

PREVALENCE OF IMPAIRED GLUCOSE TOLERANCE AMONG CHILDREN AND ADOLESCENTS WITH MARKED OBESITY

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ABSTRACT

Background Childhood obesity, epidemic in the United States, has been accompanied by an increase in the prevalence of type 2 diabetes among children and adolescents. We determined the prevalence of impaired glucose tolerance in a multiethnic cohort of 167 obese children and adolescents.

Methods All subjects underwent a two-hour oral glucose-tolerance test (1.75 mg of glucose per kilogram of body weight), and glucose, insulin, and C-peptide levels were measured. Fasting levels of proinsulin were obtained, and the ratio of proinsulin to insulin was calculated. Insulin resistance was estimated by homeostatic model assessment, and beta-cell function was estimated by calculating the ratio between the changes in the insulin level and the glucose level during the first 30 minutes after the ingestion of glucose.

Results Impaired glucose tolerance was detected in 25 percent of the 55 obese children (4 to 10 years of age) and 21 percent of the 112 obese adolescents (11 to 18 years of age); silent type 2 diabetes was identified in 4 percent of the obese adolescents. Insulin and C-peptide levels were markedly elevated after the glucose-tolerance test in subjects with impaired glucose tolerance but not in adolescents with diabetes, who had a reduced ratio of the 30-minute change in the insulin level to the 30-minute change in the glucose level. After the body-mass index had been controlled for, insulin resistance was greater in the affected cohort and was the best predictor of impaired glucose tolerance.

Conclusions Impaired glucose tolerance is highly prevalent among children and adolescents with severe obesity, irrespective of ethnic group. Impaired oral glucose tolerance was associated with insulin resistance while beta-cell function was still relatively preserved. Overt type 2 diabetes was linked to beta-cell failure. (N Engl J Med 2002;346:802-10.)

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THE epidemic of childhood obesity in the United States has been accompanied by a marked increase in the frequency of type 2 diabetes.^{1,2} In adults, type 2 diabetes develops over a long period, and most, if not all, patients initially have impaired glucose tolerance, which is an intermediate stage in the natural history of type 2 diabetes³ and predicts the risk of the development of

diabetes⁴ and cardiovascular disease.⁵ With appropriate changes in lifestyle, progression from impaired glucose tolerance to frank diabetes can be delayed or prevented.^{6,7} Thus, great emphasis has recently been placed on the early detection of glucose intolerance in adults.

Although severe obesity has a prominent role in the pathogenesis of type 2 diabetes in children and adolescents,¹ it is unknown whether it is a risk factor for impaired glucose tolerance. We undertook a study to determine the prevalence of glucose intolerance in a multiethnic cohort of obese children and adolescents. Abnormal beta-cell function, as manifested by the release of large amounts of proinsulin relative to insulin levels, is clearly present in patients with overt type 2 diabetes.^{8,9} Disproportionate hyperproinsulinemia is thought to represent an impending failure of insulin secretion in adults.⁸ The earlier an increase in the ratio of proinsulin to insulin occurs in the prediabetic phase, the more likely it is that abnormal processing of insulin by beta cells is fundamental to the pathogenesis of diabetes. We therefore examined the intracellular processing of proinsulin to determine whether alterations are present early in the development of glucose intolerance in obese children and adolescents.

METHODS

Study Population

We recruited 55 children (4 to 10 years of age) and 112 adolescents (11 to 18 years of age) who had been referred to the Yale Pediatric Obesity Clinic between 1999 and 2001. Body weight was measured with a digital scale to the nearest 0.1 kg, and height was measured in triplicate with a wall-mounted stadiometer. The body-mass index — the weight in kilograms divided by the square of the height in meters — was calculated. All subjects had a body-mass index that was higher than the 95th percentile for age and sex and were thus classified as obese.¹⁰ Approximately 58 percent of the subjects were non-Hispanic white, 23 percent were non-Hispanic black, and 19 percent were Hispanic (Table 1). A detailed medical and family history was obtained from all subjects, and a physical examination was performed, including staging of puberty on the basis of breast development in girls and genital development in boys according to the criteria of Tanner¹¹ (stage 1 indicates preadolescent charac-

