Predictors of Changes in Glucose Tolerance Status in Obese Youth

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OBJECTIVE — Type 2 diabetes in obese youth is an emerging problem. The metabolic and anthropometric predictors of change in glucose tolerance status in obese youth are unknown.

RESEARCH DESIGN AND METHODS — A total of 117 obese children and adolescents were studied by performing an oral glucose tolerance test (OGTT) at baseline and after ~2 years. Data from both OGTTs and changes in weight were examined to identify youth at highest risk for developing diabetes and the factors that have the strongest impact on glucose tolerance.

RESULTS — Eighty-four subjects had normal glucose tolerance (NGT) and 33 impaired glucose tolerance (IGT) at baseline. Eight subjects (all of whom had IGT at baseline) developed type 2 diabetes, whereas 15 subjects with IGT reverted to NGT. In this cohort, severe obesity, impaired glucose tolerance, and African-American background emerged as the best predictors of developing type 2 diabetes, whereas fasting glucose, insulin, and C-peptide were nonpredictive. Changes in insulin sensitivity, strongly related to weight change, had a significant impact on the 2-h glucose level on the follow-up study.

CONCLUSIONS — Severely obese children and adolescents with IGT, particularly of African-American descent, are at very high risk for developing type 2 diabetes over a short period of time. Parameters derived from an OGTT and not fasting samples can serve as predictors of changes in glucose tolerance.

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Over the last decade, type 2 diabetes has emerged as an increasingly common pediatric disease (1,2). In many parts of the world and among certain ethnic groups, the prevalence of type 2 diabetes in adolescents is now equal to or greater than that of type 1 diabetes (3). The global emergence of type 2 diabetes in youth parallels the increasing epidemic of childhood and adolescent obesity. The progression from normal glucose tolerance to type 2 diabetes in adults occurs through an intermediate phase of altered glucose metabolism known as impaired glucose tolerance (IGT), or pre-diabetes. Previous studies from our group and others reported a high prevalence of IGT among children and adolescents with marked obesity (4,5). Cross-sectional studies demonstrated that IGT in obese youth is associated with severe insulin resistance, β-cell dysfunction, and altered abdominal and muscle fat partitioning (6). Because of their cross-sectional nature, these studies did not examine potential metabolic predictors of changes in glucose tolerance in these obese youth.

Transition from IGT to diabetes in adults is usually a gradual phenomenon that occurs over 5–10 years (7,8) depending on the population studied. The early presentation of type 2 diabetes in youth raises the possibility of an accelerated process in these youth compared with adults, thus shortening the transition time between IGT and diabetes. In contrast to the vast literature about metabolic predictors of deterioration of glucose tolerance in adults, little is known about this process in children and adolescents. Therefore, the aim of this study was to follow obese children and adolescents at risk for diabetes longitudinally and identify baseline metabolic and anthropometric parameters associated with later deterioration of glucose metabolism. As several prospective studies are currently being designed using modified oral glucose tolerance test (OGTT) studies in large populations (using only fasting and 2-h sampling), we further tested whether data derived from these two samples can be used to predict changes in glucose tolerance. In this report, we describe our preliminary observations on the longitudinal follow-up of a multiethnic cohort of 117 obese children and adolescents who had OGTTs every 18–24 months.

RESEARCH DESIGN AND METHODS

— Participants in this cohort were recruited from the Yale Pediatric Obesity Clinic as part of a longitudinal study of the pathophysiology of type 2 diabetes in youth. All participants were between the ages of 4 and 18 years. Subjects with medical conditions or using medications that may affect glucose metabolism before their first OGTT were excluded from the study. All subjects had normal thyroid function. All subjects had a BMI that was higher than the 95th percentile for age and sex and were thus classified as obese. To standardize the BMI levels, conversion to BMI *z* scores was performed based on the Centers for Disease Control and Prevention growth charts (9). Participants were followed biannually as outpatients by the clinical

