The Diabetes Prevention Program

Design and methods for a clinical trial in the prevention of type 2 diabetes

THE DIABETES PREVENTION PROGRAM RESEARCH GROUP

The Diabetes Prevention Program is a randomized clinical trial testing strategies to prevent or delay the development of type 2 diabetes in high-risk individuals with elevated fasting plasma glucose concentrations and impaired glucose tolerance. The 27 clinical centers in the U.S. are recruiting at least 3,000 participants of both sexes, ~50% of whom are minority patients and 20% of whom are ≥65 years old, to be assigned at random to one of three intervention groups: an intensive lifestyle intervention focusing on a healthy diet and exercise and two masked medication treatment groups—metformin or placebo—combined with standard diet and exercise recommendations. Participants are being recruited during a 2 2/3–year period, and all will be followed for an additional 3 1/3 to 5 years after the close of recruitment to a common closing date in 2002. The primary outcome is the development of diabetes, diagnosed by fasting or post-challenge plasma glucose concentrations meeting the 1997 American Diabetes Association criteria. The 3,000 participants will provide 90% power to detect a 33% reduction in an expected diabetes incidence rate of at least 6.5% per year in the placebo group. Secondary outcomes include cardiovascular disease and its risk factors; changes in glycemia, β-cell function, insulin sensitivity, obesity, diet, physical activity, and health-related quality of life; and occurrence of adverse events. A fourth treatment group—troglitazone combined with standard diet and exercise recommendations—was included initially but discontinued because of the liver toxicity of the drug. This randomized clinical trial will test the possibility of preventing or delaying the onset of type 2 diabetes in individuals at high risk.

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Type 2 diabetes is a common chronic disease affecting an estimated 12% of 40- to 74-year-old people in the U.S. (1). It is a major cause of premature mortality and morbidity due to cardiovascular, renal, ophthalmic, and neurologic diseases. Although treatment of type 2 diabetes can improve hyperglycemia, normalization of glycemia and glycohemoglobin is rarely achieved or maintained. Furthermore, macrovascular disease and its risk factors are often already present in individuals at high risk of developing type 2 diabetes (2). Therefore, a policy of prevention rather than early detection and treatment of diabetes might be more effective in preventing microvascular and macrovascular complications.

People with impaired glucose tolerance (IGT), an intermediate category between normoglycemia and diabetes (1,3), defined by an oral glucose tolerance test (OGTT) are at increased risk of developing diabetes. The Diabetes Prevention Program (DPP) was developed to compare several strategies to prevent or delay type 2 diabetes in individuals with IGT.

RESEARCH GOALS

Primary

The primary research goal is a comparison of the efficacy and safety of each of three interventions (an intensive lifestyle intervention or standard lifestyle recommendations combined with metformin or placebo) in preventing or delaying the development of diabetes. Diabetes is diagnosed by fasting plasma glucose (FPG) or glucose tolerance testing according to the 1997 American Diabetes Association (ADA) criteria (1).

Secondary

Secondary research goals include assessing differences between the three treatment groups in the development of cardiovascular disease and its risk factors; changes in glycemia, β-cell function, insulin sensitivity, obesity, physical activity, nutrient intake, and health-related quality of life; and occurrence of adverse events.

Subgroup research goals

Other research goals include assessing the consistency of the effects of the interventions by baseline demographic, clinical, biochemical, and psychosocial attributes.

STUDY DESIGN

Eligibility criteria

An aim of recruitment is for at least half of the study group to be women, ~20% to be ≥65 years old, and approximately half to be composed of the following ethnic minorities: African-American, Hispanic American Indian, Asian American, and Pacific Islander.

The inclusion and exclusion criteria for the trial are summarized in Table 1. They were based on the goals of *1*) recruiting nondiabetic individuals with a high risk of progression to type 2 diabetes and 2) excluding individuals with conditions that might increase the risk of adverse effects from the interventions, severely shorten life expectancy, interfere with the conduct of the trial, or affect the assessment for incident type 2 diabetes.

The main entry criterion is IGT based on a single 75-g OGTT. Eligible individuals must have no prior diagnosis of diabetes (other than during pregnancy), be nondiabetic by 1997 ADA and 1985 World Health Organization (WHO) criteria, and have IGT: FPG <126 mg/dl (7.0 mmol/l) and 2-h post-load plasma glucose ≥140 mg/dl (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l) (1,3). In addition, to include individuals at

A complete list of the members of the Diabetes Prevention Program Research Group and their professional affiliations can be found in APPENDIX 2.

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Abbreviations: ADA, American Diabetes Association; DPP, Diabetes Prevention Program; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; OGTT, oral glucose tolerance test; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Inclusion and exclusion criteria*

