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Clinical Research Article

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Glycemic Response to Oral Dexamethasone Predicts Incident Prediabetes in Normoglycemic Subjects With Parental Diabetes

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Abbreviations: 2HPG, 2-hour postload glucose; AUC, area under the curve; FPG, fasting plasma glucose; HbA1c, hemoglobin A1C; OGTT, oral glucose tolerance test; POP-ABC, Pathobiology of Prediabetes in a Biracial Cohort; ROC, receiver operating characteristic.

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Abstract

Background: Prediabetes, an often unrecognized precursor of type 2 diabetes (T2DM), is associated with cardiometabolic complications. Here, we investigated the utility of dexamethasone challenge in predicting incident prediabetes among normoglycemic subjects with parental T2DM enrolled in the prospective Pathobiology of Prediabetes in a Biracial Cohort study.

Design and Methods: After documenting normoglycemic status with an oral glucose tolerance test (OGTT), participants ingested dexamethasone (2 mg) at 10:00 PM, and fasting plasma glucose (FPG-Dex) and cortisol were measured at 8:00 AM the next day. Subjects were followed quarterly for 5 years, the primary outcome being incident prediabetes. Serial assessments included body composition, blood chemistry, OGTT, insulin sensitivity, and secretion.

Results: We analyzed data from 190 participants (107 Black, 83 white; mean age 44.7 ± 10.0 years; body mass index [BMI] 29.8 ± 6.8 kg/m^2; fasting plasma glucose [FPG] 90.9 ± 5.7 mg/dL). Following dexamethasone ingestion, plasma cortisol was < 5 μg/dL; FPG-Dex levels displayed marked variability (81-145 mg/dL) as did delta FPG (–7 to +48 mg/dL). During 5 years of follow-up, 58 of 190 subjects (30.5%) progressed to prediabetes. FPG-Dex (116.8 ± 10.9 vs 106.9 ± 10.8 mg/dL, $P < 0.0001$) and delta FPG (23.4 ± 10.1 vs 17.0 ± 10.2 mg/dL, $P < 0.0001$) were higher in progressors than nonprogressors. FPG-Dex ($P = 0.007$) was an independent predictor of incident prediabetes in a multivariate model that included age, race, gender, BMI, waist circumference, FPG, insulin sensitivity, and secretion. In further analyses, an FPG-Dex level ≥ 107 mg/dL predicted incident prediabetes with 88% sensitivity and 49% specificity.

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Conclusions: The glycemic response to dexamethasone significantly predicted incident prediabetes among offspring of parents with T2DM, and may be a tool for uncovering latent risk of dysglycemia.

Key Words: glycemic, dexamethasone, prediabetes, parental diabetes

Prediabetes is an intermediate state of hyperglycemia in which glycemic levels are above normal but below the threshold for diabetes; it may be diagnosed based on a fasting plasma glucose (FPG) of 100 to 125 mg/dL, a 2-hour postload glucose (2HPG) of 140 to 199 mg/dL during a 75-g oral glucose tolerance test (OGTT) or hemoglobin A1c (HbA1c) level of 5.7% to 6.4% [1]. Globally, the prevalence of prediabetes was estimated to be 343 million in 2010; this number is projected to rise to 471 million by 2035 [2]. In the United States, the Centers for Disease Control and Prevention estimates that 88 million Americans, representing 34.5% of the adult population, have prediabetes [3]. Screening for prediabetes is recommended in subjects with risk factors for T2DM because prediabetes is associated with incident T2DM and diabetes complications [4, 5]. In the Diabetes Prevention Program, progression from prediabetes to diabetes occurred at an annual rate of 11% in the placebo group [6]. In the Da Qing Diabetes Prevention Study, the 30-year cumulative incidence of T2DM was 95.9% in the control group and 88.7% in the lifestyle intervention group [7]. Long-term complications of diabetes including microvascular [8-11] and macrovascular [10, 12-15] disease have been reported in patients with prediabetes. In the Diabetes Prevention Program, ~8% of subjects with prediabetes had retinopathy [8], whereas about 16% of individuals with prediabetes were found to have microalbuminuria in another study [11]. The Paris Prospective Study reported a doubling of cardiovascular mortality in middle-aged men with impaired glucose tolerance [14]. Additionally, prediabetes was associated with a 2.5-fold higher incidence of unrecognized myocardial infarction in a multiethnic population that was free of cardiovascular disease at baseline [15].

Intervention studies have demonstrated that lifestyle modification and certain medications can prevent or delay the progression to T2DM among people with prediabetes [6, 7, 16]. However, those interventions reverse prediabetes in < 50% of subjects, leaving a majority in a state of persistent prediabetes and increased risk of vascular complications [9, 17, 18]. The ability to identify normoglycemic individuals at risk for incident prediabetes would help refine the timing of early lifestyle interventions to maintain normoglycemia and prevent prediabetes and its associated complications. Although family history, demographic, anthropometric, and other risk factors can help identify individuals at increased risk for T2DM, there is currently no tool for predicting incident prediabetes among normoglycemic persons [19, 20]. Historically, glucocorticoid challenge had been used to diagnose "potential" diabetes [21, 22]. Those early studies of normoglycemic relatives of patients with T2DM demonstrated that about 35% of the subjects with a positive response to cortisone challenge developed diabetes over a 5-year period [21, 22]. More recently, other reports have used the glucoregulatory response to a high-dose dexamethasone challenge to predict incident dysglycemia in relatives of patients with T2DM [23, 24]. In the present report, we evaluated the utility of a single, oral dose (2 mg) of dexamethasone as a challenge test in predicting incident prediabetes among initially normoglycemic white and Black offspring of parents with T2DM enrolled in a longitudinal study. We tested the hypothesis that transition from normoglycemia to prediabetes would be associated with an exaggerated glycemic response to dexamethasone, compared with maintenance of normoglycemic status.

