OBJECTIVE — Family history of type 2 diabetes is a major risk factor for type 2 diabetes in youth, which is increasing. This investigation aimed to evaluate the impact of family history of type 2 diabetes on insulin secretion relative to insulin sensitivity in healthy children. β-Cell compensation for insulin sensitivity was calculated as the product of insulin sensitivity × first-phase insulin secretion, termed glucose disposition index (GDI).

RESEARCH DESIGN AND METHODS — A total of 28 healthy white children (12 boys and 16 girls, 12.1 ± 0.5 years of age) with a positive family history of type 2 diabetes and 26 healthy white children (13 boys and 13 girls, 11.5 ± 0.4 years of age) with a negative family history of type 2 diabetes underwent a 3-h 40 mU·m⁻²·min⁻¹ hyperinsulinemic-euglycemic clamp to assess insulin sensitivity and clearance and a 2-h hyperglycemic clamp to assess insulin secretion. Body composition and visceral adiposity were evaluated with dual-energy X-ray absorptiometry and computed tomography at the L₄-L₅ intervertebral space.

RESULTS — Insulin sensitivity was lower in children with a family history of type 2 diabetes versus children without a family history (8.8 ± 0.9 vs. 12.2 ± 1.1 μmol·kg⁻¹·min⁻¹ per pmol/l, \( P = 0.02 \)). Similarly, insulin clearance was lower. First- and second-phase insulin levels were not different between groups with and without a positive family history. The GDI was lower in youth with versus youth without a positive family history (4.1 ± 0.3 vs. 5.2 ± 0.5 mmol·kg⁻¹·min⁻¹, \( P = 0.039 \)). IGFBP-1 (IgFBP-1) was 60% lower in youth with versus youth without the positive family history.

CONCLUSIONS — These results demonstrate that family history of type 2 diabetes in white children is associated with decreased insulin sensitivity and clearance, decreased IGFBP-1, and an impaired relationship between insulin action and β-cell compensation. Detection of these alterations in hormonal and metabolic parameters in children with a positive family history suggests that at least some of the determinants of GDI are genetic/heritable.

Diabetes Care 28:127–131, 2005

From the Divisions of Pediatric Endocrinology, Metabolism, and Diabetes Mellitus, Children’s Hospital of Pittsburgh, Pittsburgh, Pennsylvania
Address correspondence and reprint requests to Silva A. Arslanian, MD, Division of Endocrinology, Children’s Hospital of Pittsburgh, 3705 Fifth Ave. at DeSoto St., Pittsburgh, PA 15213. E-mail: silva.arslanian@chp.edu.
Received for publication 23 February 2004 and accepted in revised form 23 September 2004.
Abbreviations: GDI, glucose disposition index; IGFBP-1, IGF binding protein-1
A table elsewhere in this issue shows conventional and Systeme International (SI) units and conversion factors for many substances.
© 2005 by the American Diabetes Association.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

T

ype 2 diabetes is increasing in children (1,2). Both obesity and family history of type 2 diabetes are associated with increased risk of type 2 diabetes in youth, irrespective of the ethnic background (3,4). Insulin resistance and β-cell failure are prerequisites for development of type 2 diabetes. However, the relative role of each remains controversial because adult studies of at-risk first-degree relatives of patients with type 2 diabetes have yielded conflicting results. Some studies have shown that the familial nature of type 2 diabetes is manifest by the presence of insulin resistance in non-diabetic first-degree relatives (5–8), whereas others have shown β-cell dysfunction (9–13). Despite the abundance of adult data, only few pediatric published studies have investigated the impact of family history of type 2 diabetes on parameters of glucose metabolism (14–17). We previously demonstrated that black children with a family history of type 2 diabetes have ~25% lower insulin-stimulated glucose disposal compared with black children without a family history of type 2 diabetes (15). On the other hand, no such differences were detected when Caucasian, African-American, and Hispanic children with versus without a family history of type 2 diabetes were studied as a group (16). In any one individual, glucose homeostasis is maintained by a reciprocal balance between insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18). This relationship is a hyperbolic function such that the product of insulin sensitivity × acute insulin response is constant and is termed the glucose disposition index (GDI) (18). Therefore, assessment of β-cell function should take into account the state of insulin sensitivity and secretion (18).
Family history of type 2 diabetes and GDI

