with diabetes, but were assessed as meeting the ADA criteria for diabetes, the relative risk (RR) with BMI and waist circumference was approximately 2.0 (slides 10-11). A pooled estimate of incident cases of diabetes for BMI (RR = 1.8) and waist circumference (RR = 2.1) indicates that both are strong predictors of diabetes (slide 12). Over a 10-year period, there was a continuous increase in risk among both men and women by BMI and waist circumference at baseline (slides 13-14).

ROC curves for BMI and waist circumference also indicate that diabetes can be predicted by BMI and waist circumference (slides 15-16). The area under the ROC curve for BMI is larger for men (0.73) than for women (0.64); for waist circumference, it is 0.72 for men and 0.65 for women. This indicates that both anthropomorphic measures are good predictors of diabetes in both men and women (slide 17). In the pooled analyses of incident diabetes relative to BMI and waist circumference independently by sex, the RR for both measures for men and women was similar (slide 18). The same data assessed for age group indicated a small increase in risk with age, with the increase in men being slightly higher than in women.

Dr. Valdez summarized these finding by stating that waist circumference is a somewhat better predictor of incident diabetes than BMI, but both appear to offer substantial predictive value. The CODA data will continue to be analyzed, and it is expected that additional findings will be published during the next few years.

AMERICAN DIABETES ASSOCIATION: ADA AND RISK FACTOR MANAGEMENT

Nathaniel Clark, M.D., M.S., R.D., National Vice President for Clinical Affairs, American Diabetes Association, Alexandria, Virginia

Dr. Clark presented an update on ADA activities that have occurred or are ongoing regarding risk factor management and prevention of T2D (slide 1). The ADA has published a list of T2D

risk factors that has been used by clinicians, and included in the ADA Standards of Care (slides 2-3). The purpose of the list is to make patients and professionals aware of the risk factors so that they can focus on prevention and treatment among high-risk individuals. Dr. Clark reviewed results of the Diabetes Prevention Program (DPP), a randomized diabetes prevention clinical trial that indicated a 58 percent reduction in diabetes through lifestyle changes and a 31 percent reduction in diabetes with the use of metformin (slides 4-5). These findings led to a series of meetings to develop recommendations to delay or prevent diabetes. The recommendations included the following (slides 6-8):

- Individuals at high risk need to understand the benefits of weight loss and exercise.
- Consider screening if a person is over age 45 years, particularly if BMI is equal to or greater than 25 kg/m^2.
- Consider screening at younger ages if BMI is equal to or greater than 25 kg/m^2 and additional risk factors are present.
- If normoglycemia, rescreen at 3-year intervals.
- Recommendations for screening include making it a part of the regular health care visit; use either fasting plasma glucose (FPG) or 2-hour post-glucose load; confirm positive findings on another day; if pre-diabetes is confirmed, screen for diabetes every 1 to 2 years.
- Interventions should include counseling on weight loss and increased physical activity in these overweight or obese; followup counseling; treatment of other CVD risk factors (e.g., tobacco, high blood pressure, dyslipidemia); and the use of drug therapy only when lifestyle modifications have been tried and further intervention is required.

Dr. Clark described the FPG criteria as Normal (less than 100 mg/dl), Impaired (IFG = 100-125 mg/dl), and Diabetes ($\geq$ 126 mg/dl) (slide 9). ADA categories for 2-hour oral glucose tolerance test (OGTT) plasma glucose levels include Normal (less than 140 mg/dl), Impaired (IGT – 140-199 mg/dl), and Diabetes ($\geq$ 200 mg/dl) (slide 10). Pre-diabetes affects approximately 41 million Americans and significantly increases the risk of developing overt diabetes as well as the risk of CVD, and diagnosis can be made either by IFG or IGT (slide 11).

Dr. Clark summarized the impact of changing the definition of diabetes from 110 mg/dl to 100 mg/dl, which took place a few years ago (slide 12). Under the old definition, the greatest number of individuals diagnosed had elevated IFT, with smaller numbers having IFG or IFG and IFT. Using the old definition, the number of people with pre-diabetes was approximately 20 million. Under the new definition, most people have IFG, with smaller numbers having IFT or IFG and IFT. This has practical consequences for prevention and treatment.

