Insulin Sensitivity in the Offspring of Women With Type 1 and Type 2 Diabetes

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OBJECTIVE — To determine if insulin sensitivity is altered in prepubertal offspring exposed to a diabetic intrauterine environment.

RESEARCH DESIGN AND METHODS — Fifteen control children, 17 offspring of type 1 diabetic women, and 10 offspring of type 2 diabetic women, aged between 5 and 10 years, underwent a frequently sampled intravenous glucose tolerance test (FSIGTT). Weight and height were measured, and body composition was calculated using bioelectrical impedance. Bergman's minimal model was applied to the glucose and insulin measurements to obtain values for insulin sensitivity (S_i), acute insulin response (AIR), and glucose effectiveness (S_g).

RESULTS — S_i was lowest in the offspring of type 2 diabetic mothers, and AIR was highest in this group, although neither of these changes reached significance (S_i, $P = 0.2$, and AIR, $P = 0.3$). Offspring of type 2 diabetic mothers had higher BMI SD scores ($P = 0.004$) and percentage fat mass ($P = 0.002$) than the children in the other two groups. The BMI SD score and percentage fat mass in the subjects, as well as maternal insulin dose, were negatively correlated with offspring insulin sensitivity.

CONCLUSIONS — Intrauterine exposure to hyperglycemia by itself was not associated with alterations in glucose regulation in prepubertal offspring. Children of mothers with type 2 diabetes, however, were overweight, and they had a tendency for a reduced S_i. The combined effect of genetic and postnatal environmental factors, rather than prenatal exposure to hyperglycemia, may place this group at risk for developing impaired glucose tolerance in later life.

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The metabolic syndrome, a constellation of obesity, hypertension, dyslipidemia, and type 2 diabetes, is believed to result from an interaction of genetic and environmental factors. Recent studies (1,2) have highlighted the importance of the prenatal environment in influencing an individual's risk of developing the metabolic syndrome, giving rise to the concept of fetal programming. Subsequent research has confirmed an association between fetal exposure to hyperglycemia and impaired glucose tolerance, a forerunner of type 2 diabetes, in postnatal life (3–5).

Prior studies have often combined offspring of mothers with type 2 and type 1 diabetes on the assumption that the degree of fetal exposure to hyperglycemia is similar in the two groups. However, the genetic factors contributing to the postnatal metabolic phenotype are not identical in the two groups. Offspring of mothers with type 2 diabetes will have a genetic predisposition to develop insulin resistance, whereas offspring of mothers with type 1 diabetes have an inherited risk of developing insulin deficiency secondary to autoimmune destruction of pancreatic β-islet cells.

The mechanism by which fetal exposure to hyperglycemia leads to impaired glucose tolerance in the second decade is unclear. Prospective data from Silverman et al. (4) indicate that childhood obesity precedes a demonstrable impairment of glucose tolerance. It is possible, however, that a more subtle abnormality in glucose homeostasis, such as insulin resistance, occurs before the development of obesity or concomitant with it. A sensitive and validated method for measuring insulin resistance in children is the frequently sampled intravenous glucose tolerance test (FIGTT) using the minimal model (6).

The aim of this study was to determine if insulin sensitivity is reduced in prepubertal children of women with pregestational diabetes compared with a group of control children whose mothers had normal glucose tolerance in pregnancy. By comparing offspring of type 1 diabetic women with offspring of type 2 diabetic women, the effect of fetal exposure to hyperglycemia alone, as well as the combined effect of prenatal hyperglycemia and an inherited risk for developing insulin resistance, can be examined.

RESEARCH DESIGN AND METHODS

— Prepubertal children age 5–10 years who were the offspring of women with type 1 or type 2 diabetes were enrolled. Women were eligible if they were diagnosed before pregnancy with either type 1 or type 2 diabetes, attended the diabetes pregnancy clinic at National Women's Hospital, and delivered singleton infants between 1992 and 1997. Pregnancy data that were collected prospectively for all diabetic women included prepregnancy weight, pregnancy

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Abbreviations: AIR, acute insulin response; FSIGTT, frequently sampled intravenous glucose tolerance test.

weight gain, placental weight, insulin dosage, and plasma fructosamine. The control group was comprised of 5- to 10-year-old prepubertal children, recruited on a volunteer basis from general practice clinics, whose mothers had normal glucose tolerance during pregnancy (based on a 50-g oral challenge between 24 and 28 weeks).

