Published in final edited form as:

J Pediatr. 2009 April ; 154(4): 562–566.e1. doi:10.1016/j.jpeds.2008.09.055.

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

Sheela N. Magge, MD, MSCE, Nicolas Stettler, MD, MSCE, Abbas F. Jawad, MSC, PHD, and Lorraine E Levitt Katz, MD

From the Division of Endocrinology and Diabetes (S.M., L.L.K.) and Division of Gastroenterology, Hepatology, and Nutrition (N.S.), The Children's Hospital of Philadelphia, Philadelphia, PA; Center for Clinical Epidemiology and Biostatistics (S.M., N.S., A.J.), and Department of Pediatrics (S.M., L.L.K., N.S.), University of Pennsylvania School of Medicine, Philadelphia, PA.

Abstract

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] $\geq$ 95th percentile) subjects, age 8 to 17 years, with at least 1 sibling age $\geq$ 12 years. The primary outcome was AGT, as assessed by the oral glucose tolerance test (2-hour glucose $\geq$ 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.

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.

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) $\geq$ 95th percentile for age and sex,⁶ age 8 to 17 years, and having at least 1 sibling age $\geq$ 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 ($\geq$ 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 back-grounds 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 $\geq$ 5 days considered as meeting current guidelines) and has been validated in adolescents.⁷

Tanner staging for pubertal assessment⁸ 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, Crymch, 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 adiposity¹⁰) 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 criteria¹²: 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 $[\text{fasting insulin } (\mu\text{IU/mL}) * \text{fasting glycemia (mmol/L)}] \div 22.5$.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 $1 \div [\log \text{fasting insulin } (\mu\text{IU/mL}) + \log \text{fasting glycemia (mg/dL} = \text{mmol/L} \times 182)]$, to provide supplemental information.¹⁶

Statistical analyses were performed using Stata version 9.0 (StataCorp, College Station, Texas), unless indicated otherwise. A *P* value $\leq .05$ 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 control groups, while adjusting for relevant variables when indicated. Given the limited sample size and the risk of overfitting the model by adjusting for too many variables, the variables included in the final adjusted regression model were only those found by univariate analyses to be significantly associated with both the outcome and the exposure (ie, confounding variables). Potential confounders analyzed included age, sex, race, ethnicity, pubertal status, positive parental T2DM history, whether the sibling age ≥ 12 years was a full or a half sibling of the participant, activity level (meeting or not meeting PACE+ guidelines), BMI, BMI *z*-score, body composition (fat free mass, fat mass, percent body fat), and waist circumference. Pubertal status was analyzed both as a categorical variable (Tanner stage) and as a dichotomous variable (prepubertal vs pubertal). The association of each of the covariates with the primary exposure (sibling group vs control group) and their association with the

primary outcome (abnormal vs normal glucose tolerance) were examined. For these univariate analyses, the Fisher exact test, *t*-test, or Wilcoxon rank-sum test was used, as appropriate. In the case of a potential confounding variable, the ORs of the association between the primary exposure and the primary outcome were compared before and after adjusting for the covariate as another method to determine whether confounding was present.¹⁷

For the secondary outcome of insulin resistance, as the distribution of HOMA (and QUICKI) deviated from normality, the variable was log-transformed. Similar to the analysis performed for the primary outcome, univariate analyses were used to identify any covariates associated with the secondary outcome and the exposure. In addition to the statistical methods described above, analysis of variance was used to test the association between the secondary outcome and Tanner stage (categorical variable). Multiple linear regression analysis was used to control for potential confounding variables.

Although the analysis adjusted for potential confounding by pubertal stage, an alternative analysis also was performed in which the main analysis for the primary outcome was repeated after all prepubertal subjects were excluded. This was done to again investigate for any evidence of confounding by pubertal status.