The prevalence of diabetes in the United States is increasing as the prevalence of obesity increases (slides 13-14). This has led to a new organization established by the ADA, "Shaping America's Health: Association for Weight Management and Obesity Prevention," a collaboration between the ADA, North American Association for the Study of Obesity (NAASO), and Shaping America's Youth (SAY) (slides 15-17). The collaboration will address scientific issues by the developing clinical guidelines and holding conferences on the science and medicine of overweight and obesity (slide 18). Medical education issues will include community

action activities coordinated by the ADA with SAY, and town meetings to discuss community mobilization and to share "best practices."

Dr. Clark presented information on the progression to T2D (slides 19-20). The question of measuring insulin levels comes about as the diagnosis of T2D does not often occur until 9 to 12 years after diabetes actually begins. In theory, tracking insulin levels over time may allow interventions early in the process to prevent T2D. A significant concern exists that clinicians are now ordering insulin levels and making clinical decisions based on these results despite the fact that the assay is not now standardized and there are no guidelines available regarding how to interpret the insulin level result. The Insulin Assay Standardization Work Group of the ADA is exploring the first part of this issue. (slide 21). The purpose of this work group is to devise protocols to determine the reproducibility and specificity of each assay. Most manufacture's of insulin assays have participated and provided assayed samples. Recommendations will be published that describe criteria that assays must meet to be "insulin specific," and a clinical advisory group will be formed to recommend how insulin assays should be used in clinical practice.

DISCUSSION: WHERE DO WE GO FROM HERE?

Dr. Fradkin asked if participants would comment on the issue of measuring glucose. A participant asked if any test is better than another in this regard. Dr. Clark responded that this has not been determined. Having a test or series of tests that could lead to the development of a risk equation such as Framingham would be helpful, but no such protocol exists at this time. A series of participants spoke about the need to develop a clear direction on this issue.
Dr. Savage mentioned that while DMI is clearly useful, adding insulin to this mix may cause confusion rather than create benefit. Another participant added that what is known does not apply to all populations.

Dr. Fradkin asked if there is a consensus that BMI and waist circumference are strong enough predictors that there is no need for a risk equation such as that used with Framingham data for heart disease. Dr. Brancati responded that, in the past, when the population has a healthier BMI, there was little T2D. As obesity becomes more prevalent, it may be important to find a way to better identify those at higher risk. Dr. Liu added that we do not know how to shift the entire population to a lower risk level, such as through weight control or reduction. Education is important, but there may be a need to lower the cutpoints for intervention if insulin resistance is present. Dr. Leonard Pogach said that current guidelines allow for lower cutpoints for the use of pharmacological interventions. Another participant outlined the manner in which intervention is recommended in the NHLBI obesity guidelines. If a person has a certain BMI without comorbidities, the clinician is requested to treat him or her differently than a person with the same BMI who has comorbidities. These guidelines recognize that treatment should be started earlier for the latter group.

Dr. Fradkin asked participants to comment on the Diabetes Prevention Program (DPP) trial and the endpoints that should be developed for diabetes prevention. Dr. Brancati commented that DPP was very expensive and was designed to create a proof-of-principle on weight loss and

diabetes prevention. It was a highly select group of people and was not designed to reveal everything about preventing diabetes in all people. Dr. Pogach said that DPP was successful in showing some things, but it did not show how to change society using social factors. Several participants commented that, when you have a common problem that affects multiple risk factors that in the aggregate are responsible for a large percentage of the chronic diseases in this country, several models that address all interventions are needed.

Dr. Fradkin asked for input on the prevention of diabetes risk factors in children. Participants commented on the importance of addressing risk factors in children, and weight maintenance appeared to be the initial area of concentration. Dietary advice and intervention can have a positive impact in children and adolescents, although it is likely that one set of dietary guidelines will not be appropriate for all children in all settings.

ADJOURNEMENT

Dr. Fradkin thanked the speakers, DMICC members, and guests for attending the meeting and participating in the discussions. She adjourned the meeting at 3:40 p.m.