

FREQUENCY OF ABNORMAL CARBOHYDRATE METABOLISM AND DIABETES IN A POPULATION-BASED SCREENING OF ADOLESCENTS

LAWRENCE M. DOLAN, MD, JUDY BEAN, PHD, DAVID D'ALESSIO, MD, ROBERT M. COHEN, MD, JOHN A. MORRISON, PHD,
ELIZABETH GOODMAN, MD, AND STEPHEN R. DANIELS, MD, PHD

Objective To document the frequency of glucose intolerance in adolescents in a population-based study of primarily African-American/Non-Hispanic whites in an urban-suburban school district.

Study design Measurement of fasting and 2-hour post-glucose load plasma glucose concentrations.

Results Carbohydrate intolerance (either impaired fasting glucose, impaired glucose tolerance, or both) was identified in 8.0%, near-diabetes (1 fasting glucose ≥ 126 mg/dL [7.0 mmol/L] and/or 2-hour glucose ≥ 200 mg/dL [11.1 mmol/L]) in 0.3%, and diabetes in 0.36% (type 1A = 0.24%; type 2 = 0.08%; undiagnosed type 2 = 0.04%). A model for abnormal carbohydrate metabolism was constructed with regression analysis in the Carbohydrate Intolerance (CI)/near-diabetes group and with logistic regression in the entire study population. Risk factors for the development of CI/near-diabetes included having a 1 unit increase in body mass index (BMI) z-score and either being non-Hispanic white or in the pubertal group. Increased fasting glucose correlated with having puberty and decreased BMI z-score, whereas 2-hour glucose correlated with increased BMI z-score. By using National Health and Nutrition Survey (NHANES) III (1988-1994) definitions, impaired fasting glucose was present in 2.0% in this study versus 1.7% (NHANES III).

Conclusion The prevalence of CI/near-diabetes was 8.3%. Undiagnosed diabetes mellitus was rare. One third of adolescents with diabetes mellitus could be classified as having type 2 diabetes mellitus. The adult model of the progression of insulin resistance to type 2 diabetes mellitus in adolescents may be valid. Despite the increase in the overweight population since NHANES III, abnormalities in glucose metabolism have not changed significantly. (*J Pediatr* 2005;146:751-8)

In adults, there is considerable evidence to support a model by which individuals at risk for the development of type 2 diabetes mellitus progress from normal carbohydrate metabolism to carbohydrate intolerance (CI) to undiagnosed diabetes mellitus before a clinical diagnosis is established.¹⁻¹⁴ It is generally assumed that adolescents in whom type 2 diabetes mellitus develops progress through these same stages.

The National Health and Nutrition Survey (NHANES) III (1988-1994) was the last comprehensive population-based assessment of the prevalence of the stages of abnormal carbohydrate metabolism in 12- to 19-year-olds.¹⁵ By using a single fasting blood glucose value in adolescents, NHANES III documented that impaired fasting glucose occurred in 1.7%, undiagnosed diabetes mellitus occurred in 0.18%, and diagnosed diabetes mellitus occurred in 0.41%. However, since the completion of NHANES III, the frequency of being overweight in adolescents, a known risk factor for the development of abnormal carbohydrate metabolism, has increased from 10.5% to 15.5%.¹⁶ As a result, NHANES III may underestimate the present frequency of the stages of abnormal carbohydrate metabolism.

See editorial, p 721.

From the Divisions of Endocrinology, Cardiology, and Biostatistics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Division of Endocrinology, University of Cincinnati College of Medicine, Cincinnati, Ohio; and Schneider Institute for Health Policy, Heller School for Social Policy and Management, Brandeis University, Waltham, Massachusetts.

Supported by grants from the National Institutes of Health (DK59183, HD41527, 0M01 RR 08084), a W.T. Grant Foundation Scholar's Award, and a Trustee Grant from Cincinnati Children's Hospital.

Submitted for publication Jul 2, 2004; last revision received Jan 12, 2005; accepted Jan 24, 2005.

Reprint requests: Lawrence M. Dolan, MD, Division of Endocrinology, Cincinnati Children's Hospital, 3333 Burnet Ave, Cincinnati, OH 45229. E-mail: Larry.Dolan@chmcc.org.

0022-3476/\$ - see front matter

Copyright © 2005 Elsevier Inc. All rights reserved.

10.1016/j.jpeds.2005.01.045

CI	Carbohydrate intolerance	IFG	Impaired fasting glucose
ANOVA	Analysis of variance	IGT	Impaired glucose tolerance
NHANES	National Health and Nutrition Survey	IAA	Insulin autoantibodies
PSD	Princeton School District	GAD	Glutamic acid decarboxylase
BMI	Body mass index	ICA 512	Islet cell antibody 512
CV	Coefficient of variation	IR	Insulin resistance
RIA	Radioimmunoassay	NHW	Non-Hispanic whites
OGT	Oral glucose tolerance	AA	African Americans

The Princeton School District (PSD) study is a prospective, epidemiologic study of the development of type 2 diabetes mellitus in adolescents in a well-defined, racially integrated (African American, Non-Hispanic white), urban-suburban school district with a wide range of socioeconomic status in each ethnic group. We report a cross-sectional evaluation of this cohort and provide a current estimate of the prevalence of abnormalities in glucose metabolism in adolescents.