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Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; IGI, insulinogenic index, IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WBISI, whole-body insulin sensitivity index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Anthropometric and fasting biochemistry values*

	NGT	IGT	*P* value
n	84	33	
M/F	29/55	9/24	0.51
Ethnicity (Caucasian/African American/Hispanic)	39/24/21	15/13/4*	0.15
Age (years)	12.7 ± 3.2	12.5 ± 2.7	NS
Height (cm)	156 ± 14	157 ± 14	NS
Weight (kg)	89 ± 26	92 ± 31	NS
BMI (kg/m^2)	35.5 ± 7.1	36.6 ± 8.7	NS
BMI *z* score	2.43 ± 0.34	2.42 ± 0.41	NS
Biochemistry values			*P* value
			Unadjusted / Adjusted
Glucose (mg/dl)	90 (89–91)	94 (89–99)	0.09 / 0.21
Glucose 120 min (mg/dl)	110 (107–113)	161 (154–169)	<0.001 / <0.001
Insulin (μU/ml)	27 (25–30)	42 (33–52)	0.025 / 0.006
Insulin 120 min (μU/ml)	119 (103–138)	311 (212–454)	0.004 / <0.001
C-peptide (pmol/l)	1,043 (953–1,152)	1,339 (1,096–1,635)	0.087 / 0.03
HOMA-IR	7.57 (6.12–9.02)	11.76 (8.23–15.29)	0.03 / 0.01
Cholesterol (mg/dl)	159 (149–168)	153 (140–166)	0.31 / 0.50
HDL cholesterol (mg/dl)	39 (37–41)	36 (33–38)	0.31 / 0.03
LDL cholesterol (mg/dl)	97 (88–106)	92 (80–103)	0.42 / 0.64
Triglycerides (mg/dl)	116 (99–132)	131 (100–161)	0.36 / 0.07
OGTT-derived indexes			
WBISI	1.73 (1.56–1.93)	0.86 (0.65–1.12)	<0.001 / <0.001
IGI	3.63 (3.12–4.26)	2.77 (2.01–3.81)	0.03 / 0.13
DI	6.35 (5.58–7.24)	2.38 (2.03–2.77)	<0.001 / <0.001

Data are expressed as means ± SD or 95% CI. Adjusted *P* values were adjusted for age, sex, ethnicity, and BMI *z* score. *One subject was of an ethnicity other than the three mentioned. NS, not significant.

staff and received nutritional guidance as well as recommendations for physical activity. The OGTT was repeated every 18–24 months for assessment of dynamics of glucose tolerance status. The protocol for longitudinal assessment of glucose metabolism was approved by the institutional review board of the Yale University School of Medicine. Written informed consent was obtained from the parents and assent from the children and adolescents.

Ninety subjects were initially classified as having normal glucose tolerance (NGT) and 39 as having IGT. Three of the 39 IGT subjects developed overt type 2 diabetes before performance of the follow-up OGTT. Data from these three subjects were used for analysis of baseline parameters only. Twelve subjects, 6 with NGT and 6 with IGT, began treatment with metformin after the first OGTT. All were females with severe acanthosis nigricans, irregular menses, and signs of hyperandrogenism (mainly significant hirsutism). All six treated subjects with NGT remained NGT on follow-up. Two