RESULTS

Of the 25 siblings of children with T2DM whose parents agreed to participate in the study, 21 attended the scheduled study visit. Of the approximately 75 control subjects whose parents agreed to participate in the study, 43 attended the scheduled study visit. For 1 individual in the sibling group and 1 individual in the control group, intravenous access could not be obtained, and thus primary outcome data were unavailable. Thus, a total of 62 children participated in the study: 20 obese subjects with a sibling with T2DM and 42 obese control subjects. The mean age of the older siblings of the members of the control group was 18.6 ± 4.7 years, indicating that most had completed puberty and had the opportunity to develop T2DM but did not. In the sibling group, the mean age of the T2DM siblings at the time of their sibling's study participation was 15.5 ± 3.5 years. The mean age of the T2DM siblings when they were diagnosed with diabetes was 13.6 ± 2.4 years, and their mean BMI at the time of diagnosis was 37.6 ± 6.7 kg/m² ($n = 17$). Of the 15 diabetic siblings in whom the HbA1c value at diabetes diagnosis was available, the mean value was 10.2 ± 2.6 .

The sibling and control groups were similar in terms of age (mean, 12.2 ± 2.6 years in the sibling group vs 12.1 ± 2.3 years in the control group; $P = .9$), sex, race (largely African American)/ethnicity, pubertal status (evaluated as both a categorical and dichotomous variable), BMI *z*-score, body composition, and presence of acanthosis nigricans (Table I; available at www.jpeds.com). The only variable found to be significantly different between the 2 groups was parental history of T2DM ($P = .02$); however, this variable was not associated with AGT ($P = .5$). No covariates were found to be significantly associated with AGT; thus, no confounders were identified for the primary outcome.

The prevalence of AGT (IGT or T2DM) was 40.0% ($n = 8$) in the group of 20 siblings, compared with 14.3% ($n = 6$) in the group of 42 controls ($P = .048$; unadjusted OR = 4.0; 95% confidence interval [CI] = 1.2 to 13.5). Table II presents the cumulative OGTT results. The prevalence of T2DM was 10% ($n = 2$) in the sibling group, compared with 0 in the control group ($P = .1$; OR could not be obtained because of 0 cells). Both cases of T2DM were diagnosed based on the 2-hour blood glucose value detected on the OGTT. In 1 case, the fasting glucose value was normal, and in the other case, impaired fasting glucose (≥ 100 mg/dL) was present as well. Of note, the prevalence of impaired fasting glucose was 5.0% ($n = 1$) in the sibling group and

2.4% ($n = 1$) in the control group. Both of these subjects also had abnormal 2-hour glucose levels, however.

Although parental history was not identified as a confounder of the relationship between glucose tolerance and sibling status based on our a priori criteria, parental history was found to be a clinically significant factor associated with sibling status. Therefore, a second, confirmatory analysis adjusting for parental history of T2DM also was performed. After adjustment, the OR was 3.6 (95% CI = 0.9 to 14.3; $P = .06$). The change in the OR from 4.0 (unadjusted model) to 3.6 (model adjusted for parental history of T2DM) represented a change of $< 10\%$, further suggesting that parental T2DM history was not a confounder.¹⁷

LogHOMA was not significantly different between the 2 groups ($P = .47$) (Table I). No variables were found to be associated with both the exposure and the outcome (logHOMA); therefore, no confounders were identified, and no adjusted analyses were performed. Our analysis also did not find any difference in insulin resistance as measured by logQUICKI (QUICKI also deviated from normality, and was log-transformed) between the 2 groups ($P = .35$) (Table I).

