

# Influence of Family History of Type 2 Diabetes on Insulin Sensitivity in Prepubertal Children

MICHAEL I. GORAN, KATE CORONGES, RICHARD N. BERGMAN, MARTHA L. CRUZ AND BARBARA A. GOWER

*Departments of Preventive Medicine (M.I.G., K.C., M.L.C.) and Physiology and Biophysics (M.I.G., R.N.B.), Keck School of Medicine, University of Southern California, Los Angeles, California 90033; and Department of Nutrition Sciences (B.A.G.), University of Alabama at Birmingham, Birmingham, Alabama 35294*

The objective of this study was to examine the influence of positive family history (FH) of type 2 diabetes (T2D) on aspects of insulin resistance in prepubertal children. Twenty-one children (Tanner stage I or II) with a positive FH were compared with children with no FH. FH was defined by presence of T2D in a parent or grandparent as assessed by interview. The two groups of children were matched for age, gender, Tanner stage, ethnicity, geographical location, and body fat mass using a pair-matched design. These 21 pairs of children included Caucasian, African American, and Hispanic children who were studied either in Birmingham, Alabama, or Los Angeles, California, using similar techniques. Insulin sensitivity ( $S_I$ ) and the acute insulin response to glucose (AIR) were de-

termined by an iv glucose tolerance test and minimal modeling, and body composition was determined by dual-energy x-ray absorptiometry. There were no significant differences in fasting glucose or insulin,  $S_I$ , AIR, the disposition index (product of  $S_I$  and AIR), or body composition between children with a FH vs. those without a FH of T2D, and there were no significant differences in these parameters when the data were analyzed separately in each ethnic group. In conclusion, a positive FH for T2D does not seem to have any significant effect on insulin sensitivity, as assessed by the minimal model and associated risk factors for T2D in young children. (*J Clin Endocrinol Metab* 88: 192–195, 2003)

CHILDHOOD OBESITY HAS reached epidemic levels in the United States (1), and the increased levels of obesity have been implicated to contribute to the alarming increase in type 2 diabetes emerging during adolescence (2). Several risk factors have already been identified as contributors to the development of type 2 diabetes in children, including increased body fat content contributing to greater insulin resistance (3, 4), ethnicity (with greater risk in African American, Hispanic, and Native American children; Refs. 5 and 6), and onset of puberty (7, 8). There is no clear explanation of how these factors increase risk, but this may be due to previously documented separate and independent effects of higher body fat, ethnicity, and onset of puberty contributing to greater insulin resistance. We hypothesize that the constellation of these risk factors may be especially problematic during the critical period of adolescent development, especially in individuals who may have compromised  $\beta$ -cell function and an inability to compensate for severe insulin resistance. One other factor that has also been hypothesized to increase risk of type 2 diabetes is a positive family history of type 2 diabetes, but this has not been widely studied in children.

Previous studies in adults suggest a strong hereditary component in risk for type 2 diabetes (9–17). Although these studies have shown an association between family history of type 2 diabetes and insulin resistance in adults, to our knowledge, only two studies have looked at the relationship between family history and insulin resistance in children. One study from 1968 used an oral glucose tolerance test to show greater intolerance to glucose in an ethnically diverse group

of obese children with a family history of type 2 diabetes (18), and another study used the insulin-clamp technique in African American children to show a lower insulin-stimulated glucose disposal in those with a positive family history (19). Because of the paucity of information on the influence of family history of type 2 diabetes, the purpose of this study was to examine this issue in more detail in a diverse group of young children. By carefully controlling for the factors already known to influence insulin resistance (*i.e.* fat mass, puberty, ethnicity), we used a pair-matched design to examine the hypothesis that insulin sensitivity would be lower in children with a positive family history of type 2 diabetes compared with children without a family history of type 2 diabetes.

## Subjects and Methods

### Subjects

Children were recruited by newspaper and radio advertisements, presentations at local schools, mailings to University and Hospital employees, and by word-of-mouth. No child was taking medications known to affect body composition (*e.g.* ritalin, GH), was diagnosed with syndromes or diseases known to affect body composition or fat distribution (*e.g.* Cushings's, Down's, type 1 diabetes), or was diagnosed with any major illness since birth. Ethnicity (Caucasian, African American, or Hispanic) was determined by self-report and was defined by all four grandparents being of the same ethnic group as the child in the study. Two children with a positive family history did not have all four grandparents of the same ethnic group and were included under "other" ethnic group. Children were included who were studied in ongoing studies either in Birmingham, Alabama, or in Los Angeles, California. The data from the study in Alabama were collected between 1997 and 2001, and the data from Los Angeles were collected between 2000 and 2001.