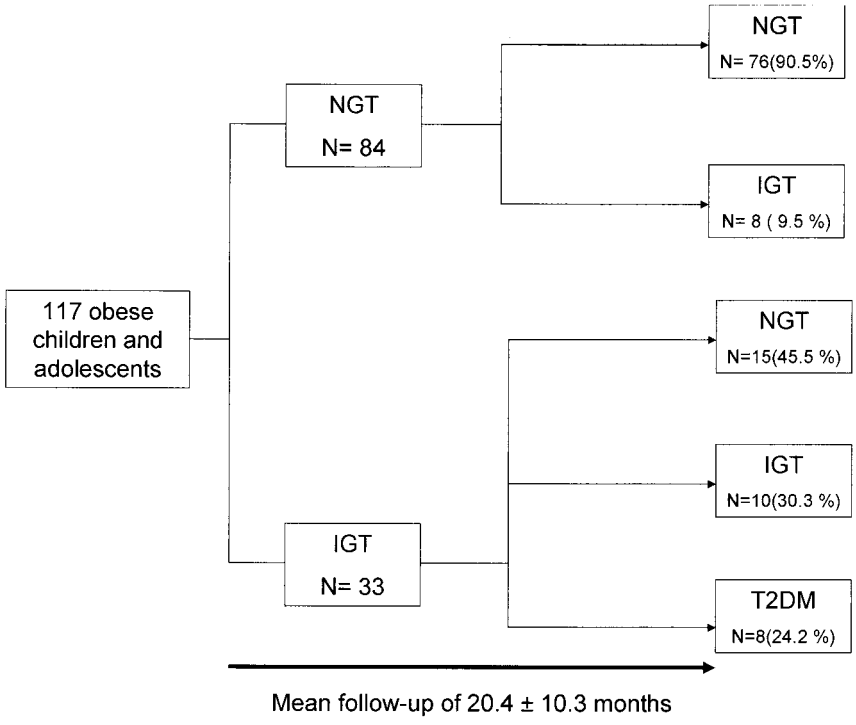

Figure 1—*Baseline and outcome glucose tolerance classification. T2DM, type 2 diabetes.*

of the treated females who were initially IGT progressed to type 2 diabetes, two converted to NGT, and two remained IGT. These 12 subjects were removed from the cohort; therefore, only 117 were analyzed for baseline data. Preliminary follow-up data about the metabolic syndrome phenotype in 77 of these patients have been previously reported (10).

OGTT

All subjects were instructed to consume a diet consisting of at least 250 g carbohydrates per day for 7 days before the study. Subjects were studied in the Yale Children's Clinical Research Center at 8:00 A.M. after a 12-h overnight fast. After the local application of a topical anesthetic cream containing 2.5% lidocaine and 2.5% prilocaine (Emla; AstraZeneca, Wilmington, DE), one antecubital intravenous catheter was inserted for blood sampling and its patency was maintained by slow infusion of normal saline. Then, each child rested while watching a videotape for 30 min. Two baseline samples were then obtained for measurements of plasma glucose, insulin, C-peptide, and lipids. Thereafter, flavored glucose (Orangedex; Custom Laboratories, Baltimore, MD) in a dose of 1.75 g/kg body wt (up to a maximum of 75 g) was given orally, and blood samples were obtained for the measurement of plasma glucose, insulin, and C-peptide every 30 min for 120 min.

Biochemical analysis

The plasma glucose level was determined with a YSI 2700 STAT Analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma lipid levels were determined by the Yale Core Lipid Laboratory with an AutoAnalyzer (model 747-200; Roche-Hitachi, Indianapolis, IN). Plasma insulin was measured with a radioimmunoassay (Linco, St. Charles, MO) that has <1% cross-reactivity with C-peptide and proinsulin. Plasma C-peptide levels were determined with an assay from Diagnostic Product (Los Angeles, CA). The intra-assay variation was 4.5% for insulin and 5.9% for C-peptide, and the interassay variation was 10% for insulin and 11% for C-peptide.

Definitions

NGT was defined as fasting plasma glucose <100 mg/dl and a 2-h plasma glucose level <140 mg/dl (11). IGT was defined as a fasting plasma glucose level <100 mg/dl and a 2-h plasma glucose level of 140–200 mg/dl. Type 2 diabetes was defined as a fasting glucose level ≥126 mg/dl, a 2-h plasma glucose level >200 mg/dl, or presentation with hyperglycemia (more than two random glucose measurements >200 mg/dl), glucosuria, polydypsia, and polyuria.

