

PATHOBIOLOGY OF PREDIABETES IN A BIRACIAL COHORT (POP-ABC): DESIGN AND METHODS

In contrast to the widely reported ethnic differences in prevalence, the incidence of type 2 diabetes was surprisingly similar (~11%) among individuals from the different US ethnic groups in the Diabetes Prevention Program (DPP). Because DPP participants had impaired glucose tolerance (IGT) at baseline, we hypothesized that ethnic disparities are initiated at the pre-IGT stage during evolution of type 2 diabetes. The Pathobiology of Prediabetes in a Biracial Cohort (POP-ABC) is designed to test that hypothesis by tracking the natural history of early dysglycemia in a biracial cohort comprising offspring of parents with type 2 diabetes. The POP-ABC study has an enrollment target of 400 participants (200 African American, 200 Caucasian), aged 18–65 years, with at least 1 parent with type 2 diabetes. All subjects must have normal fasting glucose and/or normal glucose tolerance, as determined by a 75-gram oral glucose tolerance test (OGTT). Subjects are recruited over ~3 years and followed for another 2 years, with repeated metabolic assessments. The latter include OGTT, body composition, indirect calorimetry, euglycemic clamp, beta cell function, and biochemistries. Repository specimens (DNA, RNA and proteome) are obtained for future studies. The primary outcome is the occurrence of prediabetes (IGT and/or impaired fasting glucose). The sample size provides 85% power to detect a hazard ratio of 1.75 between Black and White offspring in the primary outcome ($\alpha=.05$). Secondary endpoints include behavioral, biochemical and socioeconomic predictors of dysglycemia. The POP-ABC study will elucidate the nosogeny of ethnic disparities in glucose dysregulation. (*Ethn Dis.* 2011;21:33–39)

Key Words: Diabetes Offspring, Ethnic Disparities, Pathogenesis, Insulin Sensitivity, Beta-cell Function, Genetics, Energy Expenditure, Body Composition, Prospective Study

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INTRODUCTION

Cross-sectional studies consistently show a greater prevalence (~2-fold) of type 2 diabetes among African Americans than Caucasians.^{1–3} However, when African Americans and Caucasians with impaired glucose tolerance (IGT) were followed for ~3 years in the Diabetes Prevention Program (DPP), both groups had a similar rate of incident type 2 diabetes (~11%).⁴ The exact reasons for the ethnic differences are not known precisely. However, a collusion of genetic predisposition and environmental triggers likely accounts for the development of type 2 diabetes in any population. The nature and identity of the diabetogenes are still being actively investigated,^{5,6} but it may be even more important to understand how environmental factors (eg, diet, physical inactivity, obesity, socioeconomic factors) interact with genetic predisposition⁷ to produce ethnic disparities in the development of type 2 diabetes. Because no ethnic disparities were noted in the rate of progression from IGT to type 2 diabetes in the DPP,⁴ we hypothesized that factors that trigger ethnic disparities probably operate proximal to the IGT stage during the evolution of type 2 diabetes.

To determine the natural history of insulin secretory dysfunction and insulin resistance during the development of diabetes, and to understand how these factors interact with one another during the development of the disease, longitudinal studies are necessary in which insulin secretion and insulin action are repeatedly measured over several years in subjects as they progress from normal glucose tolerance (NGT) to higher glycemic states. Such studies are only