For this analysis, we limited maturation stage to include only children

Abbreviations: BMI, body mass index.

at Tanner stage I or II. Positive family history of type 2 diabetes was evaluated based on medical and family history and was defined by diagnosis of type 2 diabetes in any parent or grandparent of the child in question based on the medical history interview. None of the children were reported to be the products of a diabetic pregnancy. For each child who was identified as having a positive family history of type 2 diabetes, we identified a pair-matched control child from our database in whom measures of insulin sensitivity were available. Pairs of children were matched based on the following criteria: 1) ethnicity; 2) gender; 3) age; 4) Tanner stage; 5) geographical location; and 6) body fat mass. Thus, we created a data set consisting of 21 matched pairs of children (11 males and 10 females) who were very similar in physical and demographic factors, except for presence or absence of a positive family history. The Institutional Review Boards of the University of Southern California and the University of Alabama at Birmingham approved these studies. Both parents provided informed consent, and children signed a child assent form before testing commenced.

### Protocol

Children were admitted to the General Clinical Research Center in the late afternoon for an overnight visit. In the afternoon, a detailed medical history and physical examination were performed, including assessment of Tanner stage by a physician based on breast stage and pubic hair development in girls, and genitalia development in boys. The children were served dinner and an evening snack, with all food consumed before 2000 h. Consumption of only water and noncaloric, noncaffeinated beverages was permitted between 2000 h and testing the following morning. The following morning iv lines were placed and an iv glucose tolerance test was performed. Testing was completed by approximately 1200 h.

### Tolbutamide-modified, frequently sampled, iv glucose tolerance test

Insulin sensitivity, the acute insulin response to glucose, and the disposition index (product of insulin sensitivity and acute insulin response) were determined using a frequently sampled, iv glucose tolerance test in the early morning after an overnight fast, as reported previously (6). Sera were analyzed in duplicate for glucose using an Ektachem II analyzer (for studies at University of Alabama at Birmingham; Johnson & Johnson Clinical Diagnostics, New Brunswick, NJ) or using a Yellow Springs 2700 Glucose Analyzer (YSI Inc., Yellow Springs, OH) and a glucose oxidase kit (for studies at University of Southern California), and for insulin (RIA; Diagnostic Products, Los Angeles, CA). Values for glucose and insulin were entered into the MINMOD computer program (version 3.0; provided by R.N.B.) for determination of insulin sensitivity, the acute insulin response to glucose, and the disposition index.

### Total body fat

Whole body composition (fat mass and fat-free mass) was measured by dual-energy x-ray absorptiometry using a Hologic QDR 4500W densitometer (Hologic, Inc., Bedford, MA) in studies in Los Angeles and a Lunar DPX-L (pediatric software, version 1.5e; Lunar Corp., Madison, WI) in studies in Birmingham.

### Data analysis

Variables that were not normally distributed were log transformed before analysis. For ease of interpretation, data are presented in the measured untransformed scale. Parameters of interest were compared in children with a positive family history *vs.* those without using a *t* test and a significance level of 0.05. Data analysis was conducted using SPSS version 9.0 (SPSS, Inc., Chicago, IL), and values are presented as means  $\pm$  SD.

## Results

The breakdown of children with regard to ethnicity and geographical location is shown in Table 1, and a summary of their physical characteristics is shown in Table 2. There was no difference in age, body weight, body mass index (BMI),

**TABLE 1.** Summary of study participants by ethnic identity and geographical location

Ethnic group	No. of matched pairs
Caucasian (n = 8)	8 in BHM, 0 in LA
African American (n = 5)	4 in BHM, 1 in LA
Hispanic (n = 6)	0 in BHM, 6 in LA
Other (n = 2)	0 in BHM, 2 in LA
Total (n = 21)	12 in BHM, 9 in LA

BHM, Birmingham; LA, Los Angeles.

**TABLE 2.** Physical characteristics

Variable	Family history	No family history	P
Age (yr)	9.8 $\pm$ 1.7	9.4 $\pm$ 1.8	0.37
Weight (kg)	39.4 $\pm$ 10.1	39.4 $\pm$ 12.0	0.99
BMI (kg/m <sup>2</sup> )	19.9 $\pm$ 3.9	20.6 $\pm$ 4.4	0.62
Fat mass (kg)	11.2 $\pm$ 6.5	11.3 $\pm$ 7.0	0.95
Lean mass (kg)	26.4 $\pm$ 4.5	25.8 $\pm$ 5.6	0.69