When the main analysis for the primary outcome was repeated after all prepubertal subjects were excluded, the sibling group contained 18 subjects and the control group contained 28 subjects. The prevalence of AGT (IGT or T2DM) was 38.9% ($n = 7$) in the sibling group and 17.9% ($n = 5$) in the control group ($P = .17$; unadjusted OR = 2.9; 95% CI = 0.8 to 10.9). Although the difference between the 2 groups was no longer statistically significant, there was a trend toward statistical significance, with the point estimate in the direction expected. The broad confidence interval provides evidence that the sample size of this analysis was too small to exclude type 2 error when the prepubertal subjects were excluded. Of note, 2 prepubertal subjects (1 in each group), representing 12.5% of the 16 total prepubertal subjects, had AGT, suggesting that inclusion of prepubertal subjects added valuable information to the study.

DISCUSSION

Adult studies have examined first- and second-degree relatives (including siblings) of those who have developed T2DM as adults.^{4,18,19} These studies have more genetic implications than environmental implications, however, given that adult first-degree relatives usually live separately with their own nuclear families, unlike children. The few previous pediatric studies investigating the relationship between family history and glucose metabolism used intravenous glucose tolerance testing and hyperinsulinemic-euglycemic clamp studies (methods unlikely to be used for screening purposes) and have reported mixed findings. Several studies found increased insulin resistance and/or decreased glucose disposition index (a measure of beta cell compensation for insulin resistance) in children with a positive family history,^{20–22} but another study did not.²³ But not all of these studies took into account the effect of puberty, a very important potential confounder when measuring insulin resistance and glucose tolerance. In our study, puberty was analyzed both as a dichotomous variable (prepubertal and pubertal) and as a categorical variable (Tanner stage) and was not found to be a confounding variable. Previous pediatric studies also included parents and grandparents with T2DM in their definition of a positive family history. Children likely would not share as much environmental risk with their parents and grandparents as they might with their siblings, which is why we postulated that our sibling group would constitute an especially high-risk group.

The importance of risk assessment lies in disease prevention. The Diabetes Prevention Program showed that T2DM can be prevented in high-risk adults through lifestyle changes or pharmacologic intervention.²⁴ Identifying groups at high risk for T2DM during childhood, such as obese siblings of children with T2DM, could help guide the screening of obese children

for AGT by primary care providers and identify children who might benefit from participation in future pediatric T2DM prevention studies. Such future prevention studies would require the baseline expected prevalence of AGT for comparison. The current study's findings suggest that obese siblings of individuals diagnosed with T2DM during childhood should be followed closely over time and receive more frequent screening than most other obese children.

Furthermore, although the American Diabetes Association recommends a fasting glucose test to screen for T2DM, the World Health Organization suggests using an OGTT.²⁵ Data on adult kindreds suggest that using only a fasting glucose test would miss 30% of abnormal 2-hour glucose levels detected by an OGTT.¹⁹ In a previous study of obese children, using the fasting glucose test alone would have missed 68% of IGT cases and 66% of T2DM cases diagnosed by OGTT.²⁶ Interestingly, of the 14 subjects in both of our study groups identified with IGT and/or T2DM, only 2 had an abnormal fasting glucose level (≥ 100 mg/dL). Thus, using only the fasting glucose test would have missed 86% (12/14) of the subjects with AGT, including 1 of the 2 subjects in the sibling group diagnosed with T2DM. Of note, however, in our study, the prevalence of impaired fasting glucose in obese controls was 2.4%, distinctly lower than the reported overall prevalence of 7% to 11% in US adolescents^{27,28} and the prevalence of 17.8% in obese adolescents.²⁷ This may be due in part to the younger ages of our study participants (8 to 17 years vs 12 to 19 years). Furthermore, in both of the cited studies, the non-Hispanic black subjects had a much lower prevalence of impaired fasting glucose than the Mexican American and non-Hispanic white subjects. Our study group consisted mostly of non-Hispanic black children. Moreover, only 1 of the 14 subjects with AGT had an abnormal HbA1c value (6.0%). Our results suggest that perhaps individuals at particularly high risk for IGT or T2DM, such as obese siblings of children with T2DM diagnosed during childhood, especially among non-Hispanic black children, should be screened with an OGTT.