feasible in populations with a high incidence of diabetes where patients can be followed closely over several years.^{8,9} A prospective study used such a rigorous approach in initially nondiabetic Pima Indians over a 6-year period,¹⁰ and confirmed the critical roles of obesity, insulin secretory defect, and insulin resistance in predicting progression from NGT to IGT and diabetes^{9,10} in that population. However, prospective studies employing detailed and repeated metabolic assessments and real-time capture of progression from normoglycemia to higher glycemic states have rarely been reported for populations other than the Pima. The Pima Indians of Arizona are a unique demographic group with the highest rate of type 2 diabetes in the world.¹¹ Thus, pathophysiologic findings in that population may be quite different from the pattern in African Americans or Caucasians. Besides, the notion of differential susceptibility to pro-diabetic triggers is not testable in a mono-ethnic study. In the POP-ABC study, we applied a similarly rigorous approach to the identification of metabolic predictors of the transition from normal glucose tolerance to impaired glycemic states in African American and Caucasian offspring of parents with type 2 diabetes during long-term follow-up. Our study population, being at increased genetic risk for type 2 diabetes, should generate a high dysglycemic event rate. Moreover, the similar parental diabetes background should dampen differences due purely to genetic diabetes risk, while permitting the detection of those associated with ethnicity.

The primary objective of the POP-ABC study is to understand the predictors of progression from normoglycemia

Table 1. Inclusion and exclusion criteria**Inclusion**

- African American or Caucasian status
- One or both biological parents with a history of type 2 diabetes
- Aged 18–65 years
- FPG <100 mg/dL and/or 2-hr OGTT PG <140 mg/dL
- Ambulatory and in good general health

Exclusion

- Diabetes at baseline
- Use of antidiabetic medication(s)
- Use of medications known to alter insulin sensitivity or insulin secretion
- Use of systemic glucocorticoids, beta-blockers, thiazide diuretics (>25 mg/day)
- Use of any medication known to significantly affect glucose metabolism
- Use of medications for weight loss
- Enrollment in behavioral, pharmacological or combined weight loss program
- History of liposuction or bariatric surgery
- Currently pregnant or within 12 months postpartum
- Unwilling to undergo pregnancy testing
- Acute medical illness
- History of anemia or bleeding disorders
- Recent (within 6 weeks) hospitalization
- Planned relocation from the Memphis area within the next 5 years

to prediabetes (impaired fasting glucose [IFG] and/or IGT) in African Americans and Caucasians at high risk for type 2 diabetes. Our overall hypothesis is that ethnic disparities manifesting early in the pathogenesis of type 2 diabetes result in a higher rate of progression from normoglycemia to prediabetes in African Americans than Caucasians. Thus, the primary specific aim is to compare the rate of progression from normoglycemia to prediabetes (IFG or IGT) between African American and Caucasian offspring of type 2 diabetes parents during a two- to five-year follow-up period.

The primary objective of the POP-ABC study is to understand the predictors of progression from normoglycemia to prediabetes ... in African Americans and Caucasians at high risk for type 2 diabetes.

Prediabetes is diagnosed according to the 2003 revised American Diabetes Association (ADA) criteria.¹² The secondary research goal is to compare body composition, insulin action, beta cell function, socioeconomic status, energy expenditure, leptin regulation, metabolic syndrome components and adipocytokines between African American and Caucasian offspring during transition from normoglycemia to prediabetes.

STUDY DESIGN AND METHODS

The general study design involves the identification and recruitment of eligible participants, performance of serial metabolic assessments, and determination of endpoints.

Eligibility Criteria

Eligible participants were African American or Caucasian men and women who were biological offspring of parents with type 2 diabetes. Ethnicity was assessed by self-report of non-Hispanic White or non-Hispanic Black heritage. The parental history of type 2 diabetes is verified using a diabetes-focused medical

history questionnaire. The inclusion and exclusion criteria are summarized in Table 1. Pre-existing diabetes was excluded using the 1997 ADA criterion for fasting plasma glucose (FPG) (≥ 126 mg/dL)¹³ and the 1985 WHO criterion for 75-gram oral glucose tolerance test (OGTT) (2-hour plasma glucose [PG]) > 200 mg/dL.¹⁴ The goal was to enroll offspring of diabetic parents who had normal fasting glucose (NFG) and/or NGT at baseline, so as to permit detection of progression to prediabetes during follow-up. Normal fasting glucose (< 100 mg/dL) and IFG (100–125 mg/dL) was defined according to the 2003 revised ADA criteria¹² and IGT was defined by the 1985 WHO criterion (2-hour PG 140–199 mg/dL) during OGTT.¹⁴ Most exclusion criteria were chosen to reduce the risk of their confounding effects on planned assessments, body composition, insulin sensitivity and insulin secretion, among others. Because thiazide diuretics and beta-blockers can induce insulin resistance,¹⁵ persons using thiazides (>25 mg/day) or beta-blockers were excluded. The study protocol was approved by the University of Tennessee Health Science Center Institutional Review Board and all participants gave written informed consent.