Calculations

To assess β-cell function, we used the insulinogenic index, calculated as the ratio of the increment in the plasma insulin level to that in the plasma glucose level during the first 30 min after the ingestion of glucose. We found that in children and adolescents, the insulinogenic index correlates well with the early insulin response obtained during a hyperglycemic clamp study ($r = 0.68$, $P < 0.001$) (S.C., unpublished observations). A low insulinogenic index predicts the development of diabetes in adults (12).

Insulin resistance was determined by two methods: the homeostasis model assessment of insulin resistance (HOMA-IR) (13), and the whole-body insulin sensitivity index (WBISI). HOMA-IR was calculated as the product of the fasting plasma insulin level (in microunits per milliliter) and the fasting plasma glucose level (in millimoles per liter) divided by 22.5. Lower HOMA-IR values indicate higher insulin sensitivity, whereas higher values indicate lower insulin sensitivity. The estimate obtained with HOMA-IR (the insulin resistance index) correlates well ($r = -0.91$, $P < 0.001$) with measures of insulin resistance obtained from obese and nonobese children and adolescents with the use of the euglycemic-hyperinsulinemic clamp technique (14), and a similar correlation has been reported in adults (15).

The WBISI, originally described by Matsuda et al. (16), is derived from glucose and insulin levels from the full length of the OGTT. The index is calculated using the following formula:

$$\text{WBISI} = \frac{10{,}000}{\sqrt{(\text{fasting glucose} \times \text{fasting insulin})\,(\text{mean OGTT glucose} \times \text{mean OGTT insulin})}}$$

We found this index to correlate strongly with *M* values derived from the hyperinsulinemic-euglycemic clamp in obese children (17). The disposition index (18) was calculated as the product of the WBISI and the insulinogenic index (IGI). We have recently demonstrated that the hyperbolic relation of the acute insulin response (derived from the insulinogenic index) and peripheral insulin sensitivity (using WBISI) is present in obese children and has typical deterioration as a function of altered glucose metabolism (from NGT to IGT), similar to findings demonstrated in adults. The disposition index represents the insulin response in the context of the resistant milieu. We chose to use these indexes as outcome variables in this cohort, although no data are present regarding the predictive value of the IGI or the disposition index in childhood.

Statistical analysis

Data are presented as means ± SD or as means (95% CI). For parameters not normally distributed, a log transformation was used for analysis; however, for the sake of interpretation, the non–log-transformed values are presented. Comparisons of those who developed diabetes with all other subjects were performed using Student's *t* tests. Comparisons of IGT subjects who developed diabetes and who reverted to NGT were performed using the Mann-Whitney *U* test. Linear regression was used to identify predictors of the 2-h glucose on the second OGTT. All analyses were performed using SPSS version 12 for Windows (SPSS, Chicago, IL).

RESULTS

Baseline anthropometric and biochemical parameters

The initial cohort consisted of 84 subjects with NGT and 33 with IGT. Age at the initial OGTT, as well as height, weight, BMI, and BMI *z* score, were not different between the groups. As shown in Table 1, fasting glucose was slightly, yet not significantly, higher in subjects with IGT. Fasting insulin, 2-h insulin, HOMA-IR, and fasting C-peptides were significantly increased in subjects with IGT. The significance of these differences became greater after adjustment for age, ethnicity, sex, and BMI *z* score. Insulin sensitivity (expressed as WBISI) was significantly greater in subjects with NGT, as was their disposition index.