Unlike most previous studies, our study found no difference in insulin resistance between groups. One possible explanation for this is type 2 error; that is, our sample size was too small to detect a clinically significant difference in insulin resistance, because the study was powered for the primary outcome, AGT. Another possibility is that the increased risk for AGT in the siblings compared with controls is due not to a difference in insulin resistance, but rather to a difference in beta cell function²⁹ and insulin secretory capacity. In a study comparing 14 adolescents with T2DM and 20 nondiabetic obese controls using hyperinsulinemic euglycemic clamps, Gungor et al³⁰ found that those with T2DM had approximately 50% less insulin sensitivity, but approximately 75% lower first-phase insulin secretion, compared with controls. Furthermore, this dramatic decrease in insulin secretory capacity may be greater in pediatric T2DM than in adults who develop T2DM, in whom data suggests a 50% loss of beta cell function at the time of diabetes presentation.³¹ Future studies are needed to delineate the relative roles of insulin resistance and insulin secretion in the pathophysiology of pediatric T2DM.

The current study has some limitations. First, the study had a relatively small sample size, and our findings need to be reproduced in larger groups. Our sample size did not allow the exclusion of type 2 error or the examination of potential interactions by factors such as sex and race. The small sample size also did not allow us the exclusion of prepubertal subjects, who are at lower risk for AGT than pubertal subjects; however, we addressed the issue of puberty statistically in the analysis. We also found that prepubertal subjects added valuable information to the study, because 2 of the 16 Tanner stage 1 subjects had AGT. Another limitation was that parental T2DM status was determined by history, not by OGTT of both biological parents of each participant. Third, members of the exposed group included both full and half siblings of those with T2DM; however, this would only underestimate the true association for full siblings and thus bias the study findings toward the null. In addition, the control group in this study was largely a convenience sample, because this was not a population-based study. Finally, the use

of HOMA to measure insulin resistance has been validated in obese children and adolescents^{14,15} but has not been validated in those with AGT or T2DM, thus limiting our conclusions regarding differences in insulin resistance between groups.

In this study, we identified obese siblings of individuals who developed T2DM during childhood to be a pediatric population at very high risk for AGT. This finding may help target screening and future prevention studies.

Glossary

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

Acknowledgments

We thank our research assistant, Meckenzie Behr, MPH, for her diligent efforts with recruitment and study administration. We also thank the CHOP GCRC/CTRC staff, the CHOP Pediatric Research Consortium, and the CHOP DCC for its help with participant recruitment. Finally, we greatly appreciate the cooperation of the study participants and their families.

Supported by Juvenile Diabetes Research Foundation–Lawson Wilkins Pediatric Endocrine Society (LWPES) Pediatric Endocrinology Fellowship Training Grant 13-2002-454, a Children's Hospital of Philadelphia General Clinical Research Center Junior Clinical Investigators Award, an LWPES Clinical Scholars Grant, National Institutes of Health (NIH) Career Development Award K12 DK63682, and NIH Grants 5-MO1-RR-000240 and UL1RR024134 from the National Center for Research Resources (NCRR). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCRR or the NIH.

REFERENCES

1. American Diabetes Association. Type 2 diabetes in children and adolescents. *Diabetes Care* 2000;23:381–389. [PubMed: 10868870]
2. 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;48:2039–2044. [PubMed: 10512371]
3. Caprio S, Plewe G, Diamond MP, Simonson DC, Boulware SD, Sherwin RS, et al. Increased insulin secretion in puberty: a compensatory response to reductions in insulin sensitivity. *J Pediatr* 1989;114:963–967. [PubMed: 2524556]
4. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Increased insulin concentrations in nondiabetic offspring of diabetic parents. *N Engl J Med* 1988;319:1297–1301. [PubMed: 3054549]
5. Osei K, Cottrell DA, Orabella MM. Insulin sensitivity, glucose effectiveness, and body fat distribution pattern in nondiabetic offspring of patients with NIDDM. *Diabetes Care* 1991;14:890–896. [PubMed: 1773687]
6. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics* 2002;109:45–60. [PubMed: 11773541]
7. Prochaska JJ, Sallis JF, Long B. A physical activity screening measure for use with adolescents in primary care. *Arch Pediatr Adolesc Med* 2001;155:554–559. [PubMed: 11343497]