Recruitment

Our strategies for identifying and recruiting offspring of parents with type 2 diabetes included use of mass media, targeted bulk mailing, community outreach, telephone contacts and recruitment through employment groups, health fairs and area hospitals. Participant recruitment began in September 2006 and ended between December 2009 and January 2010. The overall follow-up duration will be 2–5 years, depending on time of enrollment. Potential participants were scheduled for a screening visit to the General Clinical Research Center (GCRC) (Table 2). Following verification of eligibility and execution of the informed consent procedure, a structured medical

Table 2. Screening and enrollment process

1. Initial telephone or face-to-face contact with potential participant
 - Prescreening questionnaire
 - Initial assessment for eligibility
 - Parental diabetes verification
 - Schedule clinical screening visit
 - Provide informed consent form and instructions for oral glucose tolerance test (OGTT)
2. Clinical screening visit
 - Review eligibility checklist
 - Discuss study objectives
 - Review and execute informed consent
 - Rule out pregnancy
 - Medical history
 - Anthropometry, blood pressure, physical examination
 - OGTT
 - Other laboratory measurements- complete blood count, urinalysis, liver function tests, electrolytes, serum creatinine
3. Determine final eligibility based on medical history, findings and OGTT results
 - Eligible participants: Enroll and schedule next study visit
 - Ineligible participants: Provide feedback letter for presentation to primary care provider

interview and a general physical examination were performed, and a pregnancy test was obtained (when appropriate). Other baseline laboratory tests, including urinalysis and complete blood counts also were obtained, followed by the performance of a standard 75-gram OGTT. Eligible persons were enrolled, and ineligible persons were provided a standard letter summarizing their OGTT results and advised to consult their primary care provider.

Assessments

Enrolled participants make scheduled quarterly visits to the GCRC, during which the pre-specified metabolic assessments are performed (Table 3).

Anthropometric Measurements

Body weight (in light outdoor clothing), height (without shoes), and girths (minimum waist) are measured using a standardized protocol. Body mass index (BMI) is calculated as the weight in kilograms divided by the square of the height in meters. Percent body fat, fat-free mass and fat mass are determined by dual-energy x-ray absorptiometry (DXA) (Hologic Discovery A80044A, Hologic Inc., Bedford, MA). Abdominal fat content is assessed by selecting that

region of interest using a procedure available in the DXA software.

Food Intake

A modified Block Food Frequency Questionnaire that takes into account ethnic foods is used to assess nutrient intake at baseline and semi-annually.¹⁶

Physical Activity

Physical activity is assessed using the NHANES III Physical Activity Form and the Modifiable Activity Questionnaire (MAQ), administered at baseline and during subsequent annual visits. The MAQ has been validated as a reliable instrument for physical activity assessment in a variety of minority populations and age groups.¹⁷

Socioeconomic Status

Socioeconomic status^{18,19} was determined at baseline and annually using the same standard questionnaire that was used in the DPP.⁴

Analytical Methods

Complete blood counts, plasma glucose, HbA1c, lipid profile, blood chemistries, and urine microalbumin and creatinine levels are measured in a contract laboratory, using standard

methods. Bedside plasma glucose concentration is measured with a glucose oxidase method. Plasma insulin, C-peptide, leptin, cortisol, C-reactive protein, TNF-alpha, IL-1, IL-6, adiponectin and resistin levels are measured immunochemically in our Endocrine Research Laboratory, using commercial kits.