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TABLE 1. CLINICAL CHARACTERISTICS ACCORDING TO SEX AND AGE GROUP.*

CHARACTERISTIC	CHILDREN (N=55)		ADOLESCENTS (N=112)	
	MALE (N=17)	FEMALE (N=38)	MALE (N=54)	FEMALE (N=58)
Race or ethnic group (no.)				
Non-Hispanic white	12	22	26	37
Non-Hispanic black	3	9	12	14
Hispanic	2	7	16	7
Age (yr)	8±0.3	7±0.3	14±0.2	14±0.2
Range	6–10	4–10	11–17	11–18
Weight (kg)	62±15	54±3	104±4	104±0.2
Height (cm)	138±3	133±2	166±1	162±1
Body-mass index	32±8	30±1	37±1	34±1

*Plus-minus values are means ±SE.

teristics, and stage 5 indicates adult characteristics). All subjects were otherwise in good health and had normal thyroid function; none were taking any medications. A total of 23 of the adolescent girls (approximately 40 percent) had hirsutism, oligomenorrhea, acne, and increased levels of total testosterone, suggesting the presence of the polycystic ovary syndrome. The study was approved by the Institutional Review Board of the Yale University School of Medicine. Written informed consent was obtained from the parents and oral consent from the children and adolescents.

Oral Glucose-Tolerance Test

All subjects followed a weight-maintenance diet consisting of at least 250 g of carbohydrates per day for seven days before the study, as confirmed by the fact that body weight remained stable (measured to the nearest 0.5 kg). Subjects were studied in the Children's Clinical Research Center at the Yale University School of Medicine at 8 a.m. after a 12-hour overnight fast. After the local application of a topical anesthetic cream containing 2.5 percent lidocaine and 2.5 percent prilocaine (Emla, Astra Zeneca, Wilmington, Del.), one antecubital intravenous catheter was inserted for blood sampling, and its patency was maintained by slow infusion of normal saline. Each child then rested while watching a videotape for 30 minutes. Two base-line samples were then obtained for measurements of plasma glucose, insulin, C peptide, proinsulin, and lipids. Thereafter, flavored glucose (Orangedex, Custom Laboratories, Baltimore) in a dose of 1.75 g per kilogram of body weight (up to a maximum of 75 g) was given orally, and blood samples were obtained every 30 minutes for 120 minutes for the measurement of plasma glucose, insulin, and C peptide. Impaired glucose tolerance was defined, according to the American Diabetes Association guidelines, as a fasting plasma glucose level of less than 126 mg per deciliter and a two-hour plasma glucose level of 140 to 200 mg per deciliter; type 2 diabetes was defined as a fasting glucose level of 126 mg per deciliter or higher or a two-hour plasma glucose level of more than 200 mg per deciliter.¹²

Although the oral glucose-tolerance test is the most sensitive method for detecting early diabetes, it can result in misclassification.¹³ To determine the reproducibility of the results, we repeated the test three months later in four obese children with normal glucose tolerance and in six obese children and adolescents with impaired glucose tolerance.

Biochemical Analysis

The plasma glucose level was determined with a glucose analyzer (Beckman Instruments, Brea, Calif.), and the plasma lipid

levels were determined by the Yale Core Lipid Laboratory with an AutoAnalyzer (model 747–200, Roche–Hitachi, Indianapolis). Plasma insulin was measured with a radioimmunoassay made by Linco (St. Charles, Mo.), which has less than 1 percent cross-reactivity with C-peptide and proinsulin. Plasma C-peptide levels were determined with an assay made by Diagnostic Product (Los Angeles), and total proinsulin with another radioimmunoassay kit (Linco), which has no cross-reactivity with insulin and a detection limit of 0.15 pmol. The intraassay variation was 11 percent for insulin, 13 percent for C peptide, and 9 percent for proinsulin, and the interassay variation was 12 percent for insulin, 12 percent for C peptide, and 11 percent for proinsulin.

