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

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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 L$_4$-L$_5$ 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}, $P = 0.039$). IGF binding protein-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.

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Type 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 nondiabetic 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. In adults, insulin secretion, when expressed normalized for insulin sensitivity, is more familial than either parameter alone (19). This led to the suggestion that GDI may be a very

Table 1—Characteristics of study subjects

	Subjects without family history of type 2 diabetes	Subjects with family history of type 2 diabetes	P
Sex (male/female)	13/13	12/16	—
Age (years)	11.5 ± 0.4	12.1 ± 0.5	NS
Tanner stage			
I	11	11	—
II–III	9	9	—
IV–V	6	8	—
BMI (kg/m^2)	18.8 ± 0.5	20.0 ± 0.5	NS
Fat mass (kg)	8.8 ± 1.1	11.4 ± 1.4	NS
Percentage body fat	20.7 ± 1.7	23.5 ± 1.8	NS
Visceral adipose tissue (cm^2)	18.2 ± 2.8	25.3 ± 3.7	NS
Subcutaneous adipose tissue (cm^2)	85.1 ± 14.1	139.9 ± 24.1	NS
IGF-1 (nmol/l)	35.3 ± 2.8	41.1 ± 3.3	NS
IGFBP-1 (ng/ml)	42.8 ± 7.2	16.8 ± 3.1	0.002

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 L_4-L_5 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 $\cdot$ m^{-2} $\cdot$ 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 IGF binding protein-1 (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 *t* 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. $P \le 0.05$ 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).
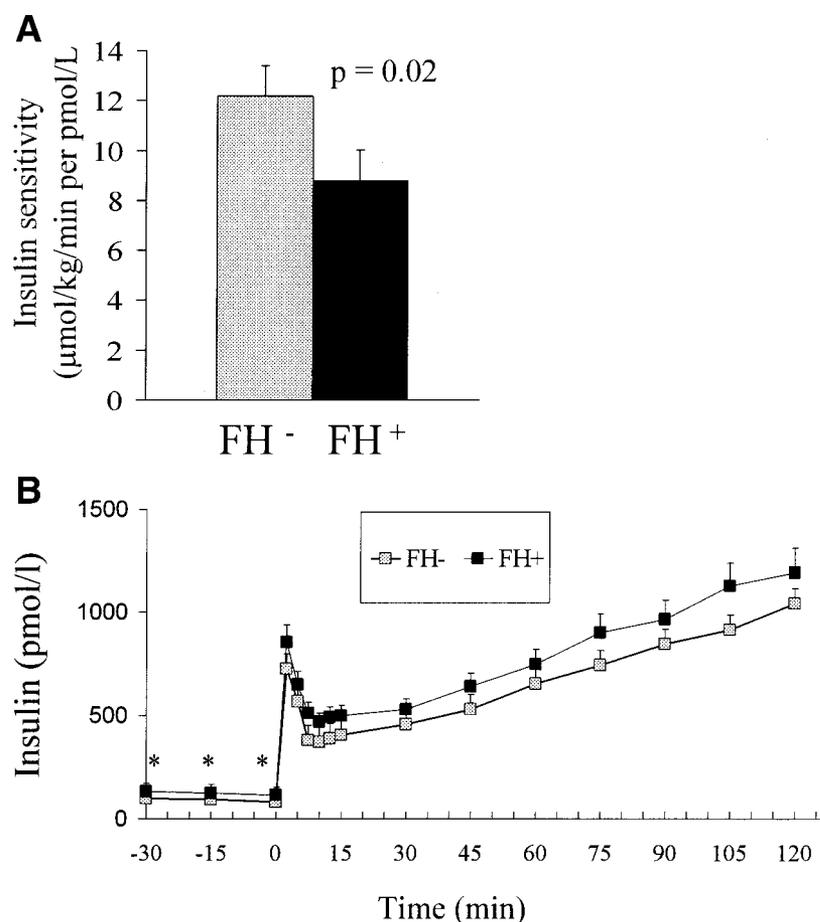
Figure 1—*In vivo insulin sensitivity measured during a hyperinsulinemic-euglycemic clamp* (A) *and insulin secretion measured during a hyperglycemic clamp* (B) *in children with a positive family history* (FH$^+$) *and those with a negative family history* (FH$^-$) *(−30, −15, and 0 min insulin levels are higher in FH$^+$ compared with FH$^-$ children;* P *= 0.017, 0.03, and 0.006, respectively).*