In Vivo Methods

In general, subjects arrive at the GCRC after an overnight fast. Single venipunctures are performed to obtain venous blood specimens for basal measurements, and serial samples are obtained via indwelling cannulas during the OGTT, intravenous glucose tolerance test (IVGTT) and hyperinsulinemic euglycemic clamp studies. During the IVGTT and clamp studies, arterialized blood specimens are obtained by warming the venipuncture arm to ~60°C. For the OGTT, participants are given written instructions not to restrict carbohydrate intake, to refrain from strenuous exercise and alcohol consumption for 24 hours, fast overnight for 12 hours, and avoid smoking in the morning of the test. After baseline blood sampling, a 75-gram oral glucose load is administered over <10 min, followed by blood sampling at 30, 60 and 120 min. Beta-cell function is assessed using the acute insulin responses to IV glucose.¹⁰ Insulin sensitivity is assessed using the hyperinsulinemic (2 mU.kg⁻¹.min⁻¹) euglycemic clamp procedure.^{20,21} Resting energy expenditure (REE)^{22,23} is determined by indirect calorimetry, using an automated ventilated hood system (Deltatrac II, SensorMedics, Yorba Linda, CA). Alterations in energy expenditure have been reported in cross-sectional studies of prediabetic persons,^{24,25} but prospective data and ethnic-specific data are lacking. Dynamic leptin response to glucocorticoid is assessed, using our previously described method.²⁶ Finally, blood specimens are obtained during the baseline visit for extraction of DNA, RNA and protein, which are stored at -80°C for future analyses.

Table 3. Schedule of visits, procedures and assessments

Visit number (month)	Screening visit	1 (Baseline)	2 (3)	3 (6)	4 (9)	5 (12)	6 (15)	7 (18)	8 (21)	9 (24)	10 (27)	11 (30)	12 (33)	13 (36)	14 (39)	15 (42)	16 (45)	17 (48)	18 (51)	19 (54)	20 (57)	21 (60)	
Informed consent	X																						
Review inclusion/exclusion	X																						
Initial medical history	X																						
Interval medical history			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs: (blood pressure, pulse, temperature, respiratory rate)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Measurement of height	X																						
Weight, BMI, waist circumference	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X																					
Oral glucose tolerance test	X					X				X				X				X					X
HbA1c, electrolytes, hematology, lipid profile	X					X				X				X				X					X
Fasting plasma glucose & insulin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine microalbumin/creatinine ratio		X				X				X				X				X					X
Adipocytokines (TNF-alpha, IL-1, IL-6, leptin, adiponectin, resistin)		X				X				X				X				X					X
Block Food Frequency Questionnaire		X		X				X				X				X					X		
NHANES III Physical Activity Questionnaire		X																					
Modifiable Activities Questionnaire		X				X				X				X				X					X
Socioeconomic Status Questionnaire		X				X				X				X				X					X
Body composition (DEXA)			X					X				X				X					X		
Indirect calorimetry		X									X									X			
Intravenous glucose tolerance test		X					X				X				X								X
Insulin sensitivity test (euglycemic clamp)					X							X									X		
Leptin secretion test			X																				X
Genetic repository blood sample	X																						

DETERMINATION OF ENDPOINTS

Primary Endpoints

The primary outcome measure is progression from NFG or NGT to prediabetes (IFG or IGT) or diabetes during 2–5 years of follow-up. For

NFG subjects whose 2hr PG was >140 but <200 mg/dL at baseline, progression of FPG to ≥100 mg/dL constitutes an endpoint occurrence. For those enrolled on the basis a 2-hour OGTT PG level of <140 mg/dL (with FPG >100 but <126 mg/dL at baseline), progression to 2-hour PG

level of ≥140 mg/dL constitutes an endpoint occurrence. During each visit, an interval medical history is obtained and concomitant medications are recorded. If initial tests during a scheduled visit indicate the occurrence of an endpoint by any of the above criteria, a confirmatory test is performed within

~6 weeks. The standard OGTT is the method of confirmation. If the second test is non-confirmatory, the subject continues in the study as scheduled. For all subjects with confirmed endpoint occurrence, the date of the initial endpoint occurrence shall be recorded as confirmed endpoint date. For subjects whose interval glucose tests remain within the normal range throughout the study period, a ≥ 20 mg/dL increase in FPG from baseline recorded at the final visit shall constitute a surrogate endpoint, as specified in the study protocol.