- Inclusion
  - Age ≥25 years
  - BMI ≥24 kg/m² (≥22 kg/m² among Asian Americans)
  - IGT (2-h plasma glucose 140–199 mg/dl based on 75-g OGTT)
  - Elevated FPG (95–125 mg/dl*), except in the American Indian centers
- Exclusion
  - Diabetes at baseline
    - FPG ≥126 mg/dl*
    - 2-h plasma glucose ≥200 mg/dl based on 75-g OGTT
    - Diabetes diagnosed by a physician and confirmed by other clinical data, other than during pregnancy
    - Ever used antidiabetic medication, other than during pregnancy
  - Medical conditions likely to limit life span and/or increase risk of intervention
    - Cardiovascular disease
      - Hospitalization for treatment of heart disease in past 6 months
      - New York Heart Association Functional Class >2
      - Left bundle branch block or third degree AV block
      - Aortic stenosis
      - Systolic blood pressure >180 mmHg or diastolic blood pressure >105 mmHg
    - Cancer requiring treatment in the past 5 years, unless the prognosis is considered good
    - Renal disease (creatinine ≥1.4 mg/dl for men, or ≥1.3 mg/dl for women, or urine protein ≥2+)†
    - Anemia (hematocrit <36% in men or <33% in women)
    - Hepatitis (based on history or serum transaminase elevation)
    - Other gastrointestinal disease (pancreatitis, inflammatory bowel disease)
    - Recent or significant abdominal surgery
    - Pulmonary disease with dependence on oxygen or daily use of bronchodilators
    - Chronic infection (e.g., HIV, active tuberculosis)
  - Conditions or behaviors likely to affect conduct of the trial
    - Unable to communicate with clinic staff
    - Unwilling to accept treatment assignment by randomization
    - Participation in another intervention research project that might interfere with DPP
    - Weight loss of >10% in past 6 months for any reason except postpartum weight loss
    - Unable to walk 0.25 miles in 10 min
    - Pregnancy and childbearing
      - Currently pregnant or within 3 months postpartum
      - Currently nursing or within 6 weeks of having completed nursing
      - Pregnancy anticipated during the course of the trial
      - Unwilling to undergo pregnancy testing or report possible pregnancy promptly
      - Unwilling to take adequate contraceptive measures, if potentially fertile
    - Major psychiatric disorder
    - Excessive alcohol intake, either acute or chronic
  - Medications and medical conditions likely to confound the assessment for diabetes
    - Thiazide diuretics
    - β-Blockers, systemic
    - Niacin, in doses indicated for lowering serum triglycerides
    - Glucocorticoids, systemic
    - Selective serotonin re-uptake inhibitors in doses indicated for weight reduction
    - Other prescription weight-loss medications
    - Thyroid disease, suboptimally treated as indicated by abnormal serum thyroid-stimulating hormone
    - Other endocrine disorders (e.g., Cushing's syndrome, acromegaly)
    - Fasting plasma triglyceride >600 mg/dl, despite treatment

*WHO criteria (3) were used to exclude diabetes (FPG ≥140 mg/dl or 2-h plasma glucose ≥200 mg/dl) until June 1997, and the FPG inclusion range was 100–139 mg/dl. †Since March 1998, a creatinine clearance of ≥75 ml/min, based on a 24-h urine collection, was required for eligibility for potential volunteers who were or would become ≥80 years of age during the study.

particularly high risk of diabetes, the FPG must be 95–125 mg/dl. However, there is no lower eligibility limit for FPG in the clinical centers enrolling only American Indians because they have an unusually high risk of type 2 diabetes even at lower levels of FPG (4).

The DPP began before the release of the new ADA diagnostic criteria in June 1997. The 1985 WHO criteria for IGT used for DPP eligibility at that time required an FPG <140 mg/dl (7.8 mmol/l) and 2-h post-load plasma glucose ≥140 mg/dl and <200 mg/dl (3). An additional DPP requirement was for the FPG to be 100–139 mg/dl. Only 7% of those enrolled in the DPP before this change in eligibility criteria would have been ineligible by the new criteria because of FPG ≥126 mg/dl but <140 mg/dl. These participants remain in the DPP, but their outcome assessment of diabetes will be done with the new criteria (1).

Although most recruitment is directed at overweight individuals aged ≥35 years, the age criterion was set at ≥25 years to include groups at high risk for type 2 diabetes in early adulthood, such as American Indians and young women with a history of gestational diabetes (4). The BMI criterion is ≥24 kg/m² because individuals with lower BMIs are at a lower risk for type 2 diabetes and may not be suitable candidates for the weight-loss goals of the interventions. The BMI criterion was set at ≥22 kg/m² for Asian Americans because of their high risk of diabetes at this range of BMIs (5).

Most exclusion criteria were chosen to reduce the risk of adverse effects related to the interventions. Individuals with clinically significant ischemic heart disease (defined in Table 1), aortic stenosis, or uncontrolled hypertension are excluded because the intensive lifestyle intervention requires increased physical activity. Individuals with renal insufficiency or congestive heart failure are excluded because of their increased risk of lactic acidosis with metformin (6,7). Also excluded are pregnant or nursing women, as well as women who anticipate pregnancy during the course of the program, because metformin has not been shown to be safe during pregnancy or nursing.

Thiazide diuretics and β-blockers are commonly used to treat hypertension (8), which often coexists with IGT. Because these agents may cause IGT (9–13), individuals using thiazides or β-blockers on a daily basis are ineligible. Such individuals may be included if they meet glycemic and other eligibility criteria after their treatment is changed to other antihypertensive drugs

Table 2—*Staged screening process for determination of eligibility*

Step	Assessment	Comments
1	Prescreening questionnaire	Initial assessment for eligibility by telephone
	Single glucose measurement	Fasting or casual, in the field or at the clinic
2	Interview	Definitive assessment of age, medical history, medication use
	Physical measurements	Assess BMI and blood pressure
	OGTT	FPG 95–125 mg/dl and 2-h plasma glucose 140–199 mg/dl
	Other laboratory assays	Liver function tests, electrolytes, serum creatinine, plasma triglycerides, complete blood count, thyroid-stimulating hormone, urinalysis
3	Run-in/behavioral trial	3-week trial of compliance with pill taking and recordkeeping
	Clinical evaluation	History and physical examination
	Electrocardiogram	Assessed for acute ischemia or dysrhythmia
4	Serum human chorionic gonadotropin	Rule out pregnancy
	Review eligibility checklist	If eligible, then randomize

without known adverse effects on glucose metabolism.

Recruitment

Clinic-specific recruitment strategies appropriate for the identified target populations include use of mass media, mail, and telephone contacts and recruitment through employment or social groups or health care systems. Recruitment workshops were held for the DPP investigators and staff to share information and assistance on recruitment, interpersonal skills and cultural sensitivity, effective transmission of information, methods for developing support systems for problem solving, and clinic-specific recruitment methods. Procedures were developed to monitor recruitment and provide a timely response to problems.

Participant recruitment began in June 1996, after completion of the protocol and manual of operations and approval by the DPP Steering Committee, the external Data Monitoring Board, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Food and Drug Administration. Recruitment is anticipated to end ~2 2/3 years after this date, in the first half of 1999. Treatment and follow-up of all participants are planned to continue until the middle of 2002.