Material and Methods

Subjects

Study participants were selected from the Pathobiology of Prediabetes in a Biracial Cohort (POP-ABC) study cohort [25, 26]. The details of the design and methods of the POP-ABC study have been described in previous reports [25, 26]. Included in this study were African-Americans and Caucasians aged 18 to 65 years, without a history of diabetes or prediabetes, who had at least 1 biological parent with T2DM and were normoglycemic during screening OGTT (FPG <100 mg/dL [5.6 mmol/L] and 2HPG <140 mg/dL [7.8 mmol/L]). Individuals who used medications that affect glucose metabolism, such as antihyperglycemic agents, steroids, and hydrochlorothiazides, were excluded from the study. Also, pregnant women, women less than 1 year postpartum, individuals hospitalized within 6 weeks before undergoing OGTT, subjects who were in a weight loss program, and had liposuction or bariatric surgery were excluded from the study. Individuals with abnormal dexamethasone suppression test (cortisol > 5 mcg/dL [138 nmol/L]) were excluded. Parental history of T2DM was captured by a questionnaire designed for this purpose [25, 27]. The protocol for this study was approved by the

institutional review board of the University of Tennessee Health Science Center and a written informed consent was obtained from each subject before participation in the study. The study was carried out at the General Clinical Research Center of the University of Tennessee, in adherence with the principles of the Helsinki Declaration.

Study procedure

One hundred and ninety subjects who fulfilled the entry criteria were invited for initial study procedures, which including a detailed medical history, physical examination, and anthropometry. A 75-g OGTT was administered. OGTT was performed between 7:00 and 11:00 AM, after fasting for about 12 hours. Venous blood samples for the measurement of glucose and insulin were obtained before (0 minute) and at 30 minutes and 120 minutes after ingestion of glucose. Blood sampling for biochemistry and HbA1c was also performed at 0 minute. Further assessments included IV glucose tolerance test, determination of insulin sensitivity by hyperinsulinemic euglycemic clamp, and body composition by dual energy X-ray absorptiometry. Dexamethasone challenge test was performed after overnight fasting, the subject ingested 2 mg of dexamethasone at 10:00 PM and presented to the research center at 8:00 AM the following day for venous blood sampling. Plasma glucose (FPG-Dex) and cortisol were measured. We calculated the difference between blood glucose after dexamethasone and the FPG (delta FPG) as FPG-Dex – FPG.

Measurement of insulin sensitivity and insulin secretion

Insulin resistance was evaluated by homeostatic model assessment of insulin resistance [28] and insulin sensitivity was assessed directly using the hyperinsulinemic euglycemic clamp [29]. Insulin secretion was assessed by homeostatic model assessment of β-cell function [28] and frequently sampled IV glucose tolerance test, as previously described [28]. The clamp procedure was performed after an overnight fast. Regular insulin was given by continuous IV infusion at the rate of 2 $mU/kg^{-1}/min^{-1}$ (14.4 $pmol/kg^{-1}/min^{-1}$) for 180 minutes. Blood glucose concentration was maintained at ~100 mg/dL (5.6 mmol/L) with a variable rate IV dextrose (20%) infusion. Arterialized blood samples were obtained every 10 minutes for measurement of glucose and insulin levels. The rate of total insulin-stimulated glucose disposal was calculated for the last 60 minutes of the insulin infusion and corrected for steady-state plasma insulin levels to determine insulin sensitivity [28]. Insulin secretion was determined by the IV administration of dextrose (25 g) after an overnight fast. Sampling for glucose and insulin in arterialized blood was performed 30 minutes before and at 2, 3, 4, 5, 7, and 10 minutes after the dextrose bolus [28, 30]. The acute insulin response was computed as the mean incremental insulin concentration from 3 to 5 minutes after the dextrose bolus [28, 30]. β-cell function was assessed by disposition index (insulin sensitivity × acute insulin secretion) [30].

Subjects were followed up quarterly, assessments included interval history, physical examination, anthropometry, and blood sampling for biochemistry. A 75-g OGTT was repeated each year to determine progression to prediabetes. Prediabetes was diagnosed as impaired fasting glucose (FPG values of 100-125 mg/dL [5.5-6.9 mmol/L] and/or impaired glucose tolerance (2HPG values of 140-199 mg/dL [7.8-11.0 mmol/L] [1].

Biochemical measurements

Plasma glucose was measured with the glucose oxidase method (Yellow Spring Instruments Co). Plasma insulin was measured immunochemically in our Endocrine Research Laboratory, using commercial ELISA kits. Plasma cortisol was measured in our endocrine research laboratory by chemiluminescent immunoassay using The IMMULITE 1000 system (Siemens Healthineers). HbA1c was measured in a clinical laboratory.