METHODS

Study Population

Students (2501 of 4273) in grades 5 through 12 of the PSD participated in the study; 1263 were Non-Hispanic white (NHW), 1117 were African American (AA), 48 were Hispanic, 37 were Asian, 32 were multiracial, and 4 were West Indian. Inclusion and exclusion criteria required a participant to have no known chronic disease and be taking no medication(s) known to affect carbohydrate metabolism. Pregnant female students were excluded.

The protocol was reviewed and approved by the institutional review board at Cincinnati Children's Hospital (CCH), written informed consent was obtained from the parent/legal guardian, and assent was obtained from the participant.

Data Collection

After a 10-hour overnight fast, the following procedures were performed in a designated area at the student's school: 1) confirmation of the length of the fast and completion of the medical history; 2) height, weight, and documentation of the stage of axillary hair; and 3) venipuncture for glucose, insulin, and estradiol or free testosterone concentrations. Parents and students completed a personal medical history for each participant, documenting chronic disease, medication use, and family history of diabetes mellitus. The blood samples were maintained on wet ice, transported to CCH, processed within 3 hours of venipuncture, and then frozen at -20 degrees. Samples were batched, and assays were performed weekly.

Participants meeting 1 or more of the following 3 criteria then underwent an oral glucose tolerance test (1.75 g/kg, maximum 75 g, of Glucola) after a 10-hour overnight fast with sampling of fasting and 2-hour glucose and insulin concentrations. Blood samples for the oral glucose loading test were obtained and processed in an identical manner to the initial fasting sample aforementioned. Criteria including: 1) being overweight (BMI >85 th percentile for age and sex as defined in NHANES I¹⁷); 2) being insulin resistant (IR; fasting insulin concentration >2 SD higher than the mean for participants of the same race, sex, and stage of sexual development who had a BMI ≤ 85 th percentile for age and sex as defined in NHANES I); or 3) having an initial fasting glucose ≥ 110 mg/dL (6.1 mmol/L).

This protocol was designed and the data was collected before the publication of the 2004 criteria for impaired fasting

glucose that lowered the glucose value from 110 mg/dL (6.1 mmol/L) to 100 mg/dL (5.5 mmol/L).¹⁸ Thus students who had an initial fasting glucose value between 100 and 109 mg/dL (5.5 mmol/L and 6.0 mmol/L) were not invited to have a 2-hour glucose load test. However, to ensure that the data in the study are presented with the most recent definition of impaired fasting glucose, the students with initial fasting glucose values of 100 to 109 mg/dL (5.5-6.0 mmol/L) are included in the impaired fasting glucose category.

The subjects were then re-classified with the results of the initial fasting glucose, the fasting glucose before glucose load, and the 2-hour post-load glucose tests. The four final classifications were based on the following criteria¹⁹: 1) normoglycemic—both fasting glucose <100 mg/dL (5.5 mmol/L) and the 2-hour glucose <140 mg/dL (7.7 mmol/L); 2) carbohydrate intolerant (CI)—either impaired fasting glucose (IFG; 1 or both fasting glucose values ≥ 100 mg/dL [5.5 mmol/L], but <126 mg/dL [7.0 mmol/L] and 2-hour glucose <140 mg/dL [7.7 mmol/L]), impaired glucose tolerance (IGT; both fasting glucose <100 mg/dL [5.5 mmol/L] and 2-hour glucose ≥ 140 mg/dL [7.7 mmol/L], but <200 mg/dL [11.1 mmol/L]), or both; 3) near-diabetes—1 fasting glucose ≥ 126 mg/dL (7.0 mmol/L), 2-hour glucose ≥ 200 mg/dL (11.1 mmol/L), or both; 4) diabetes—both fasting glucose ≥ 126 mg/dL (7.0 mmol/L).

Subjects with known or newly diagnosed diabetes mellitus also had islet cell antibody titers measured. Subjects with known diabetes mellitus had fasting plasma c-peptide levels measured. Subjects with newly diagnosed diabetes mellitus had plasma c-peptide levels measured after fasting and during a mixed meal challenge as described later.

History and Physical Examination

A family history of diabetes mellitus was defined as a self-report of a sibling, parent, or grandparent with diabetes.

Height, weight, and waist circumference were measured with standard procedures and equipment as described previously.²⁰

Axillary hair was documented in all male participants as stage I (no axillary hair), stage II (presence of any axillary hair), or stage III (adult distribution of axillary hair).²¹⁻²⁴ All research team members were trained to assess the axillary hair stage and then certified by direct comparison of blinded assessment of the stages of axillary hair to that of a board certified pediatric endocrinologist. All team members achieved a Kappa statistic of 0.8 before independently assessing the stages of axillary hair.

Pubertal status was assessed with serum estradiol concentration and the presence or absence of menarche for 2 years in female students and serum-free testosterone concentration and the stage of axillary hair in male students.