Calculations

To assess beta-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 minutes 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 ($r=0.68$, $P<0.001$). A low insulinogenic index predicts the development of diabetes in adults.^{14–17} Insulin resistance was determined by homeostatic model assessment¹⁸ and 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 insulin-resistance values indicate a higher insulin sensitivity, whereas higher values indicate a lower insulin sensitivity. The estimate obtained with homeostatic model assessment (the insulin-resistance index) correlated well ($r=-0.71$, $P<0.001$) with measures of insulin resistance obtained from obese and nonobese children and adolescents with the use of the euglycemic–hyperinsulinemic clamp technique; a similar correlation has been reported in adults.^{18,19}

Statistical Analysis

All values are expressed as means ±SE. Variables that were not normally distributed (insulin level, insulin-resistance index, proinsulin level, and two-hour plasma insulin level) were log-transformed for analysis. However, for clarity of interpretation, results are expressed as untransformed values. Differences in the means of continuous variables were tested by two-tailed t-tests. Nonparametric statistics were applied in the analyses of data that had a skewed distribution. An analysis of covariance was used to compare the plasma levels of glucose, insulin, C peptide, and proinsulin and the insulin-resistance index of subjects with normal glucose tolerance with the values for those with impaired glucose tolerance, with age and body-mass index as covariates. Multiple logistic-regression analysis was used to evaluate the model with the use of two goodness-of-fit tests (Proc Logistic procedure, SAS software, release 6.10, SAS Institute, Cary, N.C.)²⁰ and to determine the relative risks of impaired glucose tolerance among obese children and adolescents. The dependent variable in multiple logistic-regression analyses was the plasma glucose level at 120 minutes. The independent variables entered in the several models generated were age, body-mass index, fasting insulin and proinsulin levels, two-hour plasma insulin level, the insulin-resistance index, and the insulinogenic index.

RESULTS

Prevalence of Impaired Glucose Tolerance and Silent Type 2 Diabetes

A total of 25 percent of the children and 21 percent of the adolescents had impaired glucose tolerance (Table 2). Silent diabetes was diagnosed in four adolescents (4 percent). Among the children and adolescents with impaired glucose tolerance, 51 percent were non-

Hispanic white, 30 percent were non-Hispanic black, and 19 percent were Hispanic. Four adolescents — two black and two Hispanic — had diabetes. Fourteen girls with apparent cases of the polycystic ovary syndrome had normal glucose tolerance, six had impaired glucose tolerance, and two had diabetes. A total of 30 percent of the combined group of those with impaired glucose tolerance and those with frank diabetes had a parental history of type 2 diabetes; the rate was 25 percent among those with normal glucose tolerance ($P=0.54$).

More children with impaired glucose tolerance were girls, whereas the numbers of boys and girls were similar in the groups of adolescents with impaired glucose tolerance. The body-mass index was higher among adolescents with impaired glucose tolerance or diabetes than among those with normal glucose tolerance.

Reproducibility of the Oral Glucose-Tolerance Test

The mean plasma glucose levels at two hours during the first oral glucose-tolerance test (108 ± 7 mg per deciliter for subjects with normal glucose tolerance and 152 ± 3 mg per deciliter for those with impaired glucose tolerance) were similar to those obtained during the second oral glucose-tolerance test in subjects studied to determine the reproducibility of the results

(107 ± 12 mg per deciliter for subjects with normal glucose tolerance and 146 ± 3 mg per deciliter for those with impaired glucose tolerance). Thus, the diagnosis was confirmed during the second test in all six subjects with impaired glucose tolerance who were evaluated. Three non-Hispanic black girls were followed for two to five years, during which time the oral glucose-tolerance test was repeated several times. Subject 1 had impaired glucose tolerance at 6 years of age, which persisted until 11 years of age, when diabetes developed. Subject 2 had normal glucose tolerance at 8 years of age, which then progressed to impaired glucose tolerance at 12 years of age and remained impaired thereafter. Subject 3 had impaired glucose tolerance at six years of age, and frank diabetes developed at eight years of age.