Staged screening process and informed consent

A four-step combined screening, recruitment, and informed consent process provides increasing amounts of information about the DPP to participants as they progress through recruitment and screening (Table 2). Each step in the informed consent process includes verbal and written descriptions of relevant information and opportunity for discussion of questions from the volunteer, facilitating a decision of whether to proceed to the next step. A 3-week run-in, or practice, period is included in step 3 to give prospective participants a trial of compliance with pill taking (placebos only) and keeping records of diet and physical activity.

Data directly related to eligibility determination and baseline data are collected during the screening process. The staged screening process minimizes the data collection burden on potential participants and clinic staff by placing simpler, less expensive assessments (e.g., a 10-min telephone interview) earlier in the screening process, while more complex assessments are done later. A participant must complete all the components of step 1 and be judged potentially eligible before moving on to step 2, etc. In contrast, progress within each step is flexible, e.g., a participant at step 3 may schedule the clinical evaluation and electrocardiogram (Table 2) at his or her convenience. To maintain participant interest and minimize the likelihood of changes in health during baseline assessment, yet to give potential volunteers time to consider participation in an informed fashion, a window of 3–13 weeks is allowed from the OGTT in step 2 to randomization at step 4.

Outcomes

Primary outcome. The primary outcome of the DPP is the development of diabetes by the 1997 ADA criteria for FPG or 2-h plasma glucose during an OGTT (1). Although the eligibility criteria were selected to identify individuals at high risk of type 2 diabetes, a small proportion of individuals recruited into the DPP may be in the early stages of development of type 1 diabetes (14) or other specific forms of diabetes (1). It is not feasible to identify all such individuals at entry. Therefore, the primary outcome is defined as diabetes of any type.

Diabetes is assessed by testing FPG every 6 months and performing an annual 75-g OGTT. FPG is also measured whenever symptoms consistent with diabetes are noted (e.g., polyuria, polydipsia, or polyphagia). These tests are performed without interruption of the assigned treatment except that study drugs are omitted the morning of the test. If the FPG or OGTT results meet the 1997 ADA criteria for diabetes (i.e., either FPG ≥126 mg/dl or 2-h plasma glucose ≥200 mg/dl), a second FPG or OGTT is performed within 6 weeks. If both tests are diagnostic of diabetes, the participant is considered to have reached the primary outcome. Otherwise, the participant will continue on the assigned treatment. To maintain masking, a subset of participants chosen at random by the Coordinating Center has a repeat annual OGTT or semiannual test. The annual OGTT and semiannual FPG are postponed for up to 6 weeks in case of a temporary condition that could affect glucose tolerance. Participants who become pregnant during the study will have outcome assessment suspended until 6–8 weeks after delivery, when an OGTT is performed. To insure standardized assessment of outcomes, any antidiabetic medication initiated during pregnancy is stopped before the OGTT. If this is not possible, two elevated FPG determinations may be used to define diabetes in place of the OGTT. Investigators and participants remain masked to primary outcome data until progression to diabetes is confirmed.

If the primary outcome of diabetes occurs, participants, DPP investigators, and primary care providers are unmasked to the diagnosis and to subsequent measurements of plasma glucose and HbA_{1c}. For those participants in whom FPG is <140 mg/dl, all study-related oral glucose

tolerance testing is terminated, participants continue to be followed with FPG at semiannual visits, original treatment recommendations are reinforced, coded medication is continued if the participant and his/her physician agree, monitoring is intensified, and self-monitoring of blood glucose is introduced, with the goal of achieving optimal glycemic control (15). In the event that participants progress to FPG ≥140 mg/dl on two occasions, study medicines are discontinued and patients are referred for appropriate diabetes care (15) independent of the study protocol. Participants continue to be followed at scheduled intervals to collect other outcome data, including FPG at semiannual visits.

Secondary outcomes. The secondary outcomes include cardiovascular risk profile and disease; changes in glycemia, β-cell function, insulin sensitivity, renal function, body composition, physical activity, and nutrient intake; and health-related quality of life. Safety and health economics are also monitored. Mortality and morbidity, including cardiovascular events, are monitored throughout the study, and the following parameters are evaluated at specified intervals.

Glycemia. In addition to plasma glucose measured during the OGTT, HbA_{1c} is monitored to reflect recent average glycemia, to test its relationship to the OGTT, and to assess its predictive value for diabetes. Specific secondary outcomes will include the development of fasting hyperglycemia at a level of ≥140 mg/dl (7.8 mmol/l), i.e., a level greater than that required for diagnosis of diabetes, and improvement in glucose tolerance to normal.

β-Cell function and insulin sensitivity. β-Cell function is estimated from the fasting and 30-min plasma insulin and glucose during the OGTT and from the fasting plasma proinsulin. Fasting plasma insulin is used as a surrogate for insulin sensitivity.

Cardiovascular disease risk profile. Cardiovascular risk profile is assessed by cardiovascular history and symptoms, an electrocardiogram, smoking history, hemostatic and fibrinolytic factors (C-reactive protein, fibrinogen, tissue plasminogen activator), and lipoprotein profile, including derived β quantification (full β quantification if triglycerides are >400 mg/dl), LDL particle size, and LDL apolipoprotein-B.

Cardiovascular disease. Disease measures include carotid intimal wall thickness assessed by ultrasonography, arm blood pressure, and ankle:brachial systolic blood pressure.

Kidney function. Urinary albumin and creatinine concentrations in an untimed urine sample are used to determine urinary albumin excretion.

Physical activity, nutrition, and body composition. Two standardized questionnaire assessments (16–18) are used to evaluate the level of physical activity, and a semiquantitative food frequency questionnaire is used to determine nutrient intake (19). Body composition measurements include height, weight, waist and hip circumference, abdominal sagittal diameter, skin-fold thicknesses, and, in a substudy of some participants, abdominal computed tomography scanning for visceral fat content.