**TABLE 3.** Comparison of insulin and glucose measures

Variable	Family history	No family history	P
Fasting glucose (mg/dl)	91.2 $\pm$ 4.0	91.9 $\pm$ 4.3	0.62
Fasting insulin ( $\mu$ IU/ml)	10.4 $\pm$ 6.8	9.6 $\pm$ 6.1	0.70
Insulin sensitivity [ $\times 10^{-4}$ min <sup>-1</sup> ( $\mu$ IU/ml)]	6.3 $\pm$ 4.3	6.0 $\pm$ 3.8	0.79
Acute insulin response ( $\mu$ IU/ml)	996 $\pm$ 699	882 $\pm$ 608	0.58
Disposition index (min <sup>-1</sup> )	4503 $\pm$ 3890	4172 $\pm$ 2626	0.72

body fat mass, or lean mass between children with a family history of type 2 diabetes *vs.* those without a family history. Thus, the two groups of children were well matched for age and body composition. A summary of the insulin and glucose measures in the two matched groups of children is shown in Table 3. There were no significant differences in fasting glucose, fasting insulin, insulin sensitivity, the acute insulin response to glucose, or the disposition index between children with a family history of type 2 diabetes *vs.* those without. In addition, there were no differences within pairs when the data were analyzed separately by obesity status (6 pairs with a (85th BMI-age percentile *vs.* 15 pairs with a 85th BMI-age percentile), or for the three main ethnic groups studied (Caucasian, African American, and Hispanic). Figure 1 shows that the cross-sectional relationship between insulin sensitivity and body fat mass was identical in children with a family history of type 2 diabetes *vs.* those without.

## Discussion

Insulin resistance and a positive family history are both hypothesized to be significant risk factors in the development of type 2 diabetes. However, it is unclear whether these two factors serve as independent risk factors that may act through different pathways, or whether a positive family history increases risk through an effect on insulin resistance. Studies in children may be particularly useful in this regard because the potential influence of family history on insulin resistance can be studied without the confounding effects of advanced disease progression. Using a pair-matched design to control for the factors already known to influence insulin resistance in children, the main findings of the current study show no significant difference in fasting glucose and insulin,

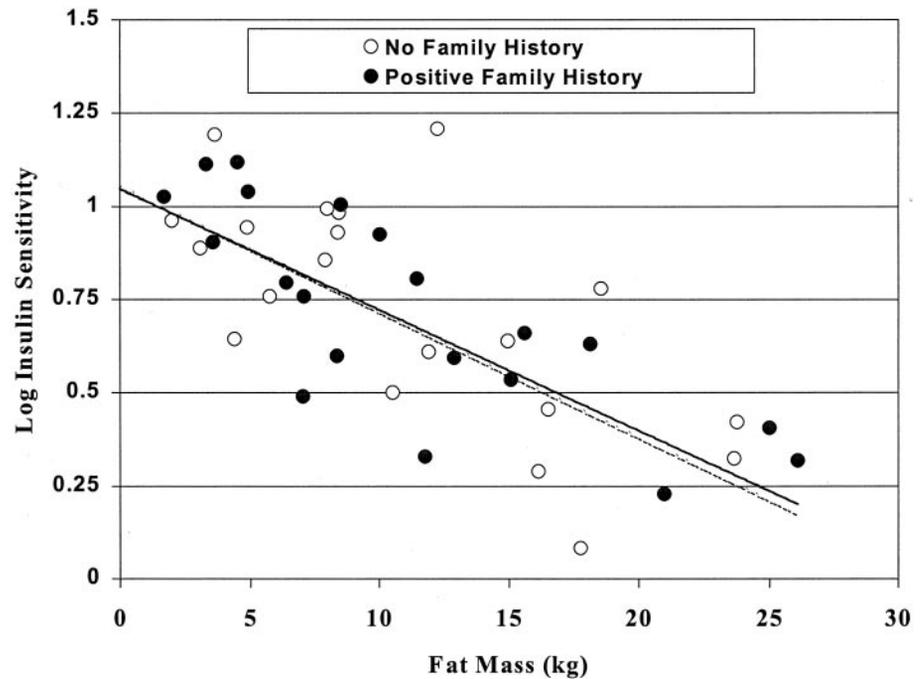


FIG. 1. Relationship between insulin sensitivity and body fat mass in children with and without a positive family history of type 2 diabetes.

insulin sensitivity, acute insulin response to glucose, and the disposition index between children with a positive family history of type 2 diabetes *vs.* those without a family history.