Table 1—Characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>Subjects without family history of type 2 diabetes</th>
<th>Subjects with family history of type 2 diabetes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.5 ± 0.4</td>
<td>12.1 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Tanner stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td>II–III</td>
<td>9</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>IV–V</td>
<td>6</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.8 ± 0.5</td>
<td>20.0 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage body fat</td>
<td>8.8 ± 1.1</td>
<td>11.4 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Visceral adipose tissue (cm²)</td>
<td>18.2 ± 2.8</td>
<td>25.3 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Subcutaneous adipose tissue (cm²)</td>
<td>85.1 ± 14.1</td>
<td>139.9 ± 24.1</td>
<td>NS</td>
</tr>
<tr>
<td>IGFBP-1 (nmol/l)</td>
<td>35.3 ± 2.8</td>
<td>41.1 ± 3.3</td>
<td>NS</td>
</tr>
<tr>
<td>IGFBP-1 (ng/ml)</td>
<td>42.8 ± 7.2</td>
<td>16.8 ± 3.1</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are means ± SE.

useful trait for identifying genetic predisposition to type 2 diabetes (18,19). Our present investigation aimed to test the hypothesis that family history of type 2 diabetes in children is associated with an impaired balance between insulin sensitivity and insulin secretion. We assessed a measure of β-cell compensation for insulin sensitivity by calculating the product of insulin sensitivity (measured during a hyperinsulinemic-euglycemic clamp) and β-cell function (measured during a hyperglycemic clamp) in white children with versus without a family history of type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 28 healthy white children (12 boys and 16 girls) with a positive family history of type 2 diabetes and 26 healthy white children with a negative family history of type 2 diabetes (13 boys and 13 girls) were studied. A positive family history was defined as the presence of known family members with type 2 diabetes in any of three generations (siblings, parents, or grandparents) (15). All studies were approved by the Human Rights Committee of the Children’s Hospital of Pittsburgh. All subjects were in good health assessed by history, physical examination, and routine hematologic and biochemical tests. Pubertal development was assessed by careful physical examination according to the criteria of Tanner and confirmed by measurements of plasma testosterone in boys, estradiol in girls, and dehydroepiandrosterone-sulfate in both boys and girls. Some of these subjects were reported previously (20,21). The clinical characteristics of the study participants are shown in Table 1.

All evaluations were performed in the General Clinical Research Center at Children’s Hospital of Pittsburgh. Each subject was studied twice, 1–3 weeks apart, once during a 3-h hyperinsulinemic-euglycemic clamp to assess insulin sensitivity and once during a 2-h hyperglycemic clamp to assess insulin secretion, in random order. Clamp experiments were performed after a 10- to 12-h overnight fast. For each study, two intravenous catheters were inserted after the skin and subcutaneous tissues were anesthetized with EMLA cream (Astra, Worcester, MA). One catheter was placed in a forearm vein for administration of insulin and glucose. The second catheter was placed in the dorsal contralateral hand vein, which was heated for sampling of arterialized blood. A fasting blood sample was obtained for measurement of proinsulin and C-peptide levels.

Body composition was assessed with dual-energy X-ray absorptiometry and intra-abdominal fat by a 10-mm single axial computed tomography scan of the abdomen at the level of L₄-L₅ vertebrae, as reported by us previously (20,21).