Health-related quality of life. The Beck Anxiety and Depression Inventories (20), the Medical Outcomes Study 36-item short form (21), and a social support questionnaire are used to assess mood, general adjustment, and health-related quality-of-life issues.

Health economics. Resource utilization, costs, health utilities, and effectiveness of treatments to prevent diabetes will be determined.

Safety. Periodic safety tests include liver function tests, serum creatinine, complete blood count, and pregnancy testing (as needed), as well as recording of adverse events and interval history.

Lifestyle interventions

Standard lifestyle recommendation. After randomization, all participants (regardless of treatment assignment) receive written information and a 20- to 30-min individual session with their case manager addressing the importance of a healthy lifestyle for the prevention of type 2 diabetes. Specifically, participants are encouraged to follow the Food Pyramid guidelines and to consume the equivalent of a National Cholesterol Education Program step 1 diet (22); to lose 5–10% of their initial weight through a combination of diet and exercise; to increase their activity gradually with a goal of at least 30 min of an activity such as walking 5 days each week; and to avoid excessive alcohol intake. All participants who smoke are encouraged to stop. These recommendations are reviewed annually with all participants.

Intensive lifestyle intervention. The intensive lifestyle intervention is based on previous literature suggesting that obesity and a sedentary lifestyle may both independently increase the risk of developing type 2 diabetes (23). The goals are essentially the same as those of the standard lifestyle recommendation, but the approach to implementation is more intensive.

The goals for the intensive lifestyle intervention are to:

- achieve and maintain a weight reduction of at least 7% of initial body weight through healthy eating and physical activity, and to
- achieve and maintain a level of physical activity of at least 150 min/week (equivalent to ~700 kcal/week) through moderate intensity activity (such as walking or bicycling).

Recognizing the difficulty of achieving long-term changes in eating and exercise behaviors and in body weight, the intensive lifestyle intervention is designed to maximize success by using the following interactive interventions: training in diet, exercise, and behavior modification skills; frequent (no less than monthly) support for behavior change; diet and exercise interventions that are flexible, sensitive to cultural differences, and acceptable in the specific communities in which they are implemented; a combination of individual and group intervention; a combination of a structured protocol (in which all participants receive certain common information) and the flexibility to tailor strategies individually to help a specific participant achieve and maintain the study goals; and emphasis on self-esteem, empowerment, and social support. A Lifestyle Resource Core developed intervention materials and provides ongoing training and support for intervention staff.

The intervention is conducted by case managers with training in nutrition, exercise, or behavior modification who meet with an individual participant for at least 16 sessions in the first 24 weeks and contact the participant at least monthly thereafter (with in-person contacts at least every 2 months throughout the remainder of the program). The initial 16 sessions represent a core curriculum, with general information about diet and exercise and behavior strategies such as self-monitoring, goal setting, stimulus control, problem solving, and relapse prevention training. Individualization is facilitated by use of several different approaches to self-monitoring and flexibility in deciding how to achieve the changes in diet and exercise. All participants are encouraged to achieve the weight-loss and exercise goals within the first 24 weeks. The weight-loss goal is attempted initially through a reduction in dietary fat intake to

<25% of calories. If weight loss does not occur with fat restriction, then a calorie goal is added.

The focus of the exercise intervention is a gradual increase in brisk walking or other activities of similar intensity. Two supervised group exercise sessions per week are provided to help participants achieve their exercise goal, but participants can also achieve the exercise goal on their own and are given flexibility in choosing the type of exercise to perform. Exercise tolerance tests (performed in individuals with preexisting coronary heart disease, and in men aged ≥40 years and postmenopausal women not using hormone replacement therapy who have at least two coronary heart disease risk factors) are used to modify the individual's exercise program.

For individuals having difficulty achieving or maintaining the weight-loss or exercise goal, a "tool box" approach is used to add new strategies for the participant. Strategies may include incentives such as items of nominal value. Additional tool box approaches may include loaning aerobic exercise tapes or other home exercise equipment, enrolling the participant in a class at an exercise facility, and use of more structured eating plans, liquid formula diets, or home visits.

Group courses are also offered quarterly during maintenance, with each course lasting 4–6 weeks and focusing on topics related to exercise, weight loss, or behavioral issues. These courses are designed to help participants achieve and maintain the weight-loss and exercise goals.

Adherence to the intervention is determined through monitoring by the case manager, measuring weight at the 6-month assessments, and self-reported physical activity and diet.

Drug interventions

Metformin and its corresponding placebo are the pharmacological treatments. They are started at a dose of 850 mg once daily and increased to 850 mg twice daily. The dosage can be adjusted if necessary because of gastrointestinal symptoms.

Adherence to study medication is assessed by pill counts and a structured interview of pill-taking behavior. A Medication Resource Workgroup was formed to enhance adherence to the medication protocol while promoting retention of participants. This group supports clinic staff, specifically the medication case managers, by providing a communication network for information, training in counseling and assessment skills, problem-solving of individual participant or clinic situations, and ideas for the tool box for medication adherence. Clinic data are reviewed by the workgroup so that patterns of poor adherence to the protocol can be identified early and interventions can be implemented.

Retention

Several potential obstacles to retention have been identified, such as dissatisfaction with randomly assigned treatment, masking of some of the test results, and time commitments. Other barriers include the demands and costs of transportation, parking, and child and elder care, which vary considerably among the target populations. Steps to maximize retention are based on recognizing these barriers and committing resources for their removal.

Adherence and retention are fostered by a comprehensive array of participant education procedures, which require the interest, responsiveness, and continuous availability of the professional staff, and motivational programs, group activities, and rewards deployed according to the judgment of each clinic. Quarterly newsletters are given to participants to encourage a sense of community within the DPP.

Program and Recruitment Coordinators were trained in motivational interviewing, an approach to changing behavior, based on several basic principles, including skillful reflective listening, expression of empathy, and acceptance of ambivalence (24). Discrepancies are developed by increasing awareness of consequences of behaviors, showing the discrepancy between present behavior and important goals.