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 than 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/m^2) 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/m^2) 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 differ-

ence 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)
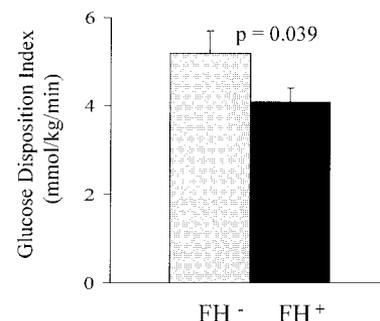

Figure 2—*GDI (insulin sensitivity × first-phase insulin) in children with a positive family history* (FH$^+$) *and those with a negative family history* (FH$^-$).

were not significantly different between the two groups (721.4 ± 101.1 vs. 552.5 ± 127.2 pmol/l and 4.0 ± 0.4 vs. 4.5 ± 0.6 mmol $\cdot$ kg^{-1} $\cdot$ 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 × 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 influ-

ences 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 × 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 β-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 conclusion 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 β-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 glucoregulation (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 β-cell compensation relative to their lower insulin sensitivity. Detection of a disturbed relationship between insulin action and β-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.

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References

1. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GLA, Saaddine J, Gregg EW, Williamson DF, Narayan KMV: Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 136: 664–662, 2000
2. Gungor N, Arslanian S: Pathophysiology of type 2 diabetes mellitus in children and adolescents. *Treat Endocrinol* 1:359–371, 2002
3. American Diabetes Association: Type 2 diabetes in children and adolescents. *Diabetes Care* 23:381–389, 2000
4. Arslanian S: Type 2 diabetes in children: clinical aspects and risk factors. *Horm Res* 57:19–28, 2002
5. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med* 113:909–915, 1990
6. Leslie RDG, Volkmann HP, Poncher M, Hanning I, Orskov H, Alberti KGMM: Metabolic abnormalities in children of non-insulin dependent diabetics. *BMJ* 293:840–842, 1986
7. Ishikawa M, Pruneda ML, Adams-Huet B, Raskin P: Obesity-independent hyperinsulinemia in nondiabetic first-degree relatives of individuals with type 2 diabetes. *Diabetes* 47:788–782, 1998
8. Gulli G, Ferrannini E, Stern M, Haffner S, DeFronzo RA: The metabolic profile of NIDDM is fully established in glucose-tolerant offspring of two Mexican-American NIDDM parents. *Diabetes* 41:1575–1586, 1992
9. O'Rahilly SP, Nugent Z, Rudenski AS, Hosker JP, Burnett MA, Darling P, Turner RC: Beta-cell dysfunction, rather than insulin insensitivity, is the primary defect in familial type 2 diabetes. *Lancet* 2: 360–364, 1986
10. Van Haeften TW, Dubbeldam S, Zonderland ML, Erkelens DW: Insulin secretion in normal glucose-tolerant relatives of type 2 diabetic subjects. *Diabetes Care* 21: 278–282, 1998
11. Alford FP, Henriksen JE, Rantzau C, Vaag A, Hew LF, Ward GM, Beck-Nielsen H: Impact of family history of diabetes on the assessment of β-cell function. *Metabolism* 47:522–528, 1998