Cutoff points for serum estradiol in female students and free testosterone concentration in male students were established. Estradiol concentration was measured in female students and free testosterone was measured in male students who underwent a physical examination and pubertal Tanner

Table I. Characteristics of the study population: the distribution by sex, pubertal status and ethnicity in the study population and the carbohydrate intolerant and near-diabetes populations

	Study population (N = 2501)				Carbohydrate intolerance (N = 199)				Near-diabetes (N = 7)			
	Male (N = 1232)		Female (N = 1269)		Male (N = 119)		Female (N = 80)		Male (N = 2)		Female (N = 5)	
	N	%	N	%	N	%	N	%	N	%	N	%
Pre-pubertal	215	17.5	82	6.5	22	18.5	3	3.8	0	0	0	0
Non-Hispanic white	120	9.7	44	3.5	14	11.8	2	2.5	0	0	0	0
African American	82	6.7	33	2.6	7	5.9	1	1.3	0	0	0	0
Other	13	1.1	5	0	1	0.8	0	0	0	0	0	0
Pubertal	494	40.1	507	40.0	58	48.7	48	60.0	2	100.0	3	60.0
Non-Hispanic white	275	22.3	276	21.7	33	27.7	34	42.5	0	0	2	40.0
African American	197	16.0	205	16.2	22	18.5	14	17.5	2	100.0	0	0
Other	22	1.8	26	2.0	3	2.5	0	0	0	0	1	20.0
Post-pubertal	518	42.0	679	53.5	38	31.9	28	35.0	0	0	2	40.0
Non-Hispanic white	247	20.0	296	23.3	20	16.8	13	16.3	0	0	0	0
African American	248	20.1	351	27.7	17	14.3	13	16.3	0	0	2	40.0
Other	23	1.9	32	2.5	1	0.8	2	2.5	0	0	0	0
Missing stage	5	0.4	1	0.1	1	0.8	1	1.3	0	0	0	0
Non-Hispanic white	3	0.2	1	0.1	0	0	1	1.3	0	0	0	0
African American	2	0.2	0	0	1	0.8	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0	0	0	0

(T) stage assessment as part of the National Growth and Health Study (females) or the Sex Hormone and Lipoprotein in Adolescent Males Study.^{20,25} The estradiol and free testosterone concentrations were grouped according to T staging: TI and TII to IV for female students (TI n = 24; TII-IV n = 60) and male students (TI n = 24; TII-IV n = 76), respectively. Receiver operating curves were generated to establish the estradiol and free testosterone concentrations that established the greatest sensitivity and specificity to identify female and male students who were in TI versus TII to IV.^{21,24}

Pubertal status (pre-pubertal, pubertal, and post-pubertal) was then assigned in the Princeton cohort by using the following definitions. In female students, pre-pubertal was defined as an estradiol level <11 pg/mL, pubertal was defined as an estradiol level >11 pg/mL without menarche or duration of menarche <2 years, and post-pubertal status was defined as the presence of menses for >2 years. In male students, pre-pubertal was defined as a free testosterone level <1.0 pg/mL, pubertal was defined as a free testosterone level >1.0 pg/ml and axillary hair <stage III, and post-pubertal status was defined as a free testosterone level >1.0 pg/mL and axillary hair stage III.

A mixed meal challenge was performed in students with newly diagnosed diabetes mellitus by having the subjects ingest 6 mL/kg (maximum of 360 mL) of a liquid nutrient drink (BOOST, Meade Johnson, Evansville, Ind) after a 10-hour fast. Blood was sampled before and every 30 minutes after the meal for 2 hours, and plasma c-peptide concentrations were measured.

Table II. Characteristics of the study population: demographic data

	Study population (N = 2501)	Carbohydrate intolerance (N = 199)	Near-diabetes (N = 7)
	Mean (SD)		
Age (years)	14.3 (2.2)	13.8 (1.9)	13.0 (2.0)
BMI	23.1 (5.9)	23.9 (6.6)	28.2 (8.4)
Z score for BMI	0.7 (1.0)	0.9 (1.1)	1.6 (0.9)

Laboratory Measurements

Plasma glucose was measured with a Hitachi model 704 automatic chemistry analyzer (glucose oxidase) with intra- and inter-assay coefficient of variations (CV) of 1.2% and 1.6%. Plasma insulin was measured by radioimmunoassay (RIA) using an anti-insulin serum raised in guinea pigs, ¹²⁵I labeled insulin (Linco, St. Louis, Mo), and a double antibody method to separate bound from free tracer. The sensitivity of the insulin RIA is 2 pM, with intra- and inter-assay CVs of 5% and 7%. Plasma C-peptide was measured with RIA (Linco) with a sensitivity of 0.1 ng/mL and intra- and inter-assay CVs of 4% to 5%. Serum estradiol was measured with RIA (Diagnostic Systems Laboratories, Webster, Tex) with a sensitivity of 2.2 pg/mL and intra- and inter-assay CVs of 8% and 9%. Serum-free testosterone was measured with RIA (Diagnostic Systems Laboratories) with a sensitivity of 0.18 pg/mL and intra- and

Table III. Frequency and glucose values in carbohydrate intolerant and near-diabetes subjects classified by type abnormality (N = 206)