Table 2—*Anthropometric and fasting biochemistry values*

	Developed type 2 diabetes (n = 8)	No type 2 diabetes (n = 109)	P value	
M/F	2/6	36/73	0.48	
Ethnicity (Caucasian/African American/Hispanic)	1/7/0	53/30/25	0.006	
Age (years)	12.7 ± 3.1	11.9 ± 3.2	0.52	
Height (cm)	155 ± 16	157 ± 14	0.75	
Weight (kg)	110 ± 37	88 ± 26	0.17	
BMI (kg/m^2)	44.8 ± 9.0	35.2 ± 7.1	0.03	
BMI z score	2.76 ± 0.21	2.41 ± 0.35	0.003	
Biochemical values			P value	
			Unadjusted	Adjusted
Glucose (mg/dl)	92.6 (78.7–106.6)	91.6 (90.0–93.1)	0.10	0.79
Glucose 120 min (mg/dl)	168 (152–184)	120 (115–125)	<0.001	<0.001
Insulin (μU/ml)	40 (24–65)	30 (27–33)	0.13	0.30
Insulin 120 min (μU/ml)	270 (134–544)	144 (121–170)	0.94	0.36
C-peptide (pmol/l)	1,339 (1,012–3,197)	1,107 (1,012–1,199)	<0.001	0.02
HOMA-IR	10.23 (6.80–13.66)	8.58 (7.06–10.11)	0.33	0.21
OGTT-derived indexes				
WBISI	0.94 (0.62–1.40)	1.48 (1.30–1.66)	0.61	0.16
IGI	2.11 (1.18–3.78)	3.52 (3.06–4.05)	0.03	0.08
Disposition index	1.99 (1.36–2.91)	5.20 (4.61–5.92)	<0.001	0.002

Data are expressed as means ± SD or 95% CI unless noted otherwise. Adjusted P values were adjusted for sex, ethnicity, and BMI z score.

Changes in glucose tolerance status

The mean interval between the two OGTTs was 20.4 ± 10.3 months. As shown in Fig. 1, 76 subjects with NGT remained so on follow-up, while 8 subjects (9.5%) deteriorated to IGT. Of the 33 subjects who were IGT at baseline, 8 developed diabetes (24.2%), 10 (30%) remained IGT, and 15 (45%) reverted to NGT.

Comparison of subjects who developed type 2 diabetes and other participants

All eight subjects who developed type 2 diabetes were IGT at baseline. These eight subjects (Table 2) were similar to the rest of the participants in their sex distribution, yet the majority (seven of eight) were African-American females (P = 0.006). Age and weight were comparable between the groups, whereas those who eventually developed diabetes had a significantly higher BMI and BMI z score and thus were relatively more obese. The 2-h glucose level was, as expected, higher in those who developed diabetes, since all were IGT on their initial study. Subjects who developed diabetes had a significantly elevated fasting C-peptide level compared with other participants.

Both indexes of insulin sensitivity (the HOMA-IR and WBISI) were not significantly different. The IGI of the acute insulin response tended to be lower in those who developed diabetes, but these differences were not statistically significant after adjustment for age, sex, ethnicity, and BMI z score. Nevertheless, these alterations in insulin sensitivity and secretion produced a significant reduction in the disposition index of obese subjects who developed type 2 diabetes. This striking difference in the disposition index remained significant after adjustment for age, sex, ethnicity, and BMI z score.

When evaluating only subjects with IGT, the BMI z score was still significantly greater in those who developed diabetes compared with their counterparts (2.76 ± 0.21 vs. 2.32 ± 0.40, P = 0.001), as was the change in BMI z score between the studies (0.024 ± 0.03 vs. −0.06 ± 0.17, P = 0.04), but the disposition index was comparable between the groups.

Comparison of subjects with IGT who developed type 2 diabetes and subjects with IGT who reverted to NGT

Subjects with IGT on the first OGTT demonstrated two distinct patterns of glucose tolerance dynamics, i.e., those who developed diabetes and those who reverted to normal glucose tolerance. As shown in Table 3, the groups were of similar age and sex distribution, yet those who developed diabetes were significantly more obese, as reflected by their BMI and BMI z score. Baseline fasting and 2-h levels of glucose, insulin, and C-peptide were similar between the groups, as was HOMA-IR. Subjects who eventually developed diabetes gained a significant amount of weight and increased their BMI, whereas those who reverted to NGT on average maintained their weight and BMI.