Exclusion criteria for all children studied included twins, prematurity (gestation <36 weeks), chronic illness, identified syndromes, and current medication known to influence insulin sensitivity. Control children were excluded if a first-degree relative had diabetes (type 1 or type 2) or if they were born small for gestational age (birth weight <10th centile). Prepubertal sexual development was determined by testicular volumes <3 ml in boys and Tanner stage 1 breast development in girls. All children had negative type 1 diabetes antibodies (insulinoma-associated protein 2 and GAD).

The women were classed as having type 1 diabetes if they had onset before age 30 years and one or more of the following: autoantibody positive (GAD, insulinoma-associated protein 2, or islet cells), ketoacidosis at presentation, normal BMI at diagnosis, no first-degree relative with type 2 diabetes, and commencement of insulin therapy at diagnosis. Women were classed as having type 2 diabetes if their BMI was >30 kg/m^2 at diagnosis and they had one or more of the following: no insulin therapy requirement, nonketosis prone, and the presence of acanthosis nigricans. Women were referred to the pregnancy diabetes clinic early in the first trimester. The type 1 diabetic women received insulin before pregnancy and were managed with four doses per day. Type 2 diabetic women were started on insulin treatment if glycemic targets were not met by dietary measures alone. The Auckland ethics committee approved the study. Written informed consent was obtained from both parents and subjects.

Procedures

After an overnight fast, all subjects were admitted to the Children's Research Centre at Starship Children's Hospital. Height was measured using a Harpenden stadiometer. Weight and foot-to-foot bioelectrical impedance were measured using a Tanita/Stellar Innovations bioelectrical impedance analyzer (Tokyo, Japan). These measurements were used to estimate fat-free mass, fat mass, and percentage body fat (7). Birth weight was converted to SD scores to adjust for gestational age and sex (8). Height and BMI were converted to SD scores to adjust for age and sex (9–12).

All subjects underwent a 90-min FSIGTT, modified for children as previously validated (6). An intravenous line was inserted, and three baseline samples were drawn (−20, −10, and 0 min). A rapid infusion of 25% dextrose at 0.3 g/kg was given over 1 min. Blood samples were drawn at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 19 min. At 20 min, insulin at 0.02 units/kg (Actrapid; Novo Nordisk, Copenhagen, Denmark) was infused over 30 s, and further samples were taken at 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, and 90 min. Two milliliters of blood were collected at each point and placed in chilled tubes containing heparin sodium.

Plasma was separated at the completion of the test and analyzed for glucose and insulin at each time point. The glucose and insulin values were entered into Bergman's minimal model to measure insulin sensitivity (S_i; insulin-mediated glucose uptake), acute insulin response (AIR; index of insulin-secreting capacity, calculated from the insulin output in the first 19 min), and glucose effectiveness (S_g; glucose uptake independent of insulin). The glucose disposal coefficient (K_g) was calculated from the slope of the logarithm of the glucose concentration between 10 and 19 min. K_g examines glucose uptake over the first 20 min of the FSIGTT and encompasses S_i, S_g, and AIR.

Assays

Plasma glucose was measured by Hitachi 911 automated random access analyzer (Tokyo, Japan) with an interassay coefficient variation of 1.2%. Insulin was determined by Abbott's IMX microparticle enzyme immunoassay with an interassay coefficient variation of <5%. Anti-GAD and anti–insulinoma-associated protein 2 antibodies were measured using RSR kits that use ^{125}I-labeled recombinant antigens (RSR, Cardiff, U.K.). Fructosamine was measured on a Beckman CX7 analyzer using a Boehringer Mannheim kit. Nondiabetic values given for fructosamine (Boehringer Mannheim, Petersburg, VT) are 210–280 μmol/l (nonpregnant range). Pregnancy ranges are: first trimester, 185–225; second trimester, 170–250; and third trimester, 160–220 μmol/l.

Statistical analysis

Data were analyzed with SAS version 8.2. ANOVA was used to compare clinical characteristics between the groups. Normally distributed data have been presented as means and SE. Square root and log transformation were used on glucose regulation parameters when data were not normally distributed and have been presented as medians and interquartile range. General linear models were used to investigate whether there was a difference in glucose regulation parameters when controlling for factors that may influence these main outcome measures. Dunnett's multiple comparison test was used to compare the three groups within the models. Significance was determined as a P value <0.05.