Procedures are in place to identify participants whose level of adherence and/or attendance should trigger recovery efforts, as well as a graded hierarchy of recovery efforts. A computer-based monitoring system allows identification of participants having problems with adherence to the protocol and those likely to drop out, thus qualifying for recovery efforts. Questionnaires are administered at baseline, semiannually, and at the end of study for purposes of predicting adherence and retention and determining the positive or negative impact of study interventions.

Since the retention of a large portion of the participants throughout the study is key to the statistical power and validity of the DPP findings, mechanisms are in place to recover those who no longer actively participate. Inactive participants continue to be contacted to remind them of the opportunity to reenter the DPP and to complete the final assessment at the end of the DPP.

Concomitant conditions

Concomitant conditions are defined as medical illnesses or conditions requiring treatment that could affect implementation of the research protocol. Since most clinical centers do not provide all primary or ancillary care, the program assists other health care providers in following guidelines for therapy of concomitant conditions. Treatments that could affect study outcomes are discouraged when appropriate alternate treatments are available. The following conditions were considered: pregnancy, lactation, hypertension, dyslipidemia, smoking, and cardiovascular diseases.

Women of child-bearing potential are asked to practice reliable contraception in view of the unknown risks of the study drugs on the fetus and mother. Safety monitoring includes pregnancy tests and monthly menstrual diaries. Women randomized to the drug treatments (including placebo) who become pregnant while taking medication are unmasked to treatment to allow counseling about the potential effects of the study drugs on the fetus, and study medication is permanently discontinued. For women who want to become pregnant, medication is discontinued until the completion of the pregnancy and nursing; medication is not unmasked.

Standard guidelines for diagnosis and treatment of hypertension in adults (25) are used, except that diuretic agents and β-adrenergic blocking agents are strongly discouraged because they may worsen glucose tolerance (9–13).

The standard and intensive lifestyle intervention diet plans meet the National Cholesterol Education Program standards for dietary management of dyslipidemia (22). At 6 months, 12 months, and annually thereafter, lipid profiles are used to determine whether individuals qualify for lipid-lowering agents. Individuals whose lipid levels during follow-up qualify them for drug therapy based on the guidelines of the National Cholesterol Education Program (22) have reached a DPP secondary outcome. Their lipid levels are unmasked to aid clinical decisions about pharmacotherapy, which will follow these guidelines (22). The use of nicotinic acid is strongly discouraged because it can worsen glucose intolerance (26).

Standard approaches are followed to reduce smoking by discussing its impact on cardiovascular disease and emphasizing the overall health benefits of quitting. Participants are given self-help materials and referred to smoking cessation programs if interested.

Cardiovascular disease incidence is likely to be increased in this population with IGT (27), and these diseases and their treatments may have an effect on DPP study outcomes, or vice versa. Participants who experience new episodes of myocardial infarction, unstable angina, or treatment for coronary heart disease (e.g., percutaneous transluminal angioplasty or coronary artery bypass graft) are eligible to continue following DPP interventions, except for participants randomized to the intensive lifestyle intervention. These participants may not resume their DPP exercise program until risk is estimated by exercise testing, which may result in modification of the exercise program. Patients who develop new-onset angina pectoris during the DPP are referred for appropriate diagnosis and/or interventions, and their exercise program is discontinued until their cardiologic evaluation is complete. Treatment of cardiac patients with β-blockers is not impeded by DPP participation.

Biostatistical considerations

Sample size goal. Several published studies have examined the rates of conversion from IGT to diabetes defined by WHO criteria (3). There were 21 studies identified that allowed computation of the participant-years of follow-up and the incidence rates of diabetes by the person-years of follow-up. Overall, the conversion rates ranged as follows: 2.3 per 100 person-years among Japanese populations, 3 per 100 person-years for Caucasians and Mexican-Americans, 4.7 per 100 person-years for Nauruans, 4.0 per 100 person-years for women with a history of gestational diabetes, and between 10 and 11 per 100 person-years for Asian Indians and Pima Indians (23,28–29). In data from six population-based cohorts provided to the DPP for calculation of conversion rates from IGT to diabetes (4) defined by WHO criteria (3), the overall conversion rate was 5.8 per 100 person-years of follow-up. To decrease the required sample size, a criterion of IGT with elevated FPG was chosen for eligibility in the DPP. For participants with an elevated FPG of 95–125 mg/dl, the conversion rate from IGT to diabetes defined by the ADA criteria (1) was 7.7 per 100 person-years of follow-up in the six studies combined (4). To allow for an additional margin of error, the DPP sample size was based on an expected conversion rate of 6.5 per 100 person-years among participants assigned to the standard lifestyle recommendations plus placebo.

The following assumptions were used to determine the sample size goal:

- The primary outcome is time to the confirmed development of diabetes by ADA criteria (1).
- Participants are uniformly randomized to one of the three treatment groups during a 2 2/3–year period, and all randomized participants are followed for an additional 3 1/3 years after the close of randomization (i.e., follow-up time for each person is between 3 1/3 and 6 years).
- The type I error rate (α) is 0.05 (two-sided) with a Bonferroni adjustment (30) for three pairwise comparisons of the three treatment groups.
- In those assigned to the standard lifestyle recommendation plus placebo, time to the development of diabetes is exponentially distributed with a diabetes development hazard rate of 6.5 per 100 person-years.
- For participants assigned to the intensive lifestyle or metformin intervention groups, the diabetes development hazard rate is reduced by ≥33%, i.e., to <4.33 per 100 person-years.

With these assumptions, the total effective sample size necessary to achieve 90% statistical power is 2,279 participants (31). Assuming that randomized participants prematurely discontinue their follow-up visits before confirmed development of diabetes with an exponential loss hazard rate of ≤10 per 100 person-years, the randomization goal of the DPP is 2,834 participants, which was increased to 3,000 participants (1,000 per group).