Glucose, Insulin, and C-Peptide Responses to an Oral Glucose Challenge

Fasting plasma glucose levels were similar in the children irrespective of whether their glucose tolerance was normal or impaired (Fig. 1). In contrast, the adolescents with impaired glucose tolerance had higher fasting plasma glucose levels (90 ± 1 mg per deciliter [5.0 ± 0.06 mmol per liter]) than those with normal glucose tolerance (82 ± 1 mg per deciliter [4.6 ± 0.06

TABLE 2. CLINICAL AND METABOLIC PHENOTYPE OF OBESE CHILDREN AND ADOLESCENTS WITH NORMAL GLUCOSE TOLERANCE, IMPAIRED GLUCOSE TOLERANCE, OR TYPE 2 DIABETES.*

VARIABLE	CHILDREN (N=55)			ADOLESCENTS (N=112)				
	NORMAL GLUCOSE TOLERANCE (N=41)	IMPAIRED GLUCOSE TOLERANCE (N=14)	P VALUE	NORMAL GLUCOSE TOLERANCE (N=85)	IMPAIRED GLUCOSE TOLERANCE (N=23)	P VALUE	TYPE 2 DIABETES (N=4)	P VALUE
Race or ethnic group (no.)								
Non-Hispanic white	25	9		53	10		0	
Non-Hispanic black	8	4		17	7		2	
Hispanic	8	1		15	6		2	
Sex (no.)								
Male	15	2		40	12		2	
Female	26	12		45	11		2	
Age (yr)	7.5 ± 0.3	8 ± 0.5		14 ± 1	15 ± 0.4		15 ± 1	
Range	4-10	5-10		11-18	12-18		11-18	
Body-mass index	30 ± 1	32 ± 1	<0.05	37 ± 0.9	41 ± 1	<0.001	41 ± 5	<0.001
Fasting insulin level (μ U/ml)	20 ± 5	34 ± 5	<0.001	30 ± 2	56 ± 7	<0.001	50 ± 10	<0.001
Fasting C-peptide level (ng/ml)	2.6 ± 0.3	3.2 ± 0.2	<0.001	3.6 ± 0.1	4.7 ± 0.3	<0.001	4.5 ± 1	<0.001
Insulin-resistance index†	5 ± 0.6	7.2 ± 1	<0.001	6.3 ± 0.4	13 ± 7	<0.001	14 ± 3	<0.001

*Plus-minus values are means \pm SE. All P values are for the comparison with the group with normal glucose tolerance. To convert values for insulin to picomoles per liter, multiply by 6; to convert values for C peptide to nanomoles per liter, multiply by 0.331.

†The insulin-resistance index was determined by homeostatic model assessment and 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 insulin-resistance values indicate a higher insulin sensitivity, whereas higher insulin-resistance values indicate a lower insulin sensitivity.