Predictors of the 2-h glucose level on the second OGTT

In the first model, we incorporated anthropometrics and parameters derived from fasting and 2-h blood sampling during the first OGTT to predict the 2-h glucose level on the second OGTT (Tables 4 and 5). The common parameters incorporated into the linear regression model were age, sex, ethnicity, time between studies, and baseline 2-h glucose. Fasting glucose, fasting and 2-h insulin, and fasting and 2-h C-peptide were first incorporated separately and then all together in the full model. As shown in Table 4, the 2-h glucose on the first OGTT and baseline BMI z score were significantly associated with 2-h glucose on study 2, whereas all other OGTT-derived parameters were

Table 3—*Comparison of subjects with IGT who developed type 2 diabetes and who reverted to NGT*

	IGT reverted to NGT	IGT progressed to type 2 diabetes	*P* value
M/F	3/12	2/6	0.58
Ethnicity (Caucasian/African American/Hispanic)	8/3/4	1/7/0	0.007
Age (years)	12.4 ± 2.5	11.9 ± 3.2	0.78
Height (cm)	155 ± 12	155 ± 16	0.48
Weight (kg)	81 ± 25	110 ± 37	0.08
BMI (kg/m^2)	33.1 ± 6.9	44.8 ± 9	0.01
BMI *z* score	2.27 ± 0.39	2.76 ± 0.21	0.01
Biochemical values			
Glucose (mg/dl)	95 (87–102)	93 (78–106)	0.92
Glucose 120 min (mg/dl)	158 (147–170)	168 (152–184)	0.06
Insulin (μU/ml)	59 (30–89)	40 (24–65)	0.41
Insulin 120 min	740 (204–1,227)	270 (134–544)	0.30
C-peptide (pmol/l)	1,560 (1,160–1,936)	1,339 (1,012–3,197)	0.63
C-peptide 120 min (pmol/l)	6,627 (4,409–8,845)	4,483 (2,486–6,481)	0.15
HOMA-IR	14.48 (6.75–22.22)	10.23 (6.80–13.66)	0.54
Weight and BMI dynamics			
Weight change (kg)	6.1 ± 8.4	27.3 ± 23.1	0.006
BMI change (kg/m^2)	1.06 ± 2.56	6.80 ± 7.08	0.025

Data are expressed as means ± SD or 95% CI unless noted otherwise.

not. African-American ethnicity was also associated with increasing 2-h glucose on the second OGTT.

In the second model, we used parameters of insulin sensitivity and secretion derived from a traditional OGTT (sampling every 30 min) and their changes over time, as well as the change in BMI *z* score, to predict the 2-h glucose level on the second OGTT. The common parameters incorporated into the linear regression model were identical to the previous model. The pairs of baseline BMI *z* score and change in BMI *z* score (model 1), baseline IGI and change in IGI (model 2), and baseline WBISI and change in WBISI (model 3) were first incorporated separately and then all together later in the full model. In the full model, the best predictors of the 2-h glucose level on the second OGTT were the baseline 2-h glucose level and BMI *z* score and the change in insulin sensitivity (WBISI) between the studies. Indeed, every 1 unit of the BMI *z* score had an impact of ~11 mg/dl glucose and every 1 unit of insulin sensitivity (WBISI) had a negative impact of ~7 mg/dl glucose. African-American ethnicity again emerged as being associated with increasing 2-h glucose on the second OGTT.

Relation of changes in weight and insulin sensitivity

As changes in insulin sensitivity emerged as having a major impact on the dynamics of glucose tolerance (2-h glucose level on the second OGTT), we tested the effect of weight changes on insulin sensitivity and glucose tolerance. Changes in weight negatively correlated with changes in the 2-h glucose level on the second OGTT ($r = -0.22$, $P = 0.02$) and changes in insulin sensitivity ($r = -0.52$, $P < 0.001$), as did a change in BMI *z* score (absolute obesity) ($r = -0.49$, $P < 0.001$ for change in sensitivity).

