Increased Prevalence of Abnormal Glucose Tolerance among Obese Siblings of Children with Type 2 Diabetes

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Objective To test the hypothesis that overweight siblings of children with type 2 diabetes mellitus (T2DM) have a higher prevalence of abnormal glucose tolerance (AGT) compared with other overweight children.

Study design This was a cross-sectional study of overweight (body mass index [BMI] ≥ 95th percentile) subjects, age 8 to 17 years, with at least 1 sibling age ≥ 12 years. The primary outcome was AGT, as assessed by the oral glucose tolerance test (2-hour glucose ≥ 140 mg/dL). The secondary outcome was insulin resistance by homeostasis model assessment (HOMA).

Results The sibling (n = 20) and control (n = 42) groups were similar in terms of age, sex, racial distribution (largely African American), pubertal status, and BMI. The prevalence of AGT in the sibling group was 40.0% (n = 8), compared with 14.3% (n = 6) in controls ($P = .048$, Fisher exact test; unadjusted odds ratio = 4.0; 95% confidence interval = 1.2 to 13.5). Univariate analysis did not identify confounders for either outcome. There were no significant differences in HOMA or hemoglobin A1c between the 2 groups.

Conclusions Overweight siblings of children with T2DM had 4 times greater odds of having AGT compared with other overweight children. This group may represent a particularly high-risk population to target for screening and pediatric T2DM prevention. *(J Pediatr 2009;154:562-6)*

Type 2 diabetes mellitus (T2DM) is caused by a combination of both genetic and environmental factors. Known risk factors include obesity (particularly increased visceral adiposity); decreased exercise; African American, Native American, Asian, or Hispanic race/ethnicity; family history; and insulin resistance.[1] Obesity decreases insulin sensitivity, as does puberty,[2] when all adolescents experience a period of relative insulin resistance thought to be secondary to increased growth hormone secretion.[3] Thus, in obese adolescents already at risk for developing T2DM, the physiological increase in insulin resistance during puberty may be sufficient to unmask disease.

Family history also is known to be important. Of children with T2DM, 74% to 100% have a first- or second-degree relative with T2DM.[1] Adult studies have shown increased insulin resistance and decreased insulin secretory capacity in the nondiabetic first-degree relatives of persons with T2DM.[4,5] Not all children with a family history of T2DM, insulin resistance, and/or obesity go on to develop T2DM, however.

To the best of our knowledge, previous studies have not specifically investigated the risk of abnormal glucose tolerance (AGT) among children who are siblings of individuals diagnosed with T2DM during childhood. This group has a unique combination of genetic and environmental risk factors. Clinical experience suggests that children with T2DM often have an obese sibling, making these siblings a particularly appropriate target for prevention trials. The aims of this study were to determine the prevalence of AGT (impaired glucose tolerance [IGT] or T2DM) and, secondarily, to assess insulin sensitivity in obese siblings of children with T2DM. We hypothesized that the obese siblings of children with T2DM have a higher prevalence of AGT and decreased insulin sensitivity compared with obese children without a sibling diagnosed with T2DM during childhood.

AGT	Abnormal glucose tolerance	IGT	Impaired glucose tolerance
BMI	Body mass index	OGTT	Oral glucose tolerance test
CHOP	The Children's Hospital of Philadelphia	OR	Odds ratio
CI	Confidence interval	QUICKI	Quantitative insulin sensitivity check index
HbA1c	Hemoglobin A1c	T2DM	Type 2 diabetes mellitus
HOMA	Homeostasis model assessment		

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METHODS

This was a cross-sectional study, conducted at the General Clinical Research Center/Clinical and Translational Research Center of The Children's Hospital of Philadelphia (CHOP). The inclusion criteria for both groups were body mass index (BMI) ≥ 95th percentile for age and sex,[6] age 8 to 17 years, and having at least 1 sibling age ≥ 12 years (the approximate average age of puberty), to increase the likelihood that control subjects also had a sibling who had the opportunity to develop T2DM but did not. The exclusion criteria for both groups were known impaired fasting glucose (≥ 100 mg/dL), IGT (defined below), diabetes (defined below), positive urine pregnancy test, genetic syndrome known to affect insulin metabolism, use of medications known to affect insulin sensitivity (eg, oral glucocorticoids, immunosuppressive drugs) within the last month, and other major organ system illness.