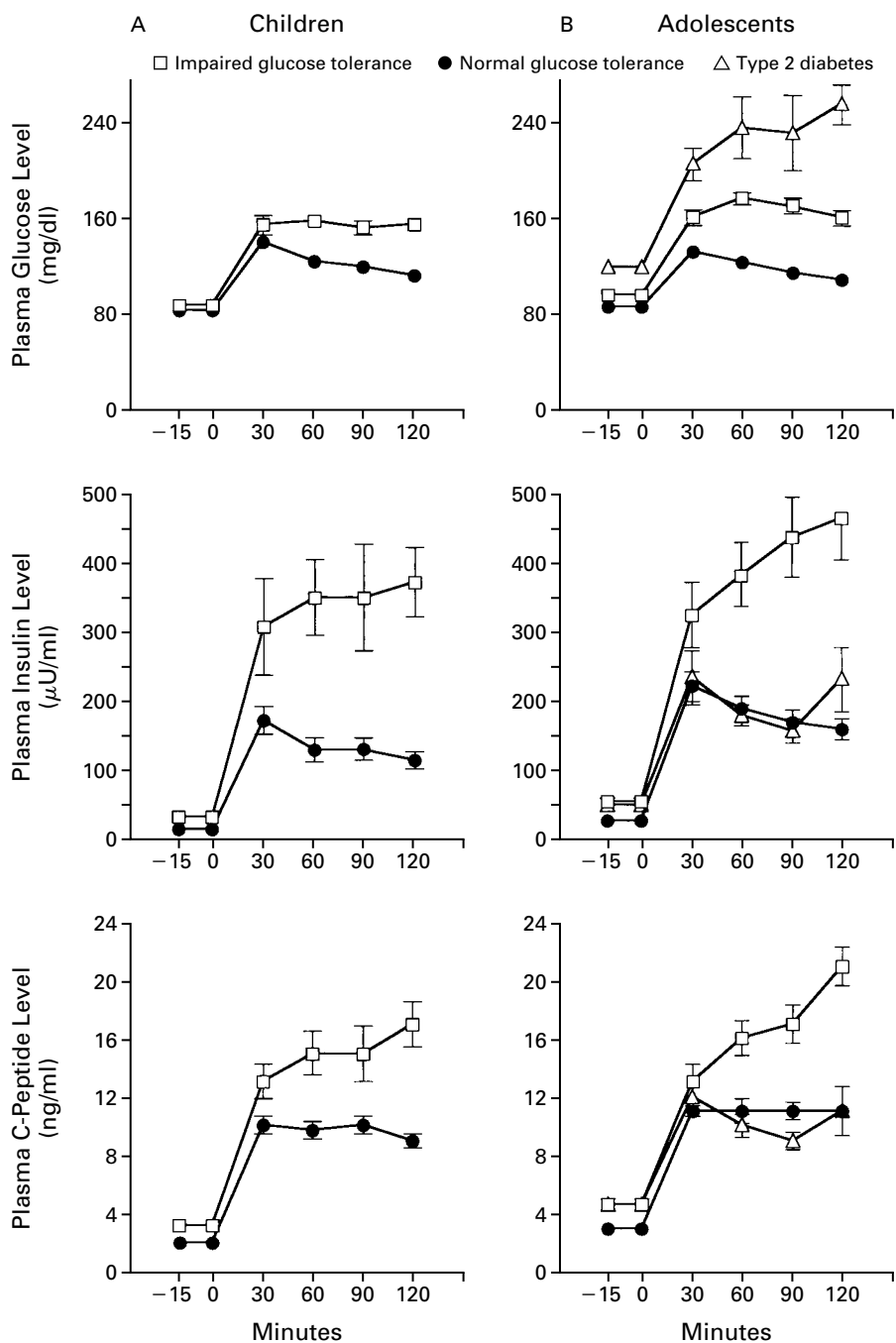


Figure 1. Mean (\pm SE) Plasma Glucose, Insulin, and C-Peptide Responses during the Oral Glucose-Tolerance Test in Obese Children (Panel A) and Adolescents (Panel B) with Normal Glucose Tolerance, Impaired Glucose Tolerance, or Type 2 Diabetes Mellitus.

Glucose (1.75 mg per kilogram) was administered at time 0. To convert values for glucose to millimoles per liter, multiply by 0.05551; to convert values for insulin to picomoles per liter, multiply by 6; to convert values for C peptide to nanomoles per liter, multiply by 0.331.

mmol per liter], $P=0.03$), and adolescents with type 2 diabetes had the highest fasting plasma glucose levels (118 ± 6 mg per deciliter [6.6 ± 0.33 mmol per liter], $P<0.001$). After the oral glucose-tolerance test, plasma glucose levels were higher in both children and adolescents with impaired glucose tolerance than in those with normal glucose tolerance and highest in subjects with frank diabetes ($P<0.001$). Fasting plasma insulin and C-peptide levels (Table 2) were higher in both children and adolescents with impaired glucose tolerance or diabetes than in subjects with normal glucose tolerance, even after adjustment for differences in the body-mass index. Similarly, the plasma insulin and C-peptide responses to oral glucose-tolerance testing were dramatically elevated in children and adolescents with impaired glucose tolerance as compared with the responses in those with normal glucose tolerance. In contrast, adolescents with silent diabetes had insulin and C-peptide responses similar to the responses in those with normal glucose tolerance.

Fasting Insulin and Proinsulin

Fasting proinsulin levels were nearly twice as high in children and adolescents with impaired glucose tolerance and diabetes as in those with normal glucose tolerance ($P<0.002$) (Fig. 2). The mean plasma proinsulin level was 1.6 ± 0.02 ng per milliliter in children with normal glucose tolerance, as compared with 2.6 ± 0.02 ng per milliliter in those with impaired glucose tolerance ($P=0.002$). The mean ratio of proinsulin to insulin was 0.11 ± 0.005 in children with normal glucose tolerance and 0.17 ± 0.01 in those with abnormal glucose tolerance. The fasting plasma proinsulin level was 2.4 ± 0.01 ng per milliliter in adolescents with normal glucose tolerance, 4.5 ± 0.06 ng per milliliter in those with impaired glucose tolerance, and 6.2 ± 0.12 in those with diabetes ($P=0.002$ for both comparisons with the adolescents with normal glucose tolerance). The ratio of proinsulin to insulin was 0.16 ± 0.002 in adolescents with normal glucose tolerance, 0.17 ± 0.02 in those with impaired glucose tolerance, and 0.23 ± 0.06 in those with diabetes ($P=0.30$ for both comparisons with the adolescents with normal glucose tolerance).