Table 4—*Linear regression model for predicting glucose at 120 min on the second OGTT using data from fasting and 2-h sampling*

	Model 1		Model 2		Model 3		Full model	
	β Coefficient	*P* value	β Coefficient	*P* value	β Coefficient	*P* value	β Coefficient	*P* value
Age	−0.63	−0.75	−0.70	0.33	−0.56	0.44	−0.55	0.45
Sex	5.49	0.24	4.68	0.30	6.80	0.14	8.24	0.07
Ethnicity								
Caucasian	7.76	0.18	7.46	0.20	9.22	0.11	8.84	0.12
African American	18.9	0.003	18.8	0.003	21.42	0.001	22.89	<0.001
Time between studies	−0.009	0.19	−0.008	0.27	0.001	0.87	−0.005	0.52
Glucose 120 min on first OGTT	0.40	<0.001	0.45	<0.001	0.41	<0.001	0.47	<0.001
BMI *z* (baseline)	14.1	0.02	14.4	0.02	14.2	0.038	15.6	0.02
Fasting glucose on first OGTT	−0.30	0.23					−0.42	0.14
Fasting insulin on first OGTT			−0.02	0.80			−0.14	0.24
Insulin 120 min on first OGTT			−0.009	0.21			−0.006	0.52
Fasting C-peptide on first OGTT					0.007	0.06	0.10	0.12
C-peptide 120 min on first OGTT					−0.002	0.10	−0.001	0.44

The β coefficient for sex compares male with female subjects.

Table 5—*Linear regression model for predicting glucose at 120 min on the second OGTT using indexes of insulin sensitivity, secretion, and their dynamics*

	Model 1		Model 2		Model 3		Full model	
	β Coefficient	*P* value	β Coefficient	*P* value	β Coefficient	*P* value	β Coefficient	*P* value
Age	−0.78	0.32	−1.22	0.10	−0.64	0.41	−0.24	0.77
Sex	5.91	0.25	6.18	0.21	4.36	0.41	5.32	0.31
Ethnicity								
Caucasian	8.0	0.16	6.5	0.28	7.82	0.21	7.4	0.24
African American	18.45	0.004	21.46	0.001	19.35	0.003	22.29	0.001
Time between studies	−0.009	0.22	−0.006	0.44	−0.005	0.54	−0.006	0.41
Glucose 120 min on first OGTT	0.38	<0.001	0.32	0.001	0.43	<0.001	0.43	<0.001
BMI *z* score (baseline)	14.38	0.02					16.49	0.03
Δ BMI *z* score	−2.66	0.81					−10.90	0.44
IGI (baseline)			−1.15	0.08			−0.90	0.23
Δ IGI			−0.68	0.15			−0.57	0.24
WBISI (baseline)					−0.34	0.89	−0.67	0.82
Δ WBISI					−6.46	0.007	−6.88	0.011

The β coefficient for sex compares male with female subjects. Hispanic ethnicity was used as a reference.

When adjusting for the baseline BMI *z* score and the 2-h glucose level on the first OGTT, the relation of weight and BMI *z* score changes with changes in sensitivity remained significant ($r = -0.41$, $P < 0.001$ and $r = -0.46$, $P < 0.001$, respectively).