The study exposure was being the full or half sibling of an individual diagnosed with T2DM mellitus during childhood (< age 18 years). The ratio of exposed (sibling) to control patients was 1:2. The sibling subjects were recruited largely from the families of the CHOP Diabetes Center for Children, with the help of the diabetes care providers. All families of patients with T2DM with a sibling meeting the inclusion criteria were approached. The control subjects were recruited from 4 CHOP primary care centers chosen because they serve populations with racial and socioeconomic backgrounds similar to those of the CHOP Diabetes Center for Children's T2DM population, which is largely African American from inner city Philadelphia. The electronic medical record was used to identify potential participants meeting the inclusion criteria, and families then were screened again over the phone. Study participation was thus limited to 1 study visit, to decrease the study burden on families. Written informed consent and age-appropriate assent were obtained on the day of the study visit from all subjects before participation, and the study design was approved by the CHOP Institutional Review Board.

Study visits took place between March 2004 and October 2006. Urine pregnancy tests were performed on menarchal females. Demographic information and medical history were obtained from the guardians and the participants. Investigators administered the PACE+ physical activity questionnaire, which measures days per week the subject performed at least 60 minutes of moderate to vigorous physical activity (with ≥ 5 days considered as meeting current guidelines) and has been validated in adolescents.[7]

Tanner staging for pubertal assessment[8] and evaluation for acanthosis nigricans was performed by a pediatric endocrinologist (physician investigator). Tanner stage was based on breast development in girls and testicular enlargement in boys. Anthropometric measurements were performed by trained research anthropometrists, using standard methods.[9] Weight was measured with the subject wearing a light gown without shoes using a digital scale (Scaletronix, White Plains, New York) that was calibrated daily. Height was measured using a wall-mounted stadiometer (Holtain, Crymych, UK). BMI was calculated as weight in kilograms divided by height in meters squared, and BMI *z*-scores were calculated using age- and sex-specific BMI reference data.[6] Waist circumference (a surrogate measure of visceral adiposity[10]) was measured at the umbilicus, using standard techniques.[11] The measurements were repeated 3 times, and average values were used. Body composition (fat mass, fat-free mass, percent body fat) was assessed by dual-energy x-ray absorptiometry using a Hologic QDR2000 absorptiometer (Hologic, Waltham, Massachusetts). Subjects were scanned in fan beam mode using standard positioning techniques and analyzed using the Hologic Enhanced Whole Body V5.71A software.

The primary outcome of the study was AGT, as defined by a 2-hour oral glucose tolerance test (OGTT) value ≥ 140 mg/dL. In preparation for the OGTT, all subjects were instructed to eat a high-carbohydrate diet for 3 days before the study, followed by a 12-hour overnight fast the night before the study visit. On the morning of the visit, a blood-drawing intravenous line was placed, and a baseline blood sample was obtained for insulin, glucose, and hemoglobin A1c (HbA1c) determinations. The subjects were then asked to ingest a glucose solution (1.75 g/kg up to a maximum of 75 g) over 2 minutes. After 120 minutes, blood was again drawn for glucose and insulin determinations. The OGTT results were interpreted according to World Health Organization criteria[12]: 2-hour blood glucose value < 140 mg/dL was normal, a value ≥ 140 mg/dL and < 200 mg/dL indicated IGT, and a value ≥ 200 mg/dL indicated diabetes mellitus.

The secondary outcome of the study was insulin resistance, as measured by homeostasis model assessment (HOMA), defined as [fasting insulin (μIU/mL) * fasting glycemia (mmol/L)] ÷ 22.5.[13] HOMA has been validated in obese children and adolescents.[14,15] Another mathematical approximation, the quantitative insulin sensitivity check index (QUICKI), was calculated as 1 ÷ [log fasting insulin (μIU/mL) + log fasting glycemia (mg/dL = mmol/L × 18 182)], to provide supplemental information.[16]

Statistical analyses were performed using Stata version 9.0 (StataCorp, College Station, Texas), unless indicated otherwise. A P value ≤ .05 was considered statistically significant. Descriptive analyses were performed using means and standard deviations for continuous variables and frequencies for categorical variables. Because of the small number of subjects in some cells, unadjusted comparisons of variables between the 2 groups were performed using the Fisher exact test for categorical variables. Continuous variables were compared using the *t*-test for independent samples for normally distributed variables (percent body fat, fat-free mass, and BMI *z*-score) and the Wilcoxon rank-sum test if the variable's distribution deviated from normality (age, weight, height, waist circumference, BMI, fat mass, HbA1c, fasting glucose, and fasting insulin).

Logistic regression was used to estimate the odds ratio (OR) of having AGT in the sibling group compared with the