Statistical analysis

Data are reported as means ± SD unless otherwise specified. Significance level was set as $P < 0.05$. Data were analyzed using Student t test, χ^2 test, logistic regression model, and receiver operating characteristic (ROC) curve analysis. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc; Cary, NC).

Results

Baseline characteristics of the subjects

We studied 190 healthy normoglycemic adult African-American and Caucasian offspring of parents with T2DM; 74.7% of whom were females and 56.3% were African-Americans (Table 1). The mean age of the cohort was 44.7 ± 10.0 years, and average body mass index was 29.8 ± 6.8 kg/m^2. The subjects were categorized and analyzed based on the presence or absence of progression from normoglycemia to prediabetes. Consistent with the main report from the entire cohort [26], male sex and older age were associated with significantly higher incidence of progression from normoglycemia to prediabetes among the participants who underwent dexamethasone challenge

Table 1. Baseline Characteristics of the Subjects

Characteristic	All	Nonprogressors (n = 132)	Progressors (n = 58)	*P* Value Progressors vs Nonprogressors
Demography and anthropometry				
Age (years)	44.7 ± 10.0	43.3 ± 10.4	48.0 ± 8.3	**0.003**
Sex (female/male)	142/48	107/25	35/23	**0.004**
Ethnicity (black/white)	107/83	76/56	31/27	0.636
BMI (kg/m^2)	29.8 ± 6.8	29.4 ± 7.2	30.7 ± 5.9	0.214
Weight (kg)	84.1 ± 20.6	82.1 ± 21.0	88.4 ± 19.1	0.055
Waist circumference (cm)	92.6 ± 14.1	90.5 ± 14.8	97.3 ± 11.7	**0.002**
Female	91.1 ± 14.3	89.6 ± 15.1	95.4 ± 10.7	0.039
Male	97.0 ± 13.0	94.1 ± 12.8	100.1 ± 12.8	0.115
Trunk fat mass (kg)	14.6 ± 7.0	14.0 ± 7.2	16.0 ± 7.2	0.073
Total fat mass (kg)	30.4 ± 13.5	30.1 ± 14.1	31.3 ± 11.8	0.565
Lipid profile				
Total cholesterol	178.6 ± 33.2	179.9 ± 33.1	184.8 ± 32.9	0.090
HDL cholesterol	53.3 ± 13.3	54.9 ± 14.5	49.9 ± 10.6	**0.017**
LDL cholesterol	107.2 ± 29.1	103.8 ± 29.0	115.0 ± 28.2	**0.014**
Triglyceride	90.8 ± 52.7	86.8 ± 52.7	99.4 ± 51.9	0.119
Glucoregulatory indices				
Fasting plasma glucose (mg/dL)	90.9 ± 5.7	89.8 ± 5.7	93.4 ± 5.0	**< 0.0001**
2-hour plasma glucose (mg/dL)	112.1 ± 16.1	111.5 ± 15.8	113.6 ± 18.7	0.434
Hemoglobin A1c	5.6 ± 0.4	5.5 ± 0.4	5.7 ± 0.5	0.102
Fasting insulin (µU/mL)	7.0 ± 4.9	6.5 ± 4.8	8.2 ± 5.0	**0.035**
HOMA-IR	1.72 ± 1.42	1.54 ± 1.29	2.12 ± 1.62	**0.012**
HOMA-B	86.0 ± 65.0	80.7 ± 63.1	97.7 ± 68.0	0.103
Si-clamp (µmol/kg FFM/min/pmol/L)	0.142 ± 0.066	0.156 ± 0.065	0.116 ± 0.060	**0.0009**
Acute insulin response (µU/mL)	86.2 ± 74.4	85.6 ± 71.0	87.4 ± 82.0	0.880
DI	10.4 ± 8.1	11.6 ± 9.1	8.3 ± 5.7	**0.034**
Dexamethasone challenge				
8 AM plasma glucose (mg/dL) (FPG-Dex)	109.9 ± 11.7	106.9 ± 10.8	116.8 ± 10.9	**< 0.0001**
8 AM cortisol (mcg/dL)	0.96 ± 0.61	1.0 ± 0.7	0.9 ± 0.3	0.109
Delta FPG (FPG-Dex – FPG)	19.0 ± 10.6	17.0 ± 10.2	23.4 ± 10.1	**<0.0001**

Boldface type indicates statistically significant.
Abbreviations: 2HPG, 2-hour postload glucose; AIR, acute insulin response; BMI, body mass index; DI, disposition index; FPG-Dex, fasting plasma glucose after ingesting dexamethasone 10 hours previous.

(Table 1). Furthermore, progressors had higher values for waist circumference (P = 0.002), low-density lipoprotein cholesterol (P = 0.014), and lower high-density lipoprotein cholesterol (P = 0.017), compared with nonprogressors. Figure 1 shows a plot of the group means with 95% confidence interval of FPG-Dex (Fig. 1a), FPG during OGTT (Fig. 1b), 2HPG during OGTT (Fig. 1c), and insulin sensitivity (Fig. 1d) in progressors vs nonprogressors.