Classification	Frequency	Initial	2-hour glucose load	
		Fasting glucose* (mg/dL) [†]	Fasting glucose* (mg/dL) [†]	2-hour glucose* (mg/dL) [†]
Initial elevated fasting only	159 (77.2%) [‡]	107.4 (6.5)	84.5 (7.6)	92.2 (19.1)
OGT elevated fasting only	17 (8.3%)	89.37 (5.7)	106.2 (5.9)	92.3 (25.3)
Initial elevated fasting and OGT elevated fasting only	11 (5.3%)	107.4 (5.5)	103.9 (2.8)	101.3 (21.0)
OGT elevated 2-hour only	7 (3.4%)	88.6 (7.4)	89.5 (8.7)	154.2 (10.8)
Initial elevated fasting and OGT elevated 2-hour only	4 (1.9%)	113.4 (3.6)	89.6 (12.2)	155.5 (20.2)
Initial elevated fasting, OGT elevated fasting and OGT elevated 2-hour only	1 (0.5%)	104.8 (n/a)	108.4 (n/a)	165.2 (n/a)
Near-diabetes	7 (3.4%)	109.8 (24.3)	94.8 (5.8)	167.4 (82.6)

OGT = Oral Glucose Tolerance; n/a = not applicable.

*Mean (SD).

†For conversion to mmol/L, divide by 18.

‡Not all subjects were asked to return for follow-up visit because of changes in the definition of carbohydrate intolerance (see Data Collection in Methods section for details).

Table IV. Factors predicting carbohydrate intolerance and near-diabetes: interactions between ethnicity and z-score for body mass index and between pubertal stage and z-score for body mass index

I-unit increase in z-score for BMI*	Adjusted odds ratio [†]	95% CI
Black	1.000	Referent
White	1.435	1.057-1.946
Pre-pubertal	1.000	Referent
Pubertal	1.578	0.936-2.661
Post-pubertal	0.721	0.417-1.245
Post-pubertal	1.000	Referent
Pubertal	2.188	1.580-3.030

*Adjusted for age and sex using CDC criteria.

†Adjusted for family history of diabetes mellitus.

inter-assay CVs of 6% and 9%. Antibody titers for insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD), and islet cell antibody 512 (ICA512) were performed at the Barbara Davis Center (Denver, Colo) as previously described, with interassay CVs of 10.3%, 6.5%, and 11.7%.²⁶⁻²⁸

Statistical Analysis

All results were conducted with SAS software, version 8.2 (SAS Institute, SAS/STAT User's Guide, version 6, 3rd ed., Cary, NC: SAS Institute; 1990). Demographic characteristics of age, sex, and ethnicity of the students who participated in the study and those who did not were examined. Tables I and II give the characteristics of the students who participated. The prevalence of the types of diabetes mellitus and their 95% CIs were calculated. By using linear regression, initial fasting glucose and 2-hour glucose, within the CI/near-diabetic group were compared across sex, ethnicity, BMI z-score, age, and

pubertal stage. Pubertal status was defined by using 2 centered variables to determine whether: 1) on average, pubertal and post-pubertal status differed from pre-pubertal status, 2) post-pubertal status differed from pubertal status. Family history of diabetes mellitus was controlled for in all model runs. The variables were examined separately. A model was then fit that included any main effects significant at the .05 level, covariates, and all possible 2-way interactions between significant main effects. Next, all non-significant interactions ($P \geq .05$) were dropped. The final model included all main effects previously defined as significant, covariates, and any interactions significant at the .05 level. Mean initial fasting glucose level, mean 2-hour glucose level, and the SDs are reported (Table III). To identify risk factors leading CI and near-diabetes, logistic regression was run for all students enrolled. The factors examined were sex, ethnicity, BMI z-score, age, and pubertal stage. A family history of diabetes mellitus was controlled for in all model runs. Pubertal stage was defined as 2 dummy variables, with the pre-pubertal students being the reference. The regression model was first run with all main effects, covariates, and all 2-way interactions between main effects. Then, a reduced model was fit that included the main effects that were statistically significant and those included in the significant interactions, covariates and only 2-way interactions that were statistically significant at the .05 level. The final model is presented in Table IV.

RESULTS

Tables I and II present the characteristics of the study population and the CI and near-diabetes populations. These data were examined with the demographic data of the non-participants. The mean age of both groups was 14 years. Although the sex distribution in the participant population was approximately 50%, a greater percentage of the total number of

female students (62.7%) in the school district than male students (54.7%) participated. When ethnicity was examined, the percent of AA students who enrolled was 58.3% of the total number in the district, 60.2% for NHW students, and 47.5% for other students. In addition, no large discrepancies in zip code distribution were seen. On the basis of these observations, the groups were not different in any meaningful way.

By using our criteria for pubertal status, 11.8% of the PSD subjects were pre-pubertal, 40.0% were pubertal, and 47.8% were post-pubertal. The prevalence of being overweight (BMI >85th% for NHANES I) was 34.9% and of insulin resistance was 15.2%.

On initial screening, IFG was found in 175 of the subjects. On the basis of the rates of being overweight, insulin resistance, and IFG on the initial blood draw, 39.7% (992/2501) of the population was defined as high risk and were asked to return for an oral glucose tolerance test (OGT). Of the 992 subjects asked to return, 890 underwent an OGT. Of these, 29 subjects had IFG detected before glucose load. In addition, 12 subjects had 2-hour post-load glucose values >140 mg/dL (>7.7 mol/L). Seven subjects were identified with near-diabetes.