8. Tanner, JM., editor. Growth at Adolescence. Vol. 2nd edition. Oxford, UK: Blackwell Scientific; 1962.
9. Cameron, N. The methods of auxologic anthropometry. In: Falkner, FT., editor. Human Growth. New York: Plenum Press; 1986. p. 3-43.
10. Taylor RW, Jones IE, Williams SM, Goulding A. Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3–19 y. *Am J Clin Nutr* 2000;72:490–495. [PubMed: 10919946]
11. Lohman, T.; Roche, AF.; Martorell, R. Anthropometric Standardization Reference Manual. Champaign, IL: Human Kinetics Books; 1988.
12. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003;26:S5–S20. [PubMed: 12502614]
13. 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;28:412–419. [PubMed: 3899825]
14. Gungor N, Saad R, Janosky J, Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. *J Pediatr* 2004;144:47–55. [PubMed: 14722518]
15. Conwell LS, Trost SG, Brown WJ, Batch JA. Indexes of insulin resistance and secretion in obese children and adolescents: a validation study. *Diabetes Care* 2004;27:314–319. [PubMed: 14747206]
16. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000;85:2402–2410. [PubMed: 10902785]
17. Woodward, M. Epidemiology: Study Design and Data Analysis. Boca Raton, FL: Chapman & Hall/CRC; 1999. p. 482
18. Herlihy OM, Barrow BA, Grant PJ, Levy JC. Hyperglycaemic siblings of type II (non-insulin-dependent) diabetic patients have increased PAI-1, central obesity and insulin resistance compared with their paired normoglycaemic sibling. *Diabetologia* 2002;45:635–641. [PubMed: 12107743]
19. Elbein SC, Hasstedt SJ, Wegner K, Kahn SE. Heritability of pancreatic beta-cell function among nondiabetic members of Caucasian familial type 2 diabetic kindreds. *J Clin Endocrinol Metab* 1999;84:1398–1403. [PubMed: 10199785]
20. 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;22:1325–1329. [PubMed: 10480778]
21. Goran MI, Bergman RN, Avila Q, Watkins M, Ball GD, Shaibi GQ, et al. Impaired glucose tolerance and reduced beta-cell function in overweight Latino children with a positive family history for type 2 diabetes. *J Clin Endocrinol Metab* 2004;89:207–212. [PubMed: 14715851]
22. Arslanian SA, Bacha F, Saad R, Gungor N. Family history of type 2 diabetes is associated with decreased insulin sensitivity and an impaired balance between insulin sensitivity and insulin secretion in white youth. *Diabetes Care* 2005;28:115–119. [PubMed: 15616243]
23. Goran MI, Coronges K, Bergman RN, Cruz ML, Gower BA. Influence of family history of type 2 diabetes on insulin sensitivity in prepubertal children. *J Clin Endocrinol Metab* 2003;88:192–195. [PubMed: 12519851]
24. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403. [PubMed: 11832527]
25. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetes Med* 1998;15:539–553.
26. Wiegand S, Maikowski U, Blankenstein O, Biebertmann H, Tarnow P, Gruters A. Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity: a problem that is no longer restricted to minority groups. *Eur J Endocrinol* 2004;151:199–206. [PubMed: 15296475]
27. Williams DE, Cadwell BL, Cheng YJ, Cowie CC, Gregg EW, Geiss LS, et al. Prevalence of impaired fasting glucose and its relationship with cardiovascular disease risk factors in US adolescents, 1999–2000. *Pediatrics* 2005;116:1122–1126. [PubMed: 16263998]