Dexamethasone challenge test

Plasma cortisol level was adequately suppressed to ~ 1 mcg/dL in all subjects, indicating the subjects ingested dexamethasone as instructed. FPG-Dex levels displayed marked variability (range 81-145 mg/dL). Similarly, the change in FPG from baseline following dexamethasone (delta FPG) ranged from –7 to +48 mg/dL. On the average, FPG-Dex was 10 mg/dL higher in progressors than nonprogressors (116.8 ± 10.9 vs 106.9 ± 10.8 mg/dL, P < 0.0001). Also, the delta FPG and the FPG were higher in the progressors (23.4 ± 10.1 vs 17.0 ± 10.2 mg/dL, P < 0.0001, and 93.4 ± 5.0 vs 89.8 ± 5.7 mg/dL, P < 0.0001), respectively. In 7 subjects (3.7%) who remained normoglycemic, FPG-Dex did not rise above FPG level supporting a robust β-cell function in these subjects, which is consistent with the higher disposition index observed in the nonprogressors (11.6 ± 9.1 vs 8.3 ± 5.7, P = 0.034).

Progression to prediabetes

During a follow-up period of 5.5 years (mean 2.70 ± 1.4 years), 58 (30.5%) of the 190 subjects recruited into the study developed prediabetes. The rate of progression to prediabetes did not differ between subjects

who had 1 parent with diabetes and those who had 2 parents with diabetes (30.2% vs 32.1%, $P = 0.827$). Forty-nine of 162 subjects with diabetes in 1 parent developed prediabetes compared with 9 of 28 subjects with diabetes in both parents. As previously reported from the POP-ABC cohort [26], older age, male gender, trunk fat, insulin resistance, and diminished insulin secretion were significant predictors of incident prediabetes. In the present report, we focused on the response to single-dose dexamethasone challenge as a potential additional predictor of prediabetes. We performed logistic regression analyses to determine the predictors of the escape from normoglycemia to prediabetes. In a univariate model, FPG-Dex ($P < 0.0001$), FPG ($P < 0.0001$), delta FPG ($P < 0.001$), and insulin sensitivity ($P < 0.002$) were predictors of incident prediabetes. However, in a multivariate logistic regression analysis, which included age, race, gender, body mass index, waist circumference, FPG, 2HPG, acute insulin response, insulin sensitivity, and disposition index as covariates, only FPG-Dex remained as independent predictor of incident prediabetes ($P = 0.007$); Table 2.

Furthermore, we performed ROC curve analyses to determine the sensitivity and specificity of FPG-Dex as well as FPG, 2HPG during OGTT, and insulin sensitivity, which are known predictors of diabetes. Results are shown in Fig. 2 and Table 3; FPG-Dex performed better than the other

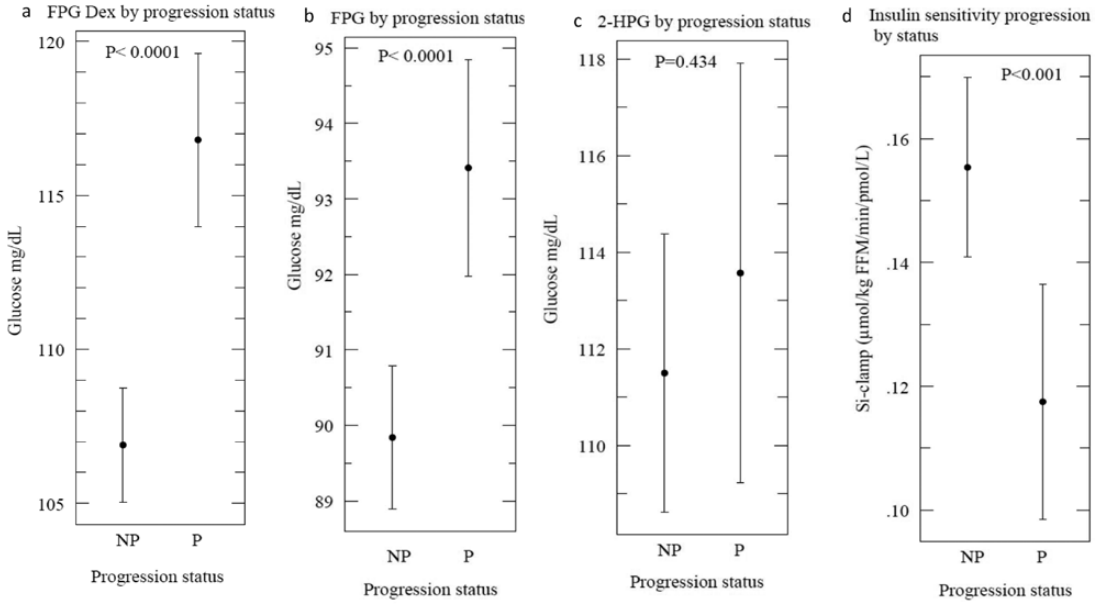

Figure 1. a: Plot of the group means with 95% confidence interval of FPG-Dex in progressors vs nonprogressors. b: Plot of the group means with 95% confidence interval of FPG during OGTT in progressors vs nonprogressors. c: Plot of the group means with 95% confidence interval of 2HPG during OGTT in progressors vs nonprogressors. d: Plot of the group means with 95% confidence interval of insulin sensitivity in progressors vs nonprogressors. 2HPG, 2-hour postload glucose; FPG-Dex, FPG-Dex, fasting plasma glucose; OGTT, oral glucose tolerance test.