CI was identified in 8.0% (199/2501) of the participants (Table III). These individuals were predominately male (59.8%) and NHW (58.8%). The means for BMI and BMI z-score among these individuals were 23.9 and 0.9, respectively. IFG only was found in 7.5% (187/2501), with 159 students having only an elevated initial fasting glucose level, 17 students having only an elevated fasting glucose level before glucose load, and 11 students having both elevated initial fasting glucose and fasting glucose before glucose load. IGT only was present in 0.3% of subjects (7/2501). Both IFG and IGT were present in 0.2% of subjects (5/2501).

Near-diabetes was identified in 0.3% (7/2501) of the participants. These individuals were predominately female (71.43%) and of AA/other ethnicity (71.43%; Table I). The mean BMI and BMI z-score in these individuals were 28.2 and 1.6, respectively.

A regression analysis was performed within the CI and near-diabetes population to identify factors that contribute to the fasting and 2-hour glucose values. For mean initial fasting glucose, the final model included ethnicity, BMI z-score, the 2 centered variables for pubertal stage, age, and history of diabetes mellitus. Decreased BMI z-score correlated with increased initial fasting glucose ($P < .01$). In addition, pubertal and post-pubertal individuals had significantly higher initial fasting glucose values than pre-pubertal individuals ($P = .02$). However, there was no significant difference between pubertal and post-pubertal subjects. For 2-hour glucose values, the final model included BMI z-score and family history of diabetes mellitus. Increased BMI z-score correlated with increased 2-hour glucose value ($P < .01$).

Logistic regression was run to identify risk factors of CI and near-diabetes (Table IV). Because the interaction between ethnicity and BMI z-score and the interaction between pubertal status and BMI z-score were statistically significant, BMI z-score must be considered when examining the risk

factors of ethnicity and pubertal status. Table IV presents the odds ratios (OR) and 95% CI for these interaction terms. When examining a 1-unit increase in z-score for BMI, CI/near-diabetes was more likely to develop in NHW participants than in AA/other participants (OR, 1.435; 95% CI, 1.057-1.946). In addition, CI/near-diabetes was more likely to develop in pubertal students than in post-pubertal students (OR, 2.188; 95% CI, 1.580-3.030).

In those subjects with an elevated initial fasting glucose value, the initial fasting glucose value was higher than the fasting glucose value before glucose load (107.4 versus 83.4 mg/dL [5.9 versus 4.6 mmol/L], respectively). This pattern was also found in subjects with IGT, IFG and IGT, and pre-diabetes (Table II).

Previously undiagnosed diabetes mellitus was identified in a 16-year-old AA male student with negative GAD, ICA512, and IAA titers, a fasting c-peptide value of 2.5 ng/mL, and a peak simulated c-peptide value of 6.7 ng/mL, confirming a diagnosis of type 2 diabetes mellitus. In addition, 8 students with known diabetes mellitus participated in the study. Six of these 8 students had positive titers for either GAD or ICA512 and a fasting c-peptide value <0.3 ng/mL, consistent with type 1A diabetes mellitus. Two students had negative ICA titers and fasting c-peptide values of 3.5 and 4.4 ng/mL, consistent with type 2 diabetes mellitus. The frequency of all types of diabetes mellitus was 0.36%; the frequency of type 1A diabetes mellitus was 0.24%; the frequency of type 2 diabetes mellitus was 0.08%; and the frequency of undiagnosed type 2 diabetes mellitus was 0.04%.

DISCUSSION

This population-based study of 9- to 20-year-old students used initial fasting glucose and subsequent fasting and post 2-hour glucose load glucose values to define the frequency and characteristics of abnormal carbohydrate metabolism. The frequency of carbohydrate intolerance, near-diabetes, and diabetes mellitus was 8.0%, 0.3%, and 0.36%, respectively. Within the CI group, 7.5% had IFG only, 0.3% had IGT only, and 0.2% had both IFG and IGT. Of subjects with a clear diagnosis of diabetes mellitus, 0.24% had type 1A and 0.08% had type 2 diabetes mellitus, with 0.04% having previously undiagnosed type 2 diabetes mellitus. Risk factors for developing CI/near-diabetes include having a 1-unit increase in BMI z-score and being either NHW or pubertal. A higher initial fasting glucose value was found in pubertal and post-pubertal subjects, and a lower BMI z-score also correlated with a higher initial fasting glucose value. However, increased BMI z-score correlated with 2-hour post glucose load glucose value. These findings provide population-based prevalence estimates of disordered carbohydrate metabolism in NHW and AA children and adolescents.

Previously, the most comprehensive estimate of abnormal carbohydrate metabolism in adolescents was NHANES III.¹⁵ In contrast to PSD, NHANES III was a national population-based analysis and included a greater sampling of Hispanic subjects. In NHANES III, classification of abnormal

glucose metabolism was based on a single fasting glucose value (≥ 110 but < 126 mg/dL [≥ 6.1 but < 7.0 mmol/L]) in 1083 of 2867 adolescents and self-report of insulin or oral hypoglycemic agent treatment to define diabetes type. In the PSD, measurements of fasting glucose value (≥ 100 but < 126 mg/dL [≥ 5.5 but < 7.0 mmol/L]) were also used as a first-order screening. Despite the passage of more than a decade, the frequencies of IFG by using the NHANES III definition in PSD and NHANES III populations were found to be 2.0% and 1.7%, respectively. These findings indicate that abnormalities in glucose metabolism, as reflected in fasting glucose levels, have not changed in the last decade. However, by using the most recent definition of IFG (≥ 100 but < 126 mg/dL [≥ 5.5 but < 7.0 mmol/L]), the frequency of IFG increased to 7.5%. Because comparable data from NHANES III are not available, it is not clear whether there has been a temporal change in the frequency of IFG in the range ≥ 100 but < 110 mg/dL (≥ 5.5 but < 6.1 mmol/L).