28. Duncan, GE. Prevalence of diabetes and impaired fasting glucose levels among US adolescents: National Health and Nutrition Examination Survey, 1999–2002; Arch Pediatr Adolesc Med. 2006. p. 523–528.
29. Leahy JL. Pathogenesis of type 2 diabetes mellitus. Arch Med Res 2005;36:197–209. [PubMed: 15925010]
30. Gungor N, Bacha F, Saad R, Janosky J, Arslanian S. Youth type 2 diabetes: insulin resistance, beta-cell failure, or both? Diabetes Care 2005;28:638–644. [PubMed: 15735201]
31. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC. UK Prospective Diabetes Study (UKPDS) Group. UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years. Diabetes Med 1998;15:297–303.

Table I

Comparison of obese subjects with (sibling group, n = 20) and without (control group, n = 42) a sibling diagnosed with T2DM during childhood

	Sibling group	Control group	<i>P</i> value *
Characteristics and history			
Age, years	12.2 ± 2.6 [†]	12.1 ± 2.3	.9 [‡]
Sex, % male	40	48	.6
Race, %			.1
American Indian/Alaskan native	0	2	
Asian	0	0	
Native Hawaiian/Pacific Islander	0	0	
Black or African American	75	93	
Caucasian	5	2	
More than one race	10	2	
Unknown or not reported	5	0	
Other	5	0	
Ethnicity, %			.2
Hispanic or Latino	20	5	
Not Hispanic or Latino	75	90	
Unknown or not reported	5	5	
Sibling age ≥ 12 years was full sibling (not half sibling), %	80	60	.2
At least one parent with h/o T2DM, %	61	27	.02
Met physical activity guidelines by PACE+, %	50	38	.4
Anthropometric measures			
Weight, kg	83.3 ± 25.7	83.6 ± 24.9	.9
Height, cm	154.6 ± 13.8	156.0 ± 12.0	.8
Waist circumference, cm	101.8 ± 16.3	99.3 ± 16.8	.6
BMI, kg/m ²	34.1 ± 6.1	33.8 ± 7.5	.8
BMI z-score	2.4 ± 0.3	2.4 ± 0.3	.6
Fat mass, kg	33.1 ± 12.7	31.9 ± 11.3	.9
Fat-free mass, kg	50.8 ± 15.5	49.1 ± 12.0	.6
Percent body fat, %	39.1 ± 6.2	38.9 ± 6.0	.9
Physical examination			
Tanner stage ≥ 2, %	90	70	.1
Tanner stage, %			.1
1	10	30	
2	15	2.5	
3	10	20	
4	20	15	
5	45	32.5	
Presence of acanthosis nigricans, %	95	95	1.0
Laboratory data			
HbA1c, %	5.2 ± 0.3	5.1 ± 0.3	.1

	Sibling group	Control group	<i>P</i> value [*]
Fasting glucose, mg/dL	89.7 ± 8.3	88.4 ± 6.1	1.0
Fasting insulin, μIU/mL	20.4 ± 11.0	20.0 ± 18.4	.4
HOMA	4.5 ± 2.4	4.4 ± 3.7	.5 [‡]
QUICKI	0.132 ± 0.01	0.136 ± 0.02	.4 [‡]

^{*} Unadjusted *P* value.

[‡] Mean values ± standard deviation.

[‡] *P* values for *t*-test comparing log-transformed variables.

Table II

OGTT results

	Sibling group (n = 20)	Control group (n = 42)
Fasting glucose, mg/dL		
100–125	1 [*]	1 [†]
≥ 126	0	0
Two-hour glucose, mg/dL		
140–199	6	6
≥ 200	2	0

^{*} This subject also had a 2-hour glucose level ≥ 200 mg/dL.

[†] This subject also had a 2-hour glucose level of 140–199 mg/dL.