Early-Phase Insulin Secretion and Insulin Resistance

Impaired glucose tolerance in children was not associated with significant differences in the early changes in the glucose level, the insulin level, or the insulinogenic index (Fig. 3). In contrast, among adolescents with impaired glucose tolerance, there were changes in the plasma glucose level at 30 minutes that were significantly greater than those that occurred in adolescents with normal glucose tolerance, although these changes were not associated with a significant increase in plasma insulin levels. Consequently, the cal-

culated insulinogenic index was slightly but not significantly lower than that among adolescents with normal glucose tolerance ($P=0.09$). On the other hand, a significant reduction in the insulinogenic index was clearly observed among the adolescents with type 2 diabetes. After adjustment for differences in age and body-mass index, the subjects with glucose intolerance or diabetes had a significantly higher insulin-resistance index than did those with normal glucose tolerance ($P<0.001$) (Table 2).

Cardiovascular Risk Factors

Fasting lipid and lipoprotein profiles were similar in all groups, except that the fasting triglyceride levels were higher among the adolescents with impaired glucose tolerance than among those with normal glucose tolerance (150 ± 20 vs. 115 ± 7 mg per deciliter [1.7 ± 0.2 vs. 1.3 ± 0.08 mmol per liter], $P=0.05$). No differences in systolic and diastolic blood pressure were observed between children or adolescents with normal glucose tolerance and those with impaired glucose tolerance.

Risk Factors Associated with Impaired Glucose Tolerance

Risk factors associated with the presence of impaired glucose tolerance included in the logistic-regression analysis were the body-mass index, age, the insulinogenic index (as a categorical variable), the fasting plasma insulin and proinsulin levels, the two-hour insulin levels, and the insulin-resistance index. Body-mass index, age, and the insulinogenic index did not significantly predict impaired glucose tolerance. However, the insulin-resistance index strongly predicted the two-hour glucose level, with an odds ratio for impaired glucose tolerance of 1.27 (95 percent confidence interval, 1.15 to 1.40) per increment of 0.24 in the insulin-resistance index ($P<0.001$); other predictors, in order of predictive power, were the fasting proinsulin level, the two-hour insulin level, and the fasting insulin level. A positive, continuous relation was found in the entire cohort between the insulin-resistance index and the two-hour glucose level ($r=0.42$, $P<0.001$).

DISCUSSION

In a multiethnic cohort of obese children and adolescents, we found a high prevalence of impaired glucose tolerance. Previously undiagnosed type 2 diabetes was detected only among the adolescents (4 percent), and all four subjects with diabetes were members of minorities. Children and adolescents with impaired glucose tolerance included both white and minority children. The risk factors associated with impaired glucose tolerance included insulin resistance, marked hyperinsulinemia both after fasting and after a glucose challenge, and hyperproinsulinemia after fasting.