In vivo insulin secretion, insulin sensitivity, and clearance
First- and second-phase insulin secretion was assessed during a 2-h hyperglycemic (12.5 mmol/l) clamp, as described by us previously (20). Insulin-stimulated glucose metabolism and insulin sensitivity and clearance were evaluated during a 3-h 40 mU · m⁻² · min⁻¹ hyperinsulinemic-euglycemic clamp according to our previously published methodology (20,21). The insulin-stimulated glucose disposal rate was calculated during the last 30 min of the euglycemic clamp to be equal to the rate of exogenous glucose infusion. Insulin sensitivity and clearance were calculated as reported by us previously (20).

During the hyperglycemic clamp, the first-phase insulin concentration was calculated as the mean of five insulin determinations at 2.5, 5.0, 7.5, 10.0, and 12.5 min of the clamp, and the second phase was calculated as the mean of eight determinations from 15 to 120 min of the clamp. The GDI was calculated as the product of insulin sensitivity × first-phase insulin level (20).

Biochemical measurements
Plasma glucose was measured by the glucose oxidase method with a glucose analyzer (YSI, Yellow Springs, OH), and the insulin concentration was determined by radioimmunoassay (20). Proinsulin, C-peptide and IGFBP-1 levels were measured at the Esoterix Endocrinology Laboratory (Calabasas Hills, CA) by immunochemiluminescent assays, and IFG-1 was measured by radioimmunoassay after acid ethanol extraction.

Statistical analysis
Comparison between children with and without a family history of type 2 diabetes was made using two-tailed Student’s test for continuous variables. Pearson or Spearman correlation analysis was used when applicable to examine bivariate relationships. To evaluate multivariate relationships, multiple regression analysis was applied. All statistical assumptions were met. Data are presented as means ± SE. P ≤ 0.05 was considered statistically significant.

RESULTS — Groups with a family history and without a family history did not differ in age, Tanner stage, BMI, fat mass, percentage of body fat, visceral adipose tissue, and subcutaneous adipose tissue (Table 1).
and second-phase insulin (826.9 ± 97.4 vs. 701.9 ± 127.9 pmol/l, P = NS) were not different between subjects with a family history and subjects without (Fig. 1). However, the GDI (insulin sensitivity × first-phase insulin) was significantly lower in children with and in children without a family history (4.1 ± 0.3 vs. 5.2 ± 0.5 mmol · kg⁻¹ · min⁻¹, respectively, P = 0.039) (Fig. 2). In a multiple regression analysis with GDI as the dependent variable, the only significant contributor was family history of type 2 diabetes (P = 0.047 with no effect of BMI or percentage of body fat.

When prepubertal children were analyzed separately, the group with a family history (n = 11) and the group without (n = 11) did not differ significantly in BMI (18.3 ± 0.6 vs. 17.3 ± 0.3 kg/m²) or fat mass (8.3 ± 1.3 vs. 6.6 ± 0.6 kg). Insulin sensitivity, insulin clearance, and fasting, first-phase, and second-phase insulin levels were not different between children with a family history and children without a family history (data not shown). However, GDI was lower in subjects who did have a family history (4.3 ± 0.2 vs. 6.3 ± 0.7 mmol · kg⁻¹ · min⁻¹, P = 0.022). When adolescents were analyzed separately, the group with a family history (n = 17) and the group without (n = 15) did not differ in BMI (21.2 ± 0.7 vs. 19.8 ± 0.8 kg/m²) or fat mass (13.4 ± 2.0 vs. 10.3 ± 1.8 kg). The group with a family history had lower insulin sensitivity (6.5 ± 0.9 vs. 9.6 ± 0.9 μmol · kg⁻¹ · min⁻¹ per pmol/l, respectively, P = 0.018), lower insulin clearance (11.9 ± 1.0 vs. 15.5 ± 1.2 ml · kg⁻¹ · min⁻¹, P = 0.036), and higher fasting insulin (151.2 ± 14.2 vs. 110.4 ± 7.8 pmol/l, P = 0.019). First-phase insulin and GDI...