RESULTS — Forty-two children were studied, including 15 control subjects, 17 offspring of type 1 diabetic women, and 10 offspring of type 2 diabetic women. The clinical characteristics of the subjects studied are shown in Table 1. There was no difference in age or height between the three groups. All subjects were born at 36–40 weeks' gestation, with the diabetes groups born at a mean of 38 weeks, compared with 40 weeks' gestation for control subjects ($P = 0.0001$). There was a trend to higher birth weight in the type 1 and type 2 diabetic offspring, but this did not reach significance ($P = 0.3$). Macrosomia, defined as birth weight SD score >2, was present in 7% of control subjects, 12% of offspring of type 1 diabetic women, and 40% offspring of type 2 diabetic women ($P = 0.07$).

The offspring of type 2 diabetic women were considerably heavier than either the control subjects or offspring of type 1 diabetic women, reflected in BMI SD scores and percentage body fat estimates. There were two extremely obese children in the type 2 diabetes group (BMI SD scores, 9.3 and 11.7). When excluded from the analysis, the difference in BMI, BMI SD score, and percentage body fat of the type 2 diabetes group remained significant ($P = 0.04$). There was no difference in lean body mass between the groups as determined by bioelectrical impedance analysis ($P = 0.7$).

Table 2 shows the maternal clinical characteristics. The type 2 diabetic

Table 1—*Clinical characteristics and glucose regulation parameters of children studied*

	Control subjects	Offspring of diabetic women		*P*
		Type 1 diabetes	Type 2 diabetes	
n	15	17	10	—
Age (years)	8.2 ± 0.4	8.4 ± 0.4	7.9 ± 0.5	0.7
Sex (male/female)	8/7	13/4	6/4	0.05
Birth weight SD score	0.8 ± 0.3	1.2 ± 0.2	1.4 ± 0.3	0.3
BMI SD score	−0.2 ± 0.6	0.7 ± 0.6	3.2 ± 0.7	0.004
Percentage body fat	26 ± 1.6	27 ± 1.5	35 ± 2.0	0.002
S_i (10^{-4}/min μU/ml)	11.8 (9.1–18.3)	11 (7.8–14)	8.4 (5.7–12)	0.2
AIR (mU/l)	366 (216–459)	386 (320–524)	411 (285–977)	0.3
S_g (10^{-2}/min^{-1})	2.07 ± 0.16	1.92 ± 0.28	1.83 ± 0.27	0.8
K_g (10^{-2} mg/d min^{-1})	2.9 ± 0.3	2.8 ± 0.3	2.8 ± 0.3	0.8
Fasting glucose (mmol/l)	4.9 ± 0.1	4.9 ± 0.1	5.0 ± 0.1	0.8
Fasting insulin (μU/ml)	4.2 (2.7–7.1)	4.1 (3.4–8.3)	6.6 (4.6–4.4)	0.4

Data are means ± SE or median (interquartile range).

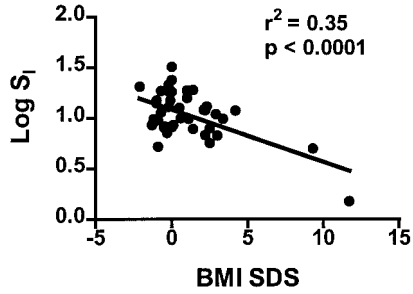

Figure 1—*Correlation between BMI SD scores and insulin sensitivity. Values for S_i have been log transformed to normalize the data.*

women were older at the time of delivery, and all were obese (BMI >30 kg/m^2) at the start of pregnancy. There was no difference between the two diabetes groups in weight gain during pregnancy or placental weight. All the type 1 diabetic women were on insulin before pregnancy, and all but one of the type 2 diabetic women required insulin during pregnancy, starting at a mean of 13 weeks (range 7–29). The maximal maternal insulin dose at term (units per kilogram) was similar in both the women with type 1 diabetes and type 2 diabetes. Plasma fructosamine was measured eight times between 20 weeks and term. Type 2 diabetic women had a lower mean fructosamine level at both time points examined; however, obesity itself is associated with lower fructosamine values in both diabetic and nondiabetic individuals (13).

The glucose regulation data of all of the subjects are shown in Table 1. In the offspring of type 2 diabetic mothers, there was a trend toward lower S_i ($P = 0.2$), while AIR ($P = 0.3$) and fasting insulin ($P = 0.4$) were increased, although none of the differences reached statistical significance. The S_g, K_g, and fasting glucose were similar across the three groups.