Assignment to treatment groups. To ensure balance among the three treatment groups with respect to anticipated differences in the participant populations and possible differences in participant management, adaptive randomization is stratified by clinical center. An adaptive randomization procedure provides a high probability of balance in treatment assignments and is unpredictable by adjusting the treatment group allocation probabilities according to the actual imbalance in the numbers of participants assigned to the groups (32).

Statistical analysis plan. The principal analyses of primary and secondary outcomes will use the intent-to-treat approach (33). The intent-to-treat analyses will include all participants in their randomly assigned treatment group regardless of a participant's adherence to the assigned treatment regimen.

The principal analysis of the DPP will be a life-table analysis of time to confirmed development of diabetes. Separate product-limit life-table estimated cumulative incidence curves will be calculated for each treatment group and the groups will be compared using a log-rank test (34). For the primary outcome analysis, participants will be considered "administratively censored" if they complete the full duration of the DPP without confirmed development of diabetes. Participants who prematurely discontinue their follow-up visits before confirmed development of diabetes will be censored as of their last follow-up visit.

Mortality prior to the development of diabetes may be a competing risk event for the primary outcome (35). To account for mortality as a competing risk event, the treatment groups will be compared on the composite event, defined as confirmed development of diabetes or all-cause mortality, whichever occurs first, using the same methods described above for the primary outcome.

Secondary time to event outcomes (e.g., mortality, cardiovascular morbidity) will be analyzed using the same life-table methods described above for the primary outcome. A proportional hazards regression model will be used to evaluate potential covariables that may modify the primary and secondary time to event outcomes (e.g., risk population defined by race/ethnicity and history of gestational diabetes, baseline fasting and 2-h glucose, clinical site). Graphical procedures will be used to assess the proportionality assumption.

Some processes may involve recurrent events, such as moving back and forth between IGT and normal glucose tolerance. For these recurrent events, the family of statistical models based on the theory of counting processes will be applied (36).

Longitudinal data analysis techniques will be used to analyze repeated measures data (e.g., glycemia, fasting lipids, blood pressure, physical activity, quality of life). These include analyses of the point prevalence of a discrete characteristic (e.g., hypertension) at successive repeated visits over time (37), multivariate rank analyses

of quantitative (2-h plasma glucose during the OGTT) or ordinal (score from the Medical Outcomes Study 36-item short form) measures over successive visits (38), a parametric linear random effects model (39) to compare participant slopes over time (e.g., rate of change in FPG) under a linearity and normality assumption, and techniques to compare participant slopes under a generalized linear models framework (40).

The Lan-DeMets (41) spending function approach will be used to adjust the probability of a type I error for testing the primary outcome when interim looks of the data are taken by the external Data Monitoring Board. The spending function corresponding to an O'Brien and Fleming (42) boundary will be used. The rate at which the type I error is spent is a function of the fraction of total information available at the time of the interim analysis (i.e., information time). For an interim analysis using the log-rank test (i.e., time to confirmed development of diabetes), the information time is the fraction of the total number of confirmed diabetes events to be accrued in the entire DPP. Since the total number of events to be accrued is unknown, an estimate of the information time will be based on the fraction of total participant exposure (43).

MANAGEMENT

Organization

Clinical centers. Each of the 27 participating clinical centers has a Principal Investigator, a Program Coordinator and additional staff to carry out the protocol that may include recruitment coordinators, dietitians, behaviorists, exercise physiologists, physicians, nurses, data collectors, and others.

Coordinating center and central resource units. The Coordinating Center is responsible for biostatistical design, analysis, and data storage and processing. Central resource units include the Central Biochemistry Laboratory, Nutrition Coding Center, Electrocardiogram Grading Center, Carotid Ultrasound Reading Center, Computed Tomography Scan Reading Center, Lifestyle Resource Core, Medication Resource Workgroup, and a public relations firm. These units serve as central laboratories and reading centers for samples collected and studies performed in the clinical centers, and they provide assistance with recruitment, treatment, and retention of participants.

NIDDK project office. The NIDDK program officer participates in the scientific efforts of the DPP Research Group and is involved in the development of the protocol and conduct of the DPP.

Steering committee and subcommittees. The Steering Committee is the representative body of the DPP Research Group. The Committee consists of the Principal Investigator from each clinical center and the Coordinating Center, and the NIDDK representative. This committee sets policies, makes decisions, and oversees the administrative aspects of the DPP Research Group.

Subcommittees, comprised of members of the Research Group, develop detailed policies and procedures and make recommendations to the Steering Committee. The chairpersons of the subcommittees are members of the Planning Committee, which serves as the forum in which the work of the subcommittees is initially reviewed and coordinated. The following subcommittees were active during the planning phase to develop the protocol and detailed study procedures: Ancillary Studies, Concomitant Conditions, Interventions, Outcomes, Publications and Presentations, Program Coordinators, Recruitment and Retention, and Screening and Eligibility.

Data monitoring board. The Data Monitoring Board provides external review and advice to the NIDDK and the Steering Committee. It consists of experts in relevant biomedical fields, biostatistics, and medical ethics who were appointed by the director of the NIDDK. Prior to the initiation of recruitment, the Data Monitoring Board reviewed all study material to ensure the scientific validity of the study and safety of participants. Its principal responsibility is to monitor the emerging results of the DPP to assess treatment effectiveness and participant safety. Based on these considerations, the board may recommend to the NIDDK that the protocol be modified or that the DPP be terminated.

Data management

Clinical centers. A remote data management system consists of a network of microcomputers, one at each clinical center and one at the Coordinating Center. Data collected on paper forms are double-entered into the local computer by clinical center staff and checked for allowed ranges and internal consistency. Electronic copies of the newly entered and updated data are transmitted weekly via telecommunications link to the Coordinating Center, where they are compiled into the DPP master database with data from all clinical centers. Weekly edit reports are sent to each clinical center with out-of-range values, inconsistencies, and discrepancies within forms. Monthly audit programs produce more detailed edits across all forms for an individual participant.

Central resources. Data from central resources (e.g., the central biochemistry laboratory) are transmitted via direct telecommunications link to the Coordinating Center, where they are compiled into the DPP master database.