CONCLUSIONS — Previous cross-sectional studies have demonstrated that IGT is a common metabolic complication of childhood obesity (4,19,20). As illustrated by the baseline assessments of children in this cohort, oral glucose tolerance testing is required to identify the problem, and this procedure also can be utilized to examine underlying pathophysiologic defects in insulin sensitivity and insulin secretion. In contrast, baseline clinical and anthropometric characteristics did not distinguish obese youth with IGT from those with NGT. Although IGT has become a well-recognized complication of childhood obesity, data on the natural history of this condition in children are minimal. Consequently, the purpose of the current investigation was to examine in a prospective, longitudinal study which clinical, anthropometric, and metabolic factors may serve as useful predictors of future changes in glucose metabolism in obese youth. As clinicians are faced with growing numbers of asymptomatic obese children, such predictors would fill the urgent need to identify youth at highest risk for development of diabetes and to direct interventions to those who may benefit the most.

One of the most important findings of this study is that IGT in obese children is indeed a transitional, "pre-diabetic" state, in that all children who developed type 2 diabetes on follow-up had IGT at baseline. It is also noteworthy that seven of eight children who developed diabetes were African American. Our data are limited in power to detect the impact of ethnicity on altered glucose metabolism, yet the observation that the majority of children who developed type 2 diabetes were African American is consistent with the increased prevalence of type 2 diabetes in African-American versus Caucasian children that has been reported in many other studies and may relate to genetically mediated differences in insulin sensitivity and insulin secretory patterns (21,22). The other important baseline clinical characteristic that predicted deterioration to type 2 diabetes was the degree of adiposity as reflected by the BMI *z* score. Compared with the group of obese youth as a whole and to other participants with IGT, children who progressed to type 2 diabetes had significantly higher BMI *z* scores at baseline, and these children continued to gain excessive weight during the follow-up period.

Except for the baseline 2-h glucose level, other metabolic factors such as fasting glucose, insulin, C-peptide, and HOMA-IR were not useful predictors of future deterioration in glucose tolerance. Even indexes of insulin sensitivity (WBISI) and early insulin responses to oral glucose (IGI) that were derived from baseline and follow-up OGTTs did not appear to be significant predictors for the development of type 2 diabetes when viewed in isolation. It should be noted, however, that obese youth who developed type 2 diabetes tended to be more insulin resistant and have lower early insulin responses to glucose loading at baseline than the group as a whole. Since the alterations in insulin sensitivity were not fully compensated by increases in insulin responses to glucose loading, the baseline disposition index, which assesses the combined deleterious effects of both of these defects, was a significant predictor of deterioration to type 2 diabetes. Moreover, insulin sensitivity was further reduced in the children who developed type 2 diabetes in association with continued weight gain. Because the disposition index is greatly influenced by genetic and intrauterine factors (23,24), one can speculate that these obese children pushed past their predetermined limitations in adjusting to worsening in insulin resistance.

Our study also clearly shows that glucose tolerance status in obese children is highly dynamic and can deteriorate rapidly. Over a relatively short follow-up period, ~10% of subjects initially classified as NGT developed IGT and 24% of subjects initially classified as IGT developed overt type 2 diabetes. These data suggest that the tempo of deterioration of β-cell function in children may be faster than in adults (25,26). It should be noted, however, that our data also indicate that obese children with IGT can revert to NGT on

follow-up testing. Such improvements in glucose tolerance do not appear to be artifacts of repeat testing, since these youth had lower BMI *z* scores at baseline and gained much less weight on follow-up than those who developed type 2 diabetes. These observations suggest that a focused and intensive intervention (similar to the one used in the Diabetes Prevention Program [27]) may be useful in managing the severely obese child with IGT.

We conclude that severely obese children (BMI *z* score >2.5) and obese children with risk factors for type 2 diabetes (a parent with type 2 diabetes or history of gestational diabetes, presence of acanthosis nigricans, or suggestive symptomatology) should undergo an OGTT. Those with 2-h glucose >140 mg/dl, specifically of ethnic minority background, require the most intensive intervention and careful observation for prevention of development of type 2 diabetes. Cessation of weight gain and not necessarily weight loss may suffice to prevent further deterioration in glucose tolerance. As the risk in these patients seems very high and the window of opportunity is narrow, pharmacological intervention, combined with lifestyle changes, should not be ruled out.

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