Secondary Outcomes

The secondary outcome measures include body composition (weight, waist circumference, total and abdominal body fat, fat-free mass), insulin sensitivity, insulin secretion, REE, metabolic syndrome components, adipocytokines, macronutrient consumption, physical activity, and socioeconomic status.

Statistical Considerations

The primary outcome variable will be analyzed using hierarchical generalized linear models (HGLMs). Our analytic strategy will link ethnic odds (and odds ratios) of becoming prediabetic over time to study predictors. Using this approach, we can develop population-averaged as well as person-specific results. Care will be taken to check and account for baseline differences between the two ethnic groups on all measures. Linear and higher order polynomial trends can be easily captured, and our models can incorporate random effects. We will also perform survival analysis taking prediabetes status as the outcome, using SAS Proc Phreg. Our model will incorporate baseline age, FPG, sex and race along with the selected risk factors (and their interactions with baseline demographic and FPG data) as predictors of survival. The time of first transition to prediabetes will be taken as the time to event. Sample size calculation assumed an

annual event rate of 10% for the composite primary endpoints (IGT, IFG, or type 2 diabetes), an extrapolation from the rate of progression from IGT to diabetes observed in the placebo arm of the DPP.⁴ The prevalence of type 2 diabetes is 1.5-to-2 times higher in African Americans than Caucasians.^{1,27} The null hypothesis is that the hazard rate is identical in the two ethnic groups. Computation of power is based on a hazard ratio of 1.75 (midway along the 1.5–2.0-fold Black/White difference in diabetes prevalence). We adopted Twisk's formula²⁸ for estimating sample size needed in repeated measures studies with a dichotomous outcome. Using Twisk's formulation, ~150 subjects per group will be sufficient to detect at least medium size marginal effects at alpha of .05 with 80% power at an attrition rate of 10%. With regard to the secondary survival analysis, using our best guess of hazards for each ethnic group (about .20 for African Americans and .11 for Caucasians) and a simple log-rank test of differences in survival curves, we estimate that 148 subjects per group would be sufficient to achieve 80% power.

Study Management and Data and Safety Monitoring

The research group holds weekly research-in-progress meetings, under the direction of the principal investigator (SDJ), to review study progress. Participants who are "out-of-window" for scheduled visits are identified and triaged to the appropriate step in our graded drop-out prevention and recovery strategies. The principal investigator and co-investigators ensure data integrity and monitor safety of the practices and procedures utilized in the POP-ABC study. Data and safety reports are made regularly to Murray Heimberg, MD, PhD, the designated institutional safety officer for the POP-ABC study. The principal investigator also confers with the study consultant, Steven Haffner, MD, regarding study-related policies.

DISCUSSION

Type 2 diabetes is characterized by obesity, insulin resistance, insulin secretory dysfunction, and increased hepatic glucose production.^{29,30} However, the sequence in which these abnormalities develop and their relative contribution to the progression from NGT to prediabetes and, ultimately, type 2 diabetes in the different ethnic groups are unknown. Weight gain predicted progression from NGT to IGT (5.2 kg vs 2.6 kg in nonprogressors) in Pima Indians; progression from IGT to type 2 diabetes was associated with a further increase in weight (13 kg vs 6 kg in nonprogressors, over 5-year follow-up period).¹⁰ Weight gain also predicted future diabetes in African Americans in the Atherosclerosis Risk In Communities study, but that study did not assess insulin sensitivity directly.³¹ The POP-ABC study will track weight changes in relation to insulin sensitivity and beta cell function among African Americans and Caucasians. In the Pima Indian study, increases in fat mass and fat-free mass accounted for the higher weight gain in persons who progressed from NGT to IGT and diabetes, compared with nonprogressors.¹⁰ However, changes in percent body fat and waist-to-hip ratio were not different between groups.¹⁰ These data suggest that, among Pima Indians, the absolute amount of weight gain rather than changes in body composition or fat distribution predicted diabetes risk, which is in discord with findings in other populations.³² This discrepancy might be due to true ethnic differences, or, perhaps, methodological imprecision of waist-to-hip ratio as a measure of central adiposity. In the POP-ABC study we are combining manual anthropometry with DXA-derived measurements of body fat, regional fat distribution, and fat-free mass, to obtain a more robust assessment of body composition.