DISCUSSION

— Treatment of diabetes is often unsuccessful in preventing its adverse outcomes, including vascular disease, neurological complications, and premature death. Prevention of type 2 diabetes would, therefore, be preferable, and may be possible through modification of risk factors (44). Despite considerable variation among people in the relative importance of genetic and environmental causes of type 2 diabetes, in all populations and ethnic groups, most patients have both insulin resistance and β-cell dysfunction. These appear to be the underlying metabolic abnormalities leading to the disease (45,46). Thus, interventions aimed at reducing insulin resistance and preserving β-cell function are anticipated to be beneficial in delaying or preventing most cases of type 2 diabetes in all populations.

Target groups and goals for prevention

A goal of diabetes prevention activities should be to maintain or improve the health of individuals at high risk of type 2 diabetes by preventing or delaying the onset of the disease and associated complications. The primary goal of the DPP is, thus, to compare several currently feasible strategies to prevent or delay type 2 diabetes. Secondary outcomes include the complications of type 2 diabetes, such as cardiovascular and renal diseases and their risk factors, and all-cause mortality rates. Because the DPP may not have sufficient duration to test treatment effects on late complications and mortality, the study will also assess the effects of the treatments on delaying or lessening the development of cardiovascular risk factors and surrogate measures of cardiovascular disease. Measurements related to β-cell function and insulin sensitivity may help explain the mechanism by which the primary outcome was achieved.

Although prevention of diabetes might require modification throughout the lives of susceptible individuals of the many predisposing physiologic abnormalities that are caused by genetic factors (most of which are currently unknown) and socioeconomic conditions, it is impractical to design interventions addressing all these factors. The logistic constraints of a randomized clinical trial dictate tests of interventions in individuals who are relatively close to the onset of disease. Thus, the DPP will enroll volunteers at high risk of developing type 2 diabetes by virtue of having IGT and elevated FPG. IGT is accompanied by insulin resistance with compensatory hyperinsulinemia that maintains glycemia in the nondiabetic range. When insulin secretion is no longer sufficient to compensate for insulin resistance, hyperglycemia worsens to the point of diabetes (47). Despite the high repeat test variability of the OGTT (48), the prognostic value of IGT has been well established in many population studies (23). The incidence of type 2 diabetes is even higher in subsets of individuals with IGT, such as those who are obese or who have higher FPG concentrations (4). Thus, these additional risk factors were included in the eligibility criteria.

Selection of the lifestyle interventions

Individuals with greater BMI or abdominal fat distribution and those who are less physically active are more likely to develop type 2 diabetes (23). Changes in diet and an increasingly sedentary lifestyle, with consequent increased body mass, have been associated with the development of type 2 diabetes in recently industrialized populations and in migrating populations that previously had a low prevalence of diabetes. Thus, it is hypothesized that lifestyle interventions aimed at reducing weight and increasing physical activity may help to prevent type 2 diabetes (44).

A goal of losing ≥7% of body weight was selected for the DPP because losses of this magnitude have been achieved and maintained in previous clinical trials and appear to improve insulin sensitivity and glycemic control in individuals with type 2 diabetes. The physical activity goal of 150 min/week of moderate activity such as walking (equivalent to ~700 kcal/week) is in agreement with the national physical activity recommendations of the Centers for Disease Control and Prevention and the American College of Sports Medicine (49). Modest increases in exercise improve insulin sensitivity and promote long-term maintenance of weight loss.

The feasibility of behavioral interventions for the prevention of type 2 diabetes has been demonstrated in Malmö, Sweden, in a study of two groups of middle-aged men with IGT (50). Men with IGT were treated with an intensive diet and exercise program for 5 years. The rate of development of diabetes in these men was only half that of a nonrandomized comparison group for whom this intervention was not provided. This study is important primarily in demonstrating the feasibility of carrying out a diet-exercise program for 5 years. The effect of treatment, however, remains uncertain because the treatment groups were not assigned at random and differed in their medical conditions at baseline.

Preventive effects of diet and exercise have been reported in a randomized clinical trial in adults with IGT in Da-Qing, China, in which interventions involving diet alone, exercise alone, or both in combination were assigned on a clinic basis (51). The 6-year cumulative incidence of diabetes was lower in all three intervention groups than in the control group receiving no interventions, and there were no significant differences between the three intervention groups.

Selection of the drug interventions

Drugs considered as a means to prevent the development of type 2 diabetes belonged to six classes: *1*) biguanides, *2*) thiazolidinediones, *3*) sulfonylureas, *4*) inhibitors of carbohydrate absorption, *5*) fatty acid oxidase inhibitors and anti-lipolytic drugs, and *6*) weight-loss agents. To be selected, drugs had to have a proven record of efficacy in lowering glycemia in people similar to those to be enrolled in the DPP, have an acceptable safety profile, and not create untoward problems in adherence or retention.

Biguanides. Metformin, the only drug considered in this category, has beneficial effects on glucose homeostasis by suppressing elevated rates of hepatic glucose production in type 2 diabetes (52). It may also have a modest effect of delaying or inhibiting glucose absorption from the gastrointestinal tract (53). Finally, metformin may improve insulin sensitivity (7). Any treatment that lowers plasma glucose can also improve insulin sensitivity by ameliorating the direct effect of hyperglycemia on insulin resistance (54,55). In some studies of nondiabetic insulin-resistant individuals, metformin directly improved insulin sensitivity, even without concomitant weight loss (56,57). This improvement in insulin sensitivity is accompanied by a lowering of plasma insulin levels, and, in some cases, is also accompanied by lowering of blood pressure and improvement in lipid profiles (58). Metformin has only a small effect on the postprandial incremental glucose level, and, therefore, the overall glycemic lowering effect is due to the reduction in FPG. Based on its mechanism of action plus a 1-year study in France, in which metformin improved risk factors for type 2 diabetes (59), this drug is an excellent intervention candidate.