12. Fernández-Castaner M, Biarnés J, Camps I, Ripollés J, Gómez N, Soler J: Beta-cell dysfunction in first-degree relatives of patients with non-insulin-dependent diabetes mellitus. *Diabet Med* 13:953–959, 1996
13. Pimenta W, Korytkowski M, Mitrakou A, Jenssen T, Yki-Jarvinen H, Evron W, Dailey G, Gerich J: Pancreatic beta-cell dysfunction as the primary genetic lesion in NIDDM. *JAMA* 273:1855–1861, 1995
14. Paulsen EP, Richenderfer L, Ginsberg-Fellner F: Plasma glucose, free fatty acids and immunoreactive insulin in sixty-six obese children. *Diabetes* 17:261–269, 1968
15. 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* 22:1325–1329, 1999
16. 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* 88:192–195, 2003
17. Goran MI, Bergman RN, Avila Quintilia, Watkins M, Ball GDC, Shaibi GQ, Weigensberg MJ, Cruz ML: Impaired glucose tolerance and reduced β-cell function in overweight latino children with a positive family history for type 2 diabetes. *J Clin Endocrinol Metab* 89:207–212, 2004
18. Kahn SE: Regulation of β-cell function in vivo: from health to disease. *Diabetes Rev* 4:372–389, 1996
19. Elbein SC, Hasstedt SJ, Wegner K, Kahn SE: Heritability of pancreatic β-cell function among nondiabetic members of Caucasian familial type 2 diabetic kindreds. *J Clin Endocrinol Metab* 84:1398–1403, 1999
20. Arslanian SA, Saad R, Lewy V, Danadian K, Janosky J: Hyperinsulinemia in African-American children: decreased insulin clearance and increased insulin secretion and its relationship to insulin sensitivity. *Diabetes* 51:3014–3019, 2002
21. Bacha F, Saad R, Gungor J, Arslanian SA: Adiponectin in youth: relationship to visceral adiposity, insulin sensitivity and β-cell function. *Diabetes Care* 27:547–552, 2004
22. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR: Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet* 340: 925–929, 1992
23. Bonora E, Gulli G, Bonadonna R, DelPrato S, Solini A, DeFronzo RA: Insulin sensitivity is not impaired in Mexican-American women without a family history of diabetes. *Diabetes Care* 18:825–833, 1995

24. Osei K, Cottrell DA, Orabella MM: Insulin sensitivity, glucose effectiveness, and body fat distribution pattern in nondiabetic offspring of patients with NIDDM. *Diabetes Care* 14:890–896, 1991
25. Laws A, Stefanick ML, Reaven GM: Insulin resistance and hypertriglyceridemia in nondiabetic relatives of patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 69:343–347, 1989
26. Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widén E, Schalin C, Groop L: Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med* 321:337–343, 1989
27. Sakul H, Pratley R, Cardon L, Ravussin E, Mott D, Bogardus C: Familiality of physical and metabolic characteristics that predict the development of non-insulin-dependent diabetes mellitus in Pima Indians. *Am J Hum Genet* 60:651–656, 1997
28. Bonadonna RC, Stumvoll M, Fritsche A, Muggeo M, Haring H, Bonora E, van Haeften TW: Altered homeostatic adaptation of first- and second-phase β-cell secretion in the offspring of patients with type 2 diabetes. *Diabetes* 52:470–480, 2003
29. Tripathy D, Wessman Y, Gullström, Tuomi T, Groop L: Importance of obtaining independent measures of insulin secretion and insulin sensitivity during the same test. *Diabetes Care* 26:1395–1401, 2003
30. Perseghin G, Ghosh S, Gerow K, Shulman GI: Metabolic defects in lean nondiabetic offspring of NIDDM parents: a cross-sectional study. *Diabetes* 46:1001–1009, 1997
31. Lee PDK, Giudice LC, Conover CA, Powell DR: Insulin-like growth factor binding protein-1: recent findings and new directions. *Proc Soc Exp Biol Med* 216:319–357, 1997
32. Attia N, Tamborlane WV, Heptula R, Maggs D, Grezman A, Sherwin RS, Caprio S: The metabolic syndrome and insulin-like growth factor regulation in adolescent obesity. *J Clin Endocrinol Metab* 83: 1467–1471, 1998
33. Mohamed-Ali V, Pinkney JH, Panahloo A, Cwyfan-Hughes S, Holly JMP, Yudkin JS: Insulin-like growth factor binding protein-1 in NIDDM: relationship with the insulin resistance syndrome. *Clin Endocrinol* 50:221–228, 1999
34. Sandhu MS, Heald AH, Gibson JM, Cruickshank JK, Dunger DB, Wareham NJ: Circulating concentrations of insulin-like growth factor-I and development of glucose intolerance: a prospective observational study. *Lancet* 359:1740–1745, 2002