The first linear model was used to examine glucose regulation parameters in all three groups when controlling for age, sex, BMI SD score, percentage body fat, birth weight SD score, and maternal BMI. BMI SD score was found to have a significant effect on S_i ($P = 0.006$), with heavier children exhibiting lower S_i values (Fig. 1). Similarly, there was a positive relationship between AIR and both BMI SD score ($P = 0.0002$) and percentage body fat ($P = 0.02$). There was no relationship found between any of the variables of age, sex, birth weight SD score, or maternal BMI on any of the measured parameters of glucose regulation.

In the second linear model, glucose regulation parameters of offspring of type 1 and type 2 diabetic women were examined when controlling for the above factors as well as the additional maternal factors of maximal insulin dose (units per kilogram) and mean fructosamine. The fructosamine value had no effect on any of the glucose regulation parameters at either of the two time ranges measured. There was, however, a relationship in both groups between the mothers' maximal insulin dose at term and decreasing S_i ($P = 0.03$) and increasing AIR in their offspring ($P = 0.007$).

CONCLUSIONS — This study is the first published assessment of insulin sensitivity using the FSIGTT in prepubertal offspring of women with diabetes. S_i was not significantly different between the control children and the offspring of women with diabetes; however, there was a trend toward a reduction in S_i in the offspring of women with type 2 diabetes. This group was substantially heavier than both the control children and the offspring of women with type 1 diabetes. Increased adiposity is likely to have contributed to the lower S_i in offspring of women with type 2 diabetes, given the negative correlation between heaviness and S_i. Maternal insulin dose was also negatively correlated with S_i in the offspring.

Previous studies of glucose regulation in offspring of diabetic women have provided conflicting results. Silverman et al. (4) reported that the incidence of impaired glucose tolerance in children between 5 and 10 years was not significantly different from that in normal children, whereas the study of Plagemann et al. (14) suggested that impaired glucose

Table 2—*Maternal characteristics*

	Control subjects	Women with diabetes		*P*
		Type 1 diabetes	Type 2 diabetes	
n	15	17	10	—
Age at delivery (years)	31 ± 1.6	29 ± 1.3	35 ± 1.6	0.02
Early pregnancy BMI (kg/m^2)	25 ± 1.4*	25 ± 1.1	37 ± 1.5	0.001
Years with diabetes before gestation	—	13 ± 1.9	7.4 ± 2.4	0.08
Maximal insulin dose at term (units/kg)	—	1.3 ± 0.1	1.1 ± 0.2	0.4
Fructosamine average (μmol/l)				
20–29 weeks	—	240 ± 7.5	193 ± 9.5	0.0007
29 weeks to delivery	—	215 ± 6.9	190 ± 8.5	0.03

Data are means ± SE. *BMI at the time of the study because early pregnancy weight was not available.

tolerance was higher than expected for this age-group. Both studies, however, compared the incidence of impaired glucose tolerance in their subjects to literature reports. With the recent increase in childhood obesity and the association between insulin resistance and obesity, conclusions based on comparisons with historical control subjects may be inaccurate. What is evident from serial evaluations of glucose homeostasis in a defined cohort of diabetic offspring is an increased incidence of impaired glucose tolerance after puberty (15). Subjects in our study were all prepubertal, therefore removing any confounding effect of pubertal status on the assessment of insulin sensitivity.

Methodological issues need to be considered when comparing studies of glucose homeostasis in the offspring of diabetic mothers. Glucose uptake into tissues is determined by insulin secretion, insulin sensitivity, and insulin-independent mechanisms. Impaired glucose tolerance exists when there is a reduction in at least two of these three variables (16). Bergman's minimal model applied to the FSIGTT is an accurate method of specifically assessing insulin sensitivity in children. By using this technique, the relative contributions of insulin resistance, insulin secretion, and insulin-independent mechanisms can be quantified separately. Such a detailed analysis is not possible with the oral glucose tolerance test. The American Diabetes Association (17) has stated that only the euglycemic insulin clamp method and the minimal model applied to the FSIGTT are able to accurately measure peripheral insulin sensitivity.