Since NHANES III (1988-1994), the percentage of overweight (as defined as a BMI ≥ 95 th percentile by Centers for Disease Control criteria) 12- to 19-year-old individuals has increased from 10.5% to 15.5% (NHANES 1999-2000).^{16,29} This increase in being overweight accompanied the appearance of type 2 diabetes mellitus in adolescents.³⁰ The frequency of overweight subjects in PSD was 19.4% (BMI ≥ 95 th percentile by Centers for Disease Control criteria),²⁹ suggesting that PSD subjects were as overweight as those in NHANES III. In this context, the stability in the prevalence of IFG (≥ 110 but < 126 mg/dL [≥ 6.1 but < 7.0 mmol/L]) is surprising. Although the constancy of normal fasting glucose values for the last 10 to 15 years is reassuring, it may be that single glucose values are not sufficiently sensitive to reflect overall glucose metabolism, a finding that is supported by the relatively low concordance of IFG and IGT in our subjects.

After screening with fasting glucose values, we performed 2-hour oral glucose tolerance tests in 890 subjects who were classified as high-risk for abnormalities in glucose metabolism (overweight, insulin resistance, abnormal initial fasting glucose value). In the high-risk group, 7 subjects (0.3% of all PSD subjects) had IGT but not IFG, 5 subjects (0.2%) had both IFG and IGT, and 7 subjects (0.3%) had near-diabetes. When added to the subjects that had IFG alone ($n = 187$), the overall prevalence of abnormal glucose metabolism in PSD was 8.3%.¹⁶ This rate may be an underestimate because we did not perform glucose loading in all subjects. However, we think that rate of IGT in the subjects not identified as high risk is very low because none of the 255 fifteen-year-old subjects in Chicago had a capillary glucose > 140 mg/dL (> 7.7 mmol/L) 90 to 120 minutes after a 100-g carbohydrate meal.³¹

There was a similar prevalence of all types of diabetes mellitus (0.36% versus 0.41%), undiagnosed type 2 diabetes mellitus (0.04% versus 0.06%), and the percentage of all diabetes mellitus that is type 2 (33% versus 30%) in PSD versus NHANES III, respectively. Both studies identified a small number of subjects with silent type 2 diabetes mellitus.

These data suggest that undiagnosed diabetes mellitus is very uncommon in adolescents and has not changed over the last decade. However, the frequency of CI and near-diabetes in PSD suggest that there are a number of adolescents who may be at risk for the development of diabetes mellitus as older adolescents or young adults.

Despite collecting and processing the initial and pre-glucose load blood samples with an identical protocol, we found a low frequency of reproducibility of IFG in PSD. One explanation is that the subjects were not fasting for the initial venipuncture. Although this possibility cannot be eliminated, all participants were mailed written instructions, received a phone call the night before, and were questioned by the research team on the morning of each venipuncture about adherence to the overnight fast. This process identified a number of subjects who were not fasting, and those subjects' tests were rescheduled. Further evidence that the PSD participants were fasting is that a comparison of initial fasting glucose and fasting glucose values before glucose load revealed that initial fasting glucose values were higher in all groups (IFG only, IGT only, IFG and IGT, pre-diabetes). This finding in subjects with and without abnormal carbohydrate metabolism suggests that lack of reproducibility of fasting glucose may be caused by an as-yet-unexplained variability of fasting glucose concentration and not ingestion of food before the venipuncture.

Logistic regression in PSD demonstrated that with a 1-unit increase in BMI z-score, NHW subjects were at a greater risk than AA/other subjects for the development of CI/near-diabetes. In addition, CI/near-diabetes was more likely to develop in pubertal students than post-pubertal subjects. These findings are consistent with data documenting increased insulin resistance (IR) with increased BMI and the physiologic rise of IR with the onset of puberty.³²⁻³⁶ The second notable finding in our analysis was that NHW students were at a higher risk for the development of CI/near-diabetes than AA students. These data are in keeping with the greater prevalence of type 1A diabetes mellitus in the adolescent NHW population than in the AA/other ethnicity population.³⁷

An analysis of the components of CI/near-diabetes (fasting and 2-hour glucose) demonstrated that students with increased BMI z-score had higher mean 2-hour post-glucose load glucose values. Also, pubertal and post-pubertal students had a higher mean fasting glucose value than pre-pubertal subjects. These findings are consistent with data documenting that pubertal subjects and those with increased BMI are more IR than pre-pubertal subjects and subjects with lower BMI.^{32-36,38-43} An unanticipated finding was the higher mean fasting glucose value associated with a decreased BMI z-score. This finding was caused in part by a subset of non-overweight NHW subjects who had non-reproducible increases in fasting glucose values.