Metformin has been used for many years outside the U.S. with a very well understood safety profile. The major serious adverse effect is lactic acidosis, which is extremely rare, and even then occurs only when the drug is used inappropriately in patients with renal insufficiency or who are undergoing surgery (60). The other major side effect of metformin relates to gastrointestinal symptoms (60), which can be minimized and usually tolerated with appropriate titration of dosage. Based on a large number of clinical trials, it appears that the percentage of patients in whom the drug must be discontinued because of gastrointestinal side effects is <5% (61). Based on these considerations, metformin was selected as a drug treatment in the DPP.

Thiazolidinediones. Drugs in this class work exclusively by enhancing tissue insulin sensitivity (62). Because troglitazone was the only agent within this class under clinical development in the U.S., it was considered for the DPP. Clinical studies show that in IGT, type 2 diabetes, or polycystic ovarian syndrome, troglitazone successfully improves insulin sensitivity, with effects ranging from 50 to 100% improvement, depending on the measure of insulin sensitivity used (63–65). The drug also lowers plasma insulin concentrations and both fasting and postprandial glycemia (63,64). In individuals with IGT treated with troglitazone, insulin sensitivity improves strikingly, accompanied by a lowering of fasting and postprandial glucose and insulin levels (64,66). In short-term studies of troglitazone-treated individuals with IGT, ~80% converted from IGT to normal glucose tolerance after 3 months of treatment (64,66). A modest decline in blood pressure and plasma triglycerides has been consistently observed, along with an increase in plasma HDL levels (65,66).

In 1997, troglitazone was approved for treating type 2 diabetes by the Food and Drug Administration in the U.S. Long-term

safety data are lacking, although in premarketing studies, no serious side effects were observed, and the frequency of side effects was comparable with that of placebo (67). A few cases of irreversible liver failure were reported in postmarketing surveillance, however, necessitating the careful monitoring of liver function during treatment. Given the acceptable safety profile, the need for only one dose per day, and an ideal mechanism of action, troglitazone was selected as one of the drug treatments in the DPP. Due to liver toxicity, however, its use in the DPP was discontinued during recruitment (see APPENDIX 1).

Other categories of drugs. The other medication classes considered were not selected because of concerns for safety, side effects, or efficacy. Sulfonylureas were seriously considered because of the role of deficient insulin secretion in the pathogenesis of type 2 diabetes. They were not chosen, however, because they can cause hypoglycemia, which can be a serious and life-threatening side effect. This risk was deemed unwarranted in a prevention study of people with IGT who were otherwise healthy.

CONCLUSIONS — Obesity and physical inactivity are potentially modifiable risk factors for type 2 diabetes. Modifying them, however, is very challenging, and it has not been clearly established whether such modification reduces the incidence of diabetes. Insulin resistance and impaired insulin secretion, the metabolic defects predicting type 2 diabetes, can also be treated pharmacologically. The hypothesis that such treatment can prevent diabetes has not been adequately tested.

Randomized clinical trials are needed to test both behavioral and drug treatments, with emphasis on measuring and enhancing compliance. The DPP is a randomized clinical trial to test three approaches to treatment of individuals with IGT and other high-risk characteristics for type 2 diabetes. These treatments include diet, exercise, and treatment of hyperglycemia and insulin resistance with metformin. The goal is to determine the most effective interventions in those at high risk of type 2 diabetes, so that in the future the tremendous burden of this disease and its complications can be reduced.

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Dedication

This paper is dedicated to the memory of Dr. Julio V. Santiago (1942–1997), who was the Principal Investigator of the Clinical Center at Washington University, St. Louis. He made extraordinary contributions to the planning, design, and implementation of the DPP. His warmth and intellectual curiosity were inspirational to all of us.

APPENDIX 1 — The original study design included four treatment arms. In addition to the three described above, the fourth group received the standard lifestyle intervention combined with the drug troglitazone given at a fixed dose of 400 mg once daily. Because tablets for metformin and troglitazone are easily distinguishable, separate placebos were prepared for each drug. To maintain drug masking, each person assigned to medication took active metformin plus a placebo corresponding to troglitazone, active troglitazone plus a placebo corresponding to metformin, or a placebo corresponding to each drug.

One DPP participant treated with troglitazone developed hepatic failure requiring liver transplantation and, in the presence of other complicating illness, subsequently died. This case was immediately reviewed by the DPP Data Monitoring Board, which concluded that, given the lack of established benefits of this drug in the DPP and the inability of intensive safety surveillance to prevent this severe adverse event, the risk to other participants of continuation was unacceptable. On the Board's recommendation, therefore, the NIDDK suspended the troglitazone treatment in the DPP on 4 June 1998. The 585 participants randomized to this drug were unmasked to their intervention assignment, and their study medication (active troglitazone plus metformin placebo) was discontinued. They will be followed for glycemia with semiannual visits until the middle of 2002. To provide these participants with basic information about weight loss, healthy eating, and exercise, they are invited to quarterly group sessions with lessons and printed materials addressing the principal educational components of the lifestyle intervention. The objective of continued follow-up is to assess differences over time in glycemia, insulinemia, and cardiovascular and adverse events within the troglitazone cohort and between the troglitazone cohort and the concurrent control group of participants treated with double-placebo during the DPP.

The other pharmacologic-treated participants were told they were not taking active troglitazone, but remained masked as to their metformin or placebo assignment. They discontinued their troglitazone placebo but continue their active or placebo metformin.

Comparison of the troglitazone cohort and the concurrent placebo control group for time to confirmed development of diabetes and other time to event outcomes (e.g., development of cardiovascular disease) will use the same life-table methods described for the principal analyses of the three treatment groups. The longitudinal data analysis techniques described for the principal analyses will also be used to assess differences over time in glycemia, insulinemia, and cardiovascular risk factors within the troglitazone cohort and between the troglitazone cohort and the concurrent placebo control group. The principal analyses of primary and secondary outcomes in the DPP will exclude the participants assigned to troglitazone, because this treatment was discontinued early.

APPENDIX 2

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