Insulin resistance has been demonstrated in both NGT and IGT first

The POP-ABC study will track weight changes in relation to insulin sensitivity and beta cell function among African Americans and Caucasians.

degree relatives of type 2 diabetes patients in many populations.^{33–35} Cross-sectional studies that compared various populations of West African descendants (including African Americans and Ghanaians) and Caucasians have reported higher degrees of insulin resistance among the West African descendants.³⁶ The Insulin Resistance Atherosclerosis Study showed higher degrees of insulin resistance among African American and Latinos than Caucasians.³⁷ The ethnic differences in insulin sensitivity persisted after adjusting for body mass index, waist to hip ratio and physical activity score in the African American but not Hispanic participants,³⁷ which suggests differential susceptibility to diabetogenic risk factors among individuals from different ethnic groups. This intriguing notion will be explored in our POP-ABC study.

The longitudinal study of Pima Indians demonstrated that impaired first-phase insulin secretion was the major predictor of progression to higher glycemic states.¹⁰ A cross-sectional study of West African offspring of diabetic parents indicated subnormal insulin secretory responses;³⁸ however, there is a dearth of longitudinal studies in Africans or African Americans. European relatives of type 2 diabetes patients have been reported to have intact first and second phases of insulin secretion.³⁹ However, the latter report was not based on prospective data, and did not account for differences in basal

glycemia. Among elderly Swedish patients, a defective first phase insulin response during IVGTT appeared to be a heritable trait that predicted incident type 2 diabetes.⁴⁰ The POP-ABC study will provide prospective integrated data on insulin secretion and insulin sensitivity (disposition index), and determine if these data display ethnic disparities among offspring of diabetic parents.

The finding of similar incident diabetes rates among individuals from the different US ethnic groups in the DPP suggests that once individuals have developed IGT, the risk of further progression to diabetes may be independent of ethnic factors. An analysis of 6 prospective studies⁴¹ conducted before the DPP on progression from IGT to diabetes also showed a lack of correlation between family history of diabetes and progression from IGT to diabetes, which, again, suggests that familial/genetic factors may have exerted their maximal effects prior to the stage of IGT (consistent with our overall hypothesis). If that is the case, then the role of ethnic factors may be better evaluated in the pre-IGT period, which is the focus of the POP-ABC study. The exact time point of the committed stage during the development of type 2 diabetes is unknown. The observation that glucose tolerance may revert to normal in ~40% of IGT subjects treated with lifestyle modification^{4,42} suggests that commitment to diabetes is far from established in many prediabetic subjects. In contrast, it has yet to be shown convincingly whether aggressive treatment of patients with newly diagnosed type 2 diabetes will reverse the underlying metabolic defects and induce lasting remission of diabetes. Thus, a window of opportunity exists for possible reversal of the prediabetic phenotype, a compelling notion in light of the current diabetes epidemic. However, a more complete pathobiologic understanding of early glucose abnormalities, including ethnic-specific triggers of dysglycemia, is a critical prereq-

uisite for the rational development and timing of preventive interventions. The elucidation of the pathobiology and ethnic nosogeny of early dysglycemia could provide novel insights into strategies for primary prevention of diabetes.

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