A cohort effect may also complicate comparisons of glucose homeostasis in different populations of subjects exposed to hyperglycemia in utero. Antenatal diabetes management has improved over the last 40 years. This is reflected in perinatal mortality data for pregnancies complicated by diabetes, and although the most dramatic improvement in perinatal mortality occurred between 1960 and the mid-1970s, there still has been a significant reduction in perinatal mortality between 1976 and 1987 (18). For this reason, studies involving offspring of diabetic mothers born before the 1980s, including recently published studies of adult subjects and previous reports of glucose homeostasis during childhood, may not be comparable with our study, which focuses on children born in the mid-1990s.

Offspring of women with type 2 diabetes were substantially heavier than control subjects and the offspring of women with type 1 diabetes, consistent with previous studies (3,5). Moreover, the work of Silverman et al. (4,15) clearly showed excessive weight gain occurring before the development of impaired glucose tolerance. It may be that offspring of women with type 2 diabetes are exposed to a unique metabolic perturbation in addition to hyperglycemia, one that does not occur in pregnant women with type 1 diabetes. An alternative explanation, however, is that genetic and postnatal environmental factors also contribute, perhaps to a greater degree than the prenatal environment, to the development of childhood obesity in the offspring of mothers with type 2 diabetes.

High maternal insulin doses were associated with reduced insulin sensitivity and increased AIR in the offspring. Previous studies (4,19) of adolescent offspring of diabetic mothers have shown that increased levels of amniotic fluid insulin were positively correlated with obesity and impaired glucose tolerance, suggesting that insulin is involved in metabolic programming of the fetus. Amniotic fluid insulin values reflect both fetal insulin secretion and maternal insulin because this can cross the placenta as part of antibody-insulin complexes (20). A direct programming effect of maternal insulin on the fetus may therefore explain the relationship between maternal insulin and offspring S_i. Alternatively, a high maternal insulin dosage could indicate poor glycemic control in the mother, with resulting exposure of the fetus to the programming effects of hyperglycemia. A third possibility is that a high maternal insulin dose is a marker of insulin resistance in the mother and that the observed relationship is explained by a familial tendency to insulin resistance.

The current study's ability to detect an alteration in glucose homeostasis in prepubertal offspring of women with diabetes may have been limited by two factors. All of the mothers appeared to have relatively good metabolic control during pregnancy, therefore reducing the potential for metabolic programming of the fetus. Even limited degrees of maternal hyperglycemia, however, can be associated with neonatal macrosomia (21). It is also possible that with a greater sample size, a significant difference in insulin sensitivity between the offspring of diabetic mothers, particularly offspring of women with type 2 diabetes, and the control subjects would have been evident. Our group has studied insulin sensitivity in prepubertal children who were born small for gestational age, prepubertal children who were born prematurely, and prepubertal twins (W.A.H., T.C., D.R., P.L.H., M.H., F.R., E.R., W.S.C., unpublished observations, for both). In all of these studies (2), there was an ~50% reduction in insulin sensitivity when the study subjects were compared with a control population of prepubertal children. The mean and SD of S_i in these control children were used for the power calculations in the current study, and the sample size provided statistical power to detect a reduction in S_i of ~50% in the offspring of type 2 diabetic women at a significance level of 0.05.

Marked insulin resistance precedes impaired glucose tolerance by many years in those at risk of developing type 2 diabetes. In a longitudinal study (22) of adult offspring of couples with type 2 diabetes followed for at least 10 years, there was a >50% reduction in S_i in those offspring who subsequently developed type 2 diabetes compared with those who remained normoglycemic. This reduction in S_i is similar to that seen in our studies of insulin sensitivity in prepubertal children using the FSIGTT. If prenatal hyperglycemia or hyperinsulinism has a primary programming effect, abnormalities in glucose regulation are likely to be present in early childhood and reduced S_i would be expected in mid to late childhood if impaired glucose tolerance were to develop during puberty, as has been reported in offspring of diabetic mothers (3,4,15).

Our data suggest that intrauterine exposure to hyperglycemia does not by itself result in altered glucose regulation parameters in prepubertal offspring of women with diabetes. However, offspring of mothers with type 2 diabetes were heavier and had a trend toward a reduced S_i when compared with normal control subjects and offspring of mothers with type 1 diabetes. We speculate that a combination of genetic and postnatal environmental factors, rather than isolated exposure to hyperglycemia, may place the offspring of mothers with type 2 diabetes

at particular risk of developing impaired glucose tolerance in later life.

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