**Fasting metabolic data**

Fasting plasma glucose levels were similar in subjects with and without a family history (5.4 ± 0.06 vs. 5.3 ± 0.04 mmol/l, respectively). However, children with a family history had higher fasting insulin levels, both during the hyperglycemic and the euglycemic clamp (124.4 ± 11.8 vs. 93.8 ± 8.7 pmol/l [P = 0.042] and 125.0 ± 10.9 vs. 95.8 ± 6.6 pmol/l [P = 0.026], respectively). C-peptide levels were also higher in subjects with a family history than in subjects without a family history (0.58 ± 0.05 vs. 0.42 ± 0.04 nmol/l, respectively, P = 0.016). There was a tendency for fasting proinsulin levels to be higher in subjects with a family history (14.7 ± 2.2 vs. 10.6 ± 1.1 pmol/l, P = 0.10). Fasting IGFBP-1 levels were significantly lower in youths with a family history than in youths without a family history; no difference in IGF-I levels was noted (Table 1). IGFBP-1 correlated with insulin sensitivity (r = 0.52, P < 0.001), insulin clearance (r = 0.35, P = 0.01), GDI (r = 0.28, P = 0.04), and fasting, first-phase, and second-phase insulin levels (r = −0.44, P = 0.001; r = −0.31, P = 0.02; and r = −0.32, P = 0.02, respectively).

**Insulin sensitivity, clearance, and secretion and GDI**

During the hyperinsulinemic-euglycemic clamp, insulin sensitivity was lower in subjects with a family history than in subjects without a family history (8.8 ± 0.9 vs. 12.2 ± 1.1 μmol · kg⁻¹ · min⁻¹ per pmol/l, respectively, P = 0.02) (Fig. 1). Similarly, insulin clearance was lower (13.5 ± 0.8 vs. 16.4 ± 0.9 ml · kg⁻¹ · min⁻¹, P = 0.02). During the hyperglycemic clamp, first-phase insulin (586.8 ± 69.9 vs. 490.0 ± 73.9 pmol/l, P = NS)
were not significantly different between the two groups (721.4 ± 101.1 vs. 532.5 ± 127.2 pmol/l and 4.0 ± 0.4 vs. 4.5 ± 0.6 mmol · kg⁻¹ · min⁻¹, respectively). IGFBP-1 levels were lower in prepubertal subjects with a family history than in subjects without (28.1 ± 5.6 vs. 68.5 ± 11.3 ng/ml, \( P = 0.004 \)) and pubertal subjects (9.4 ± 2.4 vs. 22.5 ± 4.7 ng/ml, \( P = 0.022 \)).

CONCLUSIONS — The present study demonstrates that family history of type 2 diabetes in white children and adolescents is associated with lower insulin sensitivity and lower GDI. These data could possibly offer a cross-sectional view of two potentially distinct developmental stages in the natural history of the evolution of the risk for type 2 diabetes. We postulate that the earliest metabolic alterations associated with a positive family history of type 2 diabetes manifest themselves in a lower insulin secretion relative to insulin sensitivity, i.e., an impaired balance between insulin sensitivity \( \times \) secretion. This is evident in prepubertal children. However, during puberty and the consequent stress of pubertal insulin resistance, significant differences in insulin sensitivity emerge between adolescents with a family history and those without one. The lower insulin sensitivity in adolescents with a family history is associated with lower insulin clearance, which could be an early compensation for the insulin resistance. The absence of significant differences in GDI in adolescents with a family history compared with adolescents without one could be due to the lower insulin clearance and the impact on circulating insulin levels. Future studies should assess insulin secretion using C-peptide modeling during a hyperglycemic clamp.