An adult model of CI/pre-diabetes has been developed from longitudinal data collected in Pima Indians and cross-sectional data from different ethnic populations.^{4-13,44-46} These data suggest that increased BMI, ethnic minority, and age are predictors of progression from normal carbohydrate

metabolism to CI to diabetes. In adolescents with CI or pre-diabetes, the finding of an association of mean 2-hour glucose value with increased BMI z-score is consistent with the adult model. These findings suggest that the development of CI and diabetes in adolescents and adults may follow similar routes and implies common inherent and environmental causes.

The authors gratefully acknowledge the work of the PSD research team: Tara Hamann, RN, Stacy Poe, MS, Amy Cline, RN, Elena Strickland, RN, Tara Schaefer-Kalkhoff, Sang Sam, Michelle Hull, Julie Schwarber, and the administration, staff, teachers, students, and parents of the Princeton School District.

REFERENCES

1. Ward WK, Beard JC, Halter JB, Pfeifer MA, Porte D Jr. Pathophysiology of insulin secretion in non-insulin-dependent diabetes mellitus. *Diabetes Care* 1984;7:491-502.
2. Lo SS, Tun RY, Hawa M, Leslie RD. Studies of diabetic twins. *Diabetes Metab Rev* 1991;7:223-38.
3. Mahler RJ, Adler ML. Clinical review 102: type 2 diabetes mellitus: update on diagnosis, pathophysiology, and treatment. *J Clin Endocrinol Metab* 1999;84:1165-71.
4. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, et al. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: prospective studies of Pima Indians. *N Engl J Med* 1993;329:1988-92.
5. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH. The natural history of impaired glucose tolerance in the Pima Indians. *N Engl J Med* 1988;319:1500-6.
6. Lundgren H, Bengtsson C, Blohme G, Lapidus L, Waldenstrom J. Fasting serum insulin concentration and early insulin response as risk determinants for developing diabetes. *Diabet Med* 1990;7:407-13.
7. Charles MA, Fontbonne A, Thibault N, Warnet JM, Rosselin GE, Eschwege E. Risk factors for NIDDM in white population: Paris prospective study. *Diabetes* 1991;40:796-9.
8. Haffner SM, Stern MP, Mitchell BD, Hazuda HP, Patterson JK. Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. *Diabetes* 1990;39:283-8.
9. Sicree RA, Zimmet PZ, King HO, Coventry JS. Plasma insulin response among Nauruans: prediction of deterioration in glucose tolerance over 6 years. *Diabetes* 1987;36:179-86.
10. Bogardus C. Metabolic abnormalities in the development of non-insulin-dependent diabetes mellitus. In: LeRoith D, Taylor SI, Olefsky JM, eds. *Diabetes mellitus: a fundamental and clinical text*. Philadelphia: Lippincott-Raven; 1996. p. 459-67.
11. Kadowaki T, Miyake Y, Hagura R, Akanuma Y, Kajinuma H, Kuzuya N, et al. Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 1984;26:44-9.
12. Modan M, Karasik A, Halkin H, Fuchs Z, Lusky A, Shitrit A, et al. Effect of past and concurrent body mass index on prevalence of glucose intolerance and type 2 (non-insulin-dependent) diabetes and on insulin response: the Israel study of glucose intolerance, obesity and hypertension. *Diabetologia* 1986;29:82-9.
13. Haffner SM, Miettinen H, Stern MP. Are risk factors for conversion to NIDDM similar in high and low risk populations? *Diabetologia* 1997;40:62-6.
14. Haffner SM. Epidemiology of type 2 diabetes: risk factors. *Diabetes Care* 1998;21(Suppl 3):C3-6.
15. Fagot-Campagna A, Saaddine JB, Flegal KM, Beckles GL. Diabetes, impaired fasting glucose, and elevated HbA1c in U.S. adolescents: the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2001;24:834-7.
16. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999-2000. *JAMA* 2002;288:1728-32.
17. Must A, Dallal GE, Dietz WH. Reference data for obesity: 85th and 95th percentiles of body mass index (wt/ht²) and triceps skinfold thickness. *Am J Clin Nutr* 1991;53:839-46.
18. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004;27(Suppl 1):S5-10.
19. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [comments]. *Diabetes Care* 1997;20:1183-97.
20. Obesity and cardiovascular disease risk factors in black and white girls: the NHLBI Growth and Health Study. *Am J Public Health* 1992;82:1613-20.
21. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13-23.
22. The diagnosis and treatment of endocrine disorders in childhood and adolescence. 3rd ed. Springfield, Ill: Charles C Thomas; 1965.
23. Macias-Tomei C, Lopez-Blanco M, Espinoza I, Vasquez-Ramirez M. Pubertal development in Caracas upper-middle-class boys and girls in a longitudinal context. *Am J Human Biol* 2000;12:88-96.
24. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;44:291-303.
25. Morrison JA, Sprecher DL, Biro FM, Hansen CA, Lucky AW, Wride K. Sex hormones and lipoproteins in adolescent male offspring of parents with premature coronary heart disease and a control group. *J Pediatr* 1998;133:526-32.
26. Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Jackson RA, et al. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. *Diabetes* 1996;45:926-33.
27. Vardi P, Dib SA, Tuttleman M, Connelly JE, Grinbergs M, Radzabeh A, et al. Competitive insulin autoantibody assay. Prospective evaluation of subjects at high risk for development of type I diabetes mellitus. *Diabetes* 1987;36:1286-91.
28. Grubin CE, Daniels T, Toivola B, Landin-Olsson M, Hagopian WA, Li L, et al. A novel radioligand binding assay to determine diagnostic accuracy of isoform-specific glutamic acid decarboxylase antibodies in childhood IDDM. *Diabetologia* 1994;37:344-50.
29. Kuczmariski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat* 2002;11:1-190.
30. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents [comments]. *J Pediatr* 1996;128:608-15.
31. Brickman WJ, Holland JS, Silverman BL. Prevalence of postprandial hyperglycemia in adolescents: a population-based study. *Diabetes Care* 2002;25:1887-8.
32. Cutfield WS, Bergman RN, Menon RK, Sperling MA. The modified minimal model: application to measurement of insulin sensitivity in children. *J Clin Endocrinol Metab* 1990;70:1644-50.
33. Bloch CA, Clemons P, Sperling MA. Puberty decreases insulin sensitivity. *J Pediatr* 1987;110:481-7.
34. Moran A, Jacobs DR Jr, Steinberger J, Hong CP, Prineas R, Luepker R, et al. Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes* 1999;48:2039-44.
35. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty: a contributing factor to poor glycemic control in adolescents with diabetes. *N Engl J Med* 1986;315:215-9.
36. Roemmich JN, Clark PA, Lusk M, Friel A, Weltman A, Epstein LH, et al. Pubertal alterations in growth and body composition. VI. Pubertal insulin resistance: relation to adiposity, body fat distribution and hormone release. *Int J Obes Relat Metab Disord* 2002;26:701-9.
37. *Diabetes in America*. 2nd ed. Washington, DC: National Institutes of Health; 1995. p. 293-456.
38. Svec F, Nastasi K, Hilton C, Bao W, Srinivasan SR, Berenson GS. Black-white contrasts in insulin levels during pubertal development: the Bogalusa Heart Study. *Diabetes* 1992;41:313-7.
39. Arslanian S, Suprasongsin C. Differences in the in vivo insulin secretion and sensitivity of healthy black versus white adolescents [comments]. *J Pediatr* 1996;129:440-3.