Table 2. Logistic Regression Analysis of the Predictors of Progression

Variable	Point Estimate	95% Confidence Limits	*P* Value
FPG-Dex	1.073	1.020-1.129	**0.007**
FPG	1.038	0.938-1.147	0.473
2HPG	0.985	0.957-1.014	0.303
Insulin sensitivity	0.0280	0.000-5470.629	0.565
AIR	1.003	0.992-1.014	0.638
DI	0.969	0.861-1.092	0.611
Age	1.030	0.979-1.084	0.251
Race	1.170	0.447-3.060	0.479
Gender	1.401	0.457-4.297	0.555
BMI	0.978	0.844-1.132	0.763
Waist circumference	1.030	0.956-1.110	0.437

Abbreviations: 2HPG, 2-hour postload glucose; AIR, acute insulin response; BMI, body mass index; DI, disposition index; FPG-Dex, fasting plasma glucose after ingesting dexamethasone 10 hours previous.

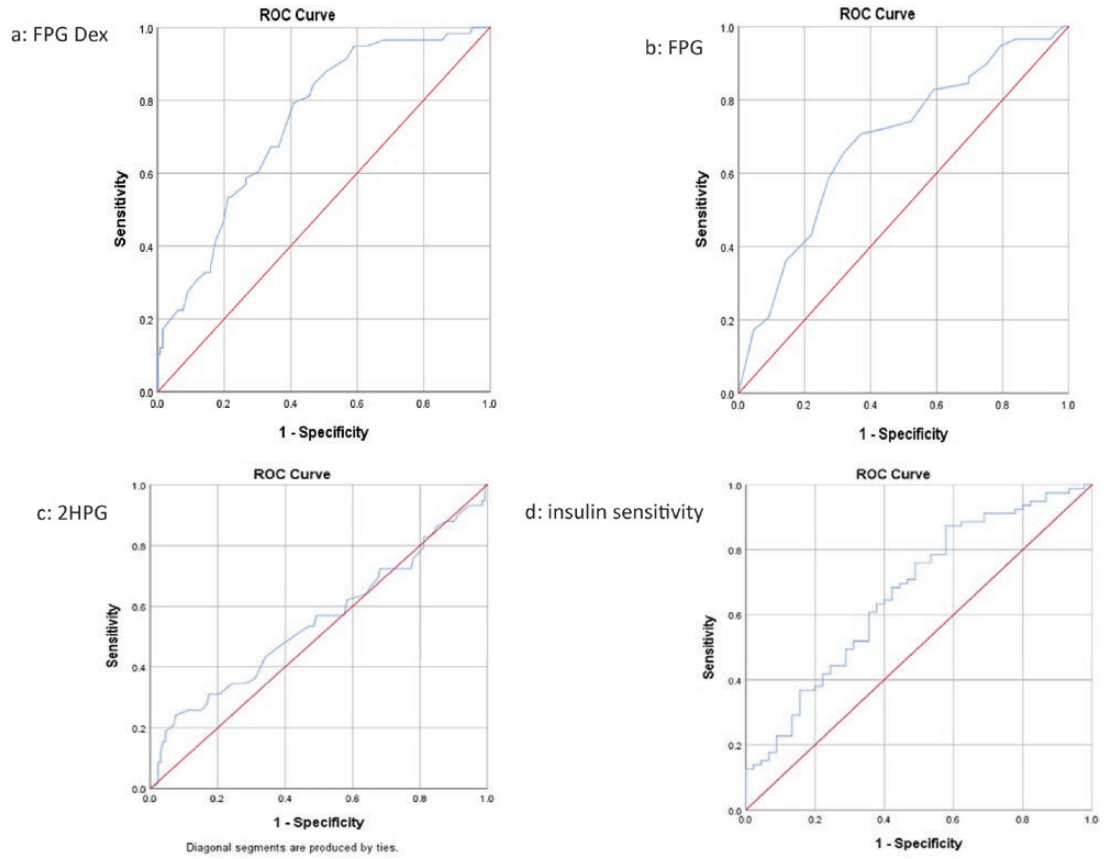

Figure 2. a: ROC curve of FPG-Dex as a predictor for incident prediabetes. b: ROC of FPG during OGTT as a predictor for incident prediabetes. c: ROC of 2HPG during OGTT as a predictor for incident prediabetes. d: ROC curve of Si-clamp as a predictor for incident prediabetes. 2HPG, 2-hour postload glucose; FPG-Dex, fasting plasma glucose; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic.

parameters. A plasma glucose of 107 mg/dL or more after dexamethasone predicted incident prediabetes with 88% sensitivity and 49% specificity. Additionally, we explored the yield of a combination of the different variables that predicted incident prediabetes in a univariate model, the combination of FPG-Dex and insulin sensitivity gave the best yield (area under the curve [AUC] = 0.78) but this was statistically comparable to FPG-Dex alone (AUC = 0.74), P = 0.12. The sensitivity and specificity of FPG-Dex as a predictor of prediabetes in the entire cohort (88% and 49%, respectively) did not differ significantly from its yield when the population was stratified by race (96% and 45% in whites vs 81% and 53% in Blacks; $P > 0.11$) and sex (86% and 51% in males vs 91% and 44% in females; $P > 0.56$).