Although both insulin resistance and insulin deficiency contribute to the pathogenesis of type 2 diabetes, considerable debate continues about which defect is the earliest. In relatives of patients with type 2 diabetes, studies have either evaluated insulin sensitivity or insulin secretion separately; only very few studies have addressed both defects simultaneously. Furthermore, most of these studies have been performed in middle-aged adults and not children. Theoretically, one would be able to detect the earliest derangements in children and at a much younger age before environmental influences set in. Adult studies have typically demonstrated that nondiabetic offspring relatives of patients with type 2 diabetes are insulin resistant/hyperinsulinemic (5,7,8,22–25). Studies that have only assessed insulin secretion have shown either low or normal insulin secretion in glucose-tolerant adults with a family history (10,13,26). When insulin secretion was expressed normalized for insulin sensitivity, adult family members of patients with type 2 diabetes showed a significantly lower product of insulin sensitivity \( \times \) acute insulin release, with an estimated heritability of 70% (19). These observations led the authors to conclude that the highly familial nature of the GDI and its strong negative correlation with diabetes makes it a superior predictive measure (19). This was also documented to be the case in Pima Indians and Caucasians (27–29). Similar findings of defective insulin secretion when related to insulin sensitivity were reported in a subgroup of very resistant normoglycemic adult offspring of patients with type 2 diabetes but not in an insulin-sensitive subgroup (30). An impaired balance between insulin sensitivity and secretion has also been reported in a very limited number of nondiabetic adult identical twins of patients with type 2 diabetes (11) and in overweight Latino children with a family history and impaired glucose tolerance (17).

In agreement with these studies, our investigation of children in the first decade of life demonstrates that when insulin secretion is evaluated in relation to insulin sensitivity, \( ~30\% \) lower compensatory \( \beta \)-cell function exists in children with a family history. This is consistent with the reported 35% lower GDI in adults who have a family history (29). If we had assessed insulin secretion alone, our conclusions would have been that there are no differences in first- or second-phase insulin secretion between children with and without family histories. If we had assessed insulin sensitivity alone, our conclusions would have been that insulin sensitivity is lower by \( ~30\% \) in children with a family history. The latter finding is consistent with our past observations in black children, in whom insulin sensitivity was lower in the presence of a family history of type 2 diabetes (15). Therefore, it seems that both insulin resistance and decreased \( \beta \)-cell compensation are the metabolic phenotype of familial type 2 diabetes. Our results, which are consistent with the adult data, differ from a previous pediatric study showing no differences in insulin sensitivity, acute insulin response, and GDI (16). The potential reasons for the inconsistent findings are the study population: one racial group in our study versus different racial groups (Caucasian, African American, Hispanic, and others) from different geographic regions in the previous study. Also, the experimental approach, minimal model intravenous glucose tolerance test versus clamp experiments, may play a role. Inclusion of children from various racial groups may create a confounding variable because the heritability of type 2 diabetes phenotype may vary among different racial groups.

There is convincing evidence that IGFBP-1 plays an integral role in glucose regulation (31). Low IGFBP-1 levels are associated with adolescent obesity (32), with insulin resistance syndrome in adult type 2 diabetes (33), and with the development of glucose intolerance in adults (34). Therefore, it has been proposed that IGFBP-1 measurements may be a useful marker in these conditions. Moreover, the present study demonstrates that youth with a family history of type 2 diabetes have significantly lower IGFBP-1 levels than children who do not have a family history. Changes in insulin sensitivity, insulin clearance, and insulin levels associated with a family history of type 2 diabetes may impact plasma levels of IGFBP-1. It remains to be determined in prospective studies whether low IGFBP-1 levels have a predictive value in conversion to type 2 diabetes.

In conclusion, white youth who have a family history of type 2 diabetes have low IGFBP-1 levels and demonstrate an impaired \( \beta \)-cell compensation relative to their lower insulin sensitivity. Detection of a disturbed relationship between insulin action and \( \beta \)-cell feedback in youth suggests that at least some of their determinants are genetic. This raises the importance of environmental intervention in the prevention of diabetes in high-risk youth.

Acknowledgments — This study was supported by U.S. Public Health Service Grants RO1-HD27503, K24-HD01357, and MO1-RR00084; the General Clinical Research Center; and Eli-Lilly.

We thank the nurses of the General Clinical Research Center for their expert nursing assistance and Pat Antonio for secretarial assist-
References