40. Arslanian S. Insulin secretion and sensitivity in healthy African-American versus American white children. *Clin Pediatr (Phila)* 1998;37:81-8.
41. Arslanian SA. Type 2 diabetes mellitus in children: pathophysiology and risk factors. *J Pediatr Endocrinol Metab* 2000;13(Suppl 6):1385-94.
42. Danadian K, Balasekaran G, Lewy V, Meza MP, Robertson R, Arslanian SA. Insulin sensitivity in African-American children with and without family history of type 2 diabetes. *Diabetes Care* 1999;22:1325-9.
43. Arslanian SA, Lewy VD, Danadian K. Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and beta-cell dysfunction and risk of cardiovascular disease. *J Clin Endocrinol Metab* 2001;86:66-71.
44. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH. A two-step model for development of non-insulin-dependent diabetes. *Am J Med* 1991;90:229-35.
45. Banerji MA, Chaiken RL, Gordon D, Kral JG, Lebovitz HE. Does intra-abdominal adipose tissue in black men determine whether NIDDM is insulin-resistant or insulin-sensitive? *Diabetes* 1995;44:141-6.
46. Haffner SM, D'Agostino R, Saad MF, Rewers M, Mykkanen L, Selby J, et al. Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites: the Insulin Resistance Atherosclerosis Study. *Diabetes* 1996;45:742-8.

50 Years Ago in *The Journal of Pediatrics*

PSEUDOMONAS INFECTIONS IN INFANTS ASSOCIATED WITH HIGH-HUMIDITY ENVIRONMENTS

Hoffman MA, Finberg L. *J Pediatr* 1955;46:626-30

Pediatricians from Baltimore City Hospitals report the extraordinary occurrence of 13 cases of *Pseudomonas aeruginosa* infections in the premature infant nursery in a 1-year period after the implementation of the use of high-humidity atmosphere and mist in infant incubators. It was thought that such environments would be beneficial, especially in infants with a risk for or evidence of hyaline membrane disease. Infections included septicemia, noma (ulcerative necrosis) of the face, conjunctivitis, and omphalitis. Although *Pseudomonas aeruginosa* was not isolated from distilled water used to humidify, the ubiquity of the organism in the environment, its minimal requirements for growth, and its enhancement of growth in humid habitat probably account for high-density inoculation. Intrinsically limited and extrinsically violated skin barriers of the premature infant created the second half of the tragic story.

The downsides of recent “advances” in neonatology—such as the use of corticosteroids, indomethacin, topical petrolatum, central venous catheters, and potent broad-spectrum antibiotics—remind us how naïve it is to assume that intended therapies won’t have unintended consequences.

Sarah S. Long, MD
 Section of Infectious Diseases
 St. Christopher’s Hospital for Children
 Philadelphia, PA 19134
YMPD1445

10.1016/j.jpeds.2005.01.058