Table 3. Sensitivity and Specificity of the Variables Predicting Progression

Variable	AUC	Cutoff Point	Sensitivity	Specificity
FPG-Dex	0.74	110	0.79	0.59
		107	0.88	0.49
FPG	0.69	90	0.74	0.48
		89	0.83	0.41
2HPG	0.55	107	0.69	0.33
		108	0.72	0.32
Insulin sensitivity	0.67	0.163	0.78	0.42
		0.173	0.80	0.38

2HPG, 2-hour postload glucose; FPG-Dex, fasting plasma glucose.

Discussion

As previously reported, our POP-ABC study cohort of healthy, normoglycemic African-American and Caucasian offspring of parents with T2DM developed incident prediabetes at an annual rate of ~11% during an average follow-up period of 2.7 years [26]. At baseline, subjects who progressed to prediabetes were significantly older, had more truncal adiposity, and exhibited glucoregulatory perturbations including insulin resistance, diminished β-cell function, and a higher FPG compared with those who remained normoglycemic [26]. In the present report, we analyzed response to a single-dose oral dexamethasone challenge in relation to progression from normoglycemia to prediabetes. We found that individuals who progressed to prediabetes showed a significantly higher

glucose excursion after dexamethasone challenge. A multivariate regression analysis, which included demographic, anthropometric, and key glucoregulatory parameters, showed that FPG-Dex was an independent predictor of incident prediabetes. Furthermore, ROC curve analysis demonstrated that FPG-Dex performed better than the indices derived from a 75-g OGTT in predicting progression to prediabetes, with a sensitivity and specificity of 88% and 49%, respectively.

Available evidence indicate that interventions such as lifestyle modification [6, 7, 16] and medications [6, 31-33] can prevent or delay incident T2DM in subjects with prediabetes; but these interventions did not reverse prediabetes in a majority of the subjects. Thus, most individuals with prediabetes remained in a state of dysglycemia with increased risk of vascular complications [9, 17, 18]. The ability to detect normoglycemic individuals at risk for incident prediabetes would be useful in the timing of early lifestyle interventions to maintain normoglycemia and prevent prediabetes and its associated complications. Thus, a simple, affordable, convenient and readily available test that predicts incident prediabetes would be valuable. Currently, the diagnosis of prediabetes may require OGTT, which is time consuming, and may be expensive for populations with limited resources. Furthermore, FPG and 2HPG, derived from OGTT, have not proved to be robust predictors of incident diabetes [34-36] or prediabetes [37], although the utility of blood glucose values may be improved by the addition of insulin secretion/insulin resistance index to the predictive model [34, 35]. Consistent with these observations, we have found that FPG and 2HPG values during OGTT were inferior to FPG-Dex in predicting incident prediabetes.

Corticosteroids induce hyperglycemia mainly by increasing insulin resistance [38-40]. The administration of dexamethasone worsened the insulin resistance, which placed a demand on an erstwhile well compensated, subtle β-cell deficit in subjects who progressed to prediabetes. β-cell function assessed by the disposition index was notably lower in the subjects who developed incident prediabetes in our cohort [26]. Although insulin resistance is present in subjects who develop prediabetes and T2DM, evidence from monogenic diabetes and inherited forms of insulin resistance, such as mutation in human insulin receptor, suggests that β-cell function may be the ultimate determinant of incident dysglycemia [41-44]. Consequently, models for the prediction of T2DM that have included insulin secretion/insulin resistance ratio or disposition index have performed better than those based on OGTT-derived blood glucose levels alone [34]. Interestingly, disposition index did not predict incident prediabetes in a regression model that included FPG-Dex in the present study. Thus, the responses to dexamethasone challenge might have captured the combined effects of insulin resistance and β-cell function in our cohort of high-risk subjects with parental T2DM. Clearly, an ability of dexamethasone challenge to predict incident prediabetes among normoglycemic subjects could help direct the selection of high-risk individuals for targeted lifestyle interventions aimed at preventing prediabetes and associated complications [6, 7, 16].

Historically, the cortisone-glucose tolerance test was used to diagnose potential diabetes, this procedure uncovered subclinical defect in carbohydrate metabolism in apparently healthy relatives of patients with diabetes [21, 22]. In these early studies, 35% of the relatives of patients with T2DM who had a positive response during OGTT after cortisone challenge developed diabetes over ~ 5 years [21, 22]. More recent studies have used plasma glucose response during OGTT after high-dose dexamethasone administration to predict incident dysglycemia in relatives of subjects with T2DM [23, 24]. In 1 of these studies, where the subjects were followed-up for 7 years, the 2HPG was a good predictor of incident diabetes (AUC = 0.92); 2HPG > 200 mg/dL predicted incident T2DM with 88% sensitivity and 74% specificity. It is noteworthy that these earlier studies performed OGTT after steroid challenge. We have investigated the predictive value of a single blood glucose level obtained after an overnight dexamethasone ingestion in normoglycemic subjects. The method employed in our study yielded a comparable sensitivity level and has the advantage of being readily available, affordable, convenient, and simple. Another difference between prior studies and this report is that our sample size was much larger, although our follow-up period was shorter than that of the previous studies [23, 24]. Also, some of the subjects in prior studies had impaired glucose tolerance at baseline, whereas we have investigated only healthy euglycemic offspring of parents with T2DM [24].