The hereditary component of type 2 diabetes and insulin resistance has been studied extensively in adults, with most studies showing greater insulin resistance in offspring of diabetics (9–13, 15–17, 19). However, we have only been able to identify two previous studies that have examined the influence of family history of type 2 diabetes on insulin resistance during childhood. In one study from 1968, 66 black, Puerto Rican, and white obese children between 4 and 16 yr of age were studied (18). Fasting glucose and insulin were similar in children with and without a positive family history of diabetes. Because this report published the raw data, we were able to reclassify the children for impaired glucose tolerance based on recent American Diabetes Association guidelines (20). Impaired glucose tolerance (or prediabetes) was evident in 24% of children with a positive family history of diabetes *vs.* 9% in those without, and the insulin response at 1 h postglucose was almost double in the children with a positive family history ( $63.6 \pm 48.3$  *vs.*  $100.3 \pm 77$   $\mu\text{U}/\text{ml}$ ;  $P = 0.03$ ). Although the two groups were matched for percentage over ideal body weight, they were not matched for body fat content, and the group with a positive family history was almost 2.5 yr older ( $10.9 \pm 2.8$  *vs.*  $8.5 \pm 2.6$  yr), raising the possibility of maturational differences in the two groups. In another study with strong outcome measures, 9 prepubertal, healthy African American children with a positive family history of type 2 diabetes were compared with 13 matched children with no family history (19). The groups were matched for age, BMI, degree of adiposity, and physical fitness. There were no differences in fasting glucose and insulin levels, but using the hyperinsulinemic euglycemic clamp technique, the group with a positive family history had lower insulin-stimulated glucose disposal and lower nonoxidative glucose disposal or glucose storage (19).

Taken together with the current study, previous results indicate that, in children, fasting glucose and insulin may not be affected by a positive family history. However, family history may affect the glucose and insulin response to an oral glucose load and insulin sensitivity as assessed by the clamp technique. In contrast, insulin sensitivity when measured by the iv glucose tolerance test may not be affected by a positive family history. The clamp technique may be more sensitive to detecting small differences, and methodological differences may account for some of the discrepant findings. In addition, other factors may need to be considered. One critical factor that may explain these discrepant findings and the difference from what has been observed in adults is age, and more specifically perhaps, maturation stage. Pubertal development is associated with a transient reduction in insulin sensitivity and a compensatory increase in insulin secretion (8). Although no longitudinal studies have tracked changes from mid-puberty to the end of puberty, cross-sectional studies show a recovery of insulin sensitivity by the end of puberty. One possible hypothesis is that the difference in insulin sensitivity due to a positive family history develops during or after puberty. More specifically, there may be a reduced likelihood of full recovery of prepubertal levels of insulin sensitivity in children with a positive family history.

It also could be hypothesized that the influence of a positive family history on insulin resistance during childhood may be different among particularly susceptible subgroups such as the obese or different ethnic groups, so that other studies using careful matching in different states of obesity and among different ethnic groups may be warranted. One limitation of the current study was that we only had limited numbers of matched pairs within each of the obesity groups (6 of the 21 pairs had a 85th BMI-age percentile) and the ethnic groups studied (eight Caucasian pairs, five African American pairs, six Hispanic pairs, and two “other” pairs). Thus, future studies may be warranted to look at the effects

of family history of type 2 diabetes within specific ethnic groups. This may be particularly important given the well documented ethnic differences in insulin resistance (5, 6), as well as the likelihood of ethnic differences in the associated compensatory responses to insulin resistance (21).

Several other limitations of this study may be worth considering. First, degree of family history was determined based on an interview and not based on actual measures. For example, some families expressing no family history of type 2 diabetes may, in fact, have familial cases of hidden type 2 diabetes. Future studies should base family history on more objective criteria as assessed, for example, by evaluation of diagnostic tests in family members including an oral glucose tolerance test. Second, many studies have not considered the issue of whether the affected family member is the mother *vs.* the father, nor the extent of family history with regard to numbers of affected individuals. One previous study showed that the risk of type 2 diabetes was transmitted primarily through an affected parent and increased even more when both the parent and the grandparent had the disease (15). In the current study, we did not evaluate the separate contribution of an affected parent *vs.* an affected grandparent because our evaluation of family history did not identify who the affected first- or second-degree relative was. It is possible that the potential effect of family history was diluted by inclusion of children with affected grandparents and further studies comparing the effects of first- *vs.* second-degree family history are needed.

In summary, we used a pair-matched design to identify pairs of prepubertal children who were matched for gender, ethnicity, geographical location, age, and body fat content but differed with regard to reported family history of type 2 diabetes. There were no significant differences in fasting glucose and insulin, insulin sensitivity, acute insulin response to glucose, and the disposition index between children with a positive family history of type 2 diabetes *vs.* those without a family history. In conclusion, these results support the hypothesis that a positive family history of type 2 diabetes does not have any significant effect on insulin resistance and associated risk factors for type 2 diabetes in young children.

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Address all correspondence and requests for reprints to: Michael I. Goran, Ph.D., Department of Preventive Medicine, University of Southern California, 1540 Alcazar Street, Room 208-D, Los Angeles, California 90033. E-mail: goran@usc.edu.

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