The cumulative incidence of prediabetes was 30% in this study, which is consistent with our earlier report [26] and comparable with the rate of 31% over 4 years reported in Pima Indians [45]. Another study conducted in India had reported cumulative incidence of 23% over 3.5 years of follow-up [37].

The strengths of the present study include the large sample size, enrollment of a diverse cohort, and the extensive phenotypic characterization of study participants. Other strengths include the simplicity of the single-dose dexamethasone protocol, reliance on fasting plasma glucose (a readily available measure) and the high sensitivity of ~90%. However, the specificity of the dexamethasone challenge test was relatively modest at 50%, and the restriction

of enrollment to offspring of parents with T2DM limits the generalizability of our findings.

Conclusion

In our well-characterized biracial cohort of normoglycemic subjects with parental diabetes, we have demonstrated that the 8 AM plasma glucose response following to a single oral 2-mg dose of dexamethasone administered at 10 PM the previous night predicted incident prediabetes with ~ 90% sensitivity and ~50% specificity over a 2.7-year follow-up. This finding, if validated by further studies, would be a valuable tool for identification of people at risk of prediabetes, thereby facilitating early intervention for prevention of dysglycemia.

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POP-ABC Research Group

Current members: Samuel Dagogo-Jack, MD (Principal Investigator), Ebenezer Nyenwe, MD, Jim Wan, PhD.

Past members: Emmanuel Chapp-Jumbo, MBBS (2009-2011), Chimaroke Edeoga, MBBS, MPH (2007-2013), Ruben Cuervo, MD (2006-2007), Sotonte Ebenibo, MBBS, MPH (2011-2014), Nonso Egbuonu, MBBS (2007-2010), Nicoleta Ionica, MD (2007-2008), Dorota Malinowski, MD (2007-2008); Ann Ammons, BS (2008-2017).

Consultant: Steven Haffner, MD; Data and Safety Officer: Murray Heimberg, MD, PhD.

Author Contributions: S.D.-J.: Principal investigator, design of study, drafting, review and revision of manuscript; E.N.: data collection, drafting and revision of manuscript; D.J.: data collection, review and revision of manuscript; and J.W.: statistical analysis, review and revision of the manuscript.

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Disclosure Summary: The authors have nothing to declare.

Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References and Notes

1. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes—2020. *Diabetes Care* 2020; **43**(Supplement 1): S14-S31.
2. International Diabetes Federation. *IDF Diabetes Atlas*. 7th ed. Brussels, Belgium: International Diabetes Federation; 2015.
3. Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2020*. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2020.
4. American Diabetes Association. Prevention or delay of type 2 diabetes: standards of medical care in diabetes—2020. *Diabetes Care* 2020;**43**(Supplement 1):S32-S36.
5. International Diabetes Federation. Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care. Brussels, Belgium: International Diabetes Federation; 2017.
6. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;**346**(6):393-403.
7. Gong Q, Zhang P, Wang J, et al.; Da Qing Diabetes Prevention Study Group. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing diabetes prevention outcome study. *Lancet Diabetes Endocrinol*. 2019;**7**(6):452-461.
8. Diabetes Prevention Program Research Group. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the diabetes prevention program. *Diabet Med*. 2007; **24**:137–144.
9. Perreault L, Pan Q, Schroeder EB, et al.; Diabetes Prevention Program Research Group. Regression from prediabetes to normal glucose regulation and prevalence of microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS). *Diabetes Care*. 2019;**42**(9):1809-1815.
10. Brannick B, Wynn A, Dagogo-Jack S. Prediabetes as a toxic environment for the initiation of microvascular and macrovascular complications. *Exp Biol Med (Maywood)*. 2016;**241**(12):1323-1331.
11. Bahar A, Makhlough A, Yousefi A, Kashi Z, Abediankenari S. Correlation between prediabetes conditions and microalbuminuria. *Nephrourol Mon*. 2013;**5**(2):741-744.
12. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol*. 2010;**55**(13):1310-1317.
13. Brannick B, Dagogo-Jack S. Prediabetes and cardiovascular disease: pathophysiology and interventions for prevention and risk reduction. *Endocrinol Metab Clin North Am*. 2018;**47**(1):33-50.
14. Balkau B, Eschwège E, Papoz L, et al. Risk factors for early death in non-insulin dependent diabetes and men with known glucose tolerance status. *BMJ*. 1993;**307**(6899):295-299.
15. Stacey RB, Leaverton PE, Schocken DD, Peregoy JA, Bertoni AG. Prediabetes and the association with unrecognized myocardial infarction in the multi-ethnic study of atherosclerosis. *Am Heart J*. 2015;**170**(5):923-928.
16. Tuomilehto J, Lindström J, Eriksson JG, et al.; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus

by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;**344**(18):1343-1350.
17. Perreault L, Qing Pan Q, Mather KJ, Watson KE, Hamman RF, Kahn SE, for the Diabetes Prevention Program Research Group. Regression from pre-diabetes to normal glucose regulation is associated with long-term reduction in diabetes risk: results from the diabetes prevention program outcomes study. *Lancet*. 2012;**379**:2243-2251.
18. Sallar A, Dagogo-Jack S. Regression from prediabetes to normal glucose regulation: state of the science. *Exp Biol Med (Maywood)*. 2020;**245**(10):889-896.
19. Groop L, Forsblom C, Lehtovirta M, et al. Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects. *Diabetes*. 1996;**45**(11):1585-1593.
20. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham offspring study. *Diabetes*. 2000;**49**(12):2201-2207.
21. Fajans SS, Conn JW. An approach to the prediction of diabetes mellitus by modification of the glucose tolerance test with cortisone. *Diabetes*. 1954;**3**(4):296-302; discussion, 302.
22. Fajans SS, Conn JW. Comments on the cortisone-glucose tolerance test. *Diabetes*. 1961;**10**:63-67.
23. Durck TT, Henriksen JE, Egede MB, et al. The metabolic responses induced by acute dexamethasone predict glucose tolerance and insulin secretion over 10 years in relatives of type 2 diabetic subjects. *Diabetes Metab Res Rev*. 2013;**29**(6):492-498.
24. Taheri N, Aminorroaya A, Ismail-Beigi F, Amini M. Dexamethasone stress test: a pilot clinical study for identification of individuals highly prone to develop type 2 diabetes. *Endocr Pract*. 2018;**24**(10):894-899.
25. Dagogo-Jack S, Edeoga C, Nyenwe E, Chapp-Jumbo E, Wan J. Pathobiology of Prediabetes in a Biracial Cohort (POP-ABC): design and methods. *Ethn Dis*. 2011;**21**(1):33-39.
26. Dagogo-Jack S, Edeoga C, Ebenibo S, Nyenwe E, Wan J; Pathobiology of Prediabetes in a Biracial Cohort (POP-ABC) Research Group. Lack of racial disparity in incident prediabetes and glycemic progression among black and white offspring of parents with type 2 diabetes: the pathobiology of prediabetes in a biracial cohort (POP-ABC) study. *J Clin Endocrinol Metab*. 2014;**99**(6):E1078-E1087.
27. Dagogo-Jack S, Edeoga C, Ebenibo S, Chapp-Jumbo E; Pathobiology of Prediabetes in a Biracial Cohort (POP-ABC) Research Group. Pathobiology of Prediabetes in a Biracial Cohort (POP-ABC) study: baseline characteristics of enrolled subjects. *J Clin Endocrinol Metab*. 2013;**98**(1):120-128.
28. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;**28**(7):412-419.
29. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979;**237**(3):E214-E223.
30. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest*. 1999;**104**(6):787-794.
31. DeFronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med*. 2011;**364**(12):1104-1115.
32. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;**27**(1):155-161.
33. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trail Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;**359**(9323):2072-2077.
34. Abdul-Ghani MA, Williams K, DeFronzo RA, Stern M. What is the best predictor of future type 2 diabetes? *Diabetes Care*. 2007;**30**(6):1544-1548.
35. Muhammad A, Abdul-Ghani M, DeFronzo RA. Plasma glucose concentration and prediction of future risk of type 2 diabetes. *Diabetes Care* 2009;**32**:S194-S198.
36. World Health Organization. *Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/IDF Consultation*. Geneva: World Health Organization; 2006.
37. Sai Prasanna N, Amutha A, Pramodkumar TA, et al. The 1h post glucose value best predicts future dysglycemia among normal glucose tolerance subjects. *J Diabetes Complications*. 2017;**31**(11):1592-1596.
38. Nicod N, Giusti V, Besse C, Tappy L. Metabolic adaptations to dexamethasone-induced insulin resistance in healthy volunteers. *Obes Res*. 2003;**11**(5):625-631.
39. Tamez-Pérez HE, Quintanilla-Flores DL, Rodríguez-Gutiérrez R, González-González JG, Tamez-Peña AL. Steroid hyperglycemia: prevalence, early detection and therapeutic recommendations: a narrative review. *World J Diabetes*. 2015;**6**(8):1073-1081.
40. Suh S, Park MK. Glucocorticoid-induced diabetes mellitus: an important but overlooked problem. *Endocrinol Metab (Seoul)*. 2017;**32**(2):180-189.
41. O'Rahilly S. Human genetics illuminates the paths to metabolic disease. *Nature*. 2009;**462**(7271):307-314.
42. Maedler K. Beta cells in type 2 diabetes - a crucial contribution to pathogenesis. *Diabetes Obes Metab*. 2008;**10**(5):408-420.
43. Maedler K, Donath MY. Beta-cells in type 2 diabetes: a loss of function and mass. *Horm Res*. 2004;**62**(Suppl 3):67-73.
44. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA; San Antonio metabolism study. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia*. 2004;**47**(1):31-39.
45. Knowler WC, Pettitt DJ, Saad MF, Bennett PH. Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. *Diabetes Metab Rev*. 1990;**6**(1):1-27.