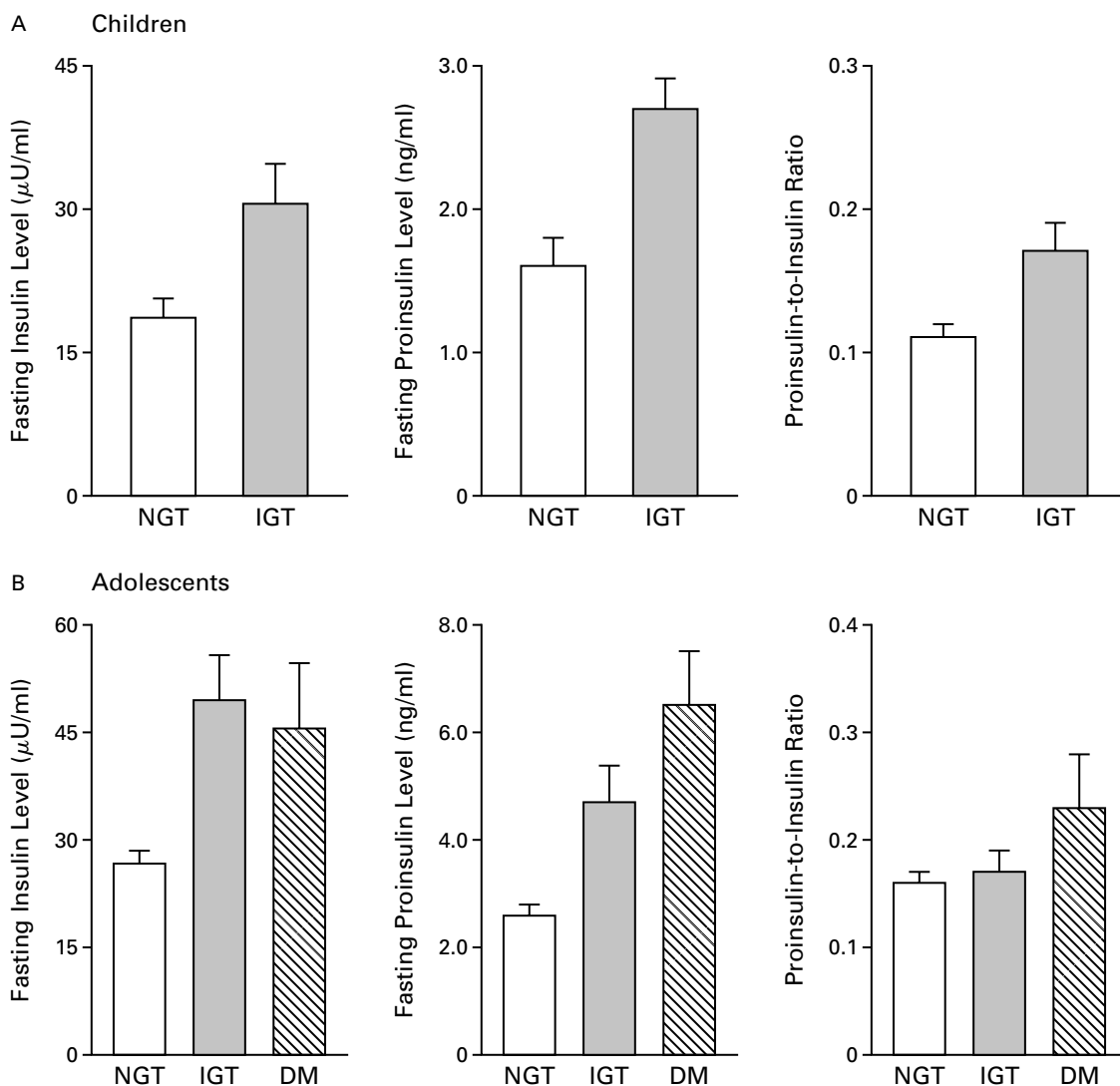


Figure 2. Mean (\pm SE) Fasting Insulin and Proinsulin Levels and Proinsulin-to-Insulin Ratio in Obese Children (Panel A) and Adolescents (Panel B) with Normal Glucose Tolerance (NGT), Impaired Glucose Tolerance (IGT), or Type 2 Diabetes Mellitus (DM). To convert values for insulin to picomoles per liter, multiply by 6; to convert values for proinsulin to picomoles per liter, multiply by 0.00939.

Like Arslanian et al.,²¹ we also found impaired glucose tolerance in some obese adolescents with the polycystic ovary syndrome. On the other hand, our study did not confirm that a family history of type 2 diabetes is a risk factor for impaired glucose tolerance, perhaps because we studied a group of high-risk obese children and adolescents. Although children and adolescents with mildly impaired glucose tolerance provide a unique model that can help us identify the early events that lead to diabetes without the confounding effects of aging and hyperglycemia, there is little information

available about risk factors associated with impaired glucose tolerance in young persons. Our data indicate that insulin resistance is a strong predictor of the two-hour plasma glucose levels in obese children and adolescents. Thus, it may play an important part in the transition from normal to impaired glucose tolerance.

The degree of obesity was not found to be a significant risk factor, possibly because the majority of our subjects were severely obese. The effects of obesity on the deterioration of glucose tolerance are most likely mediated by its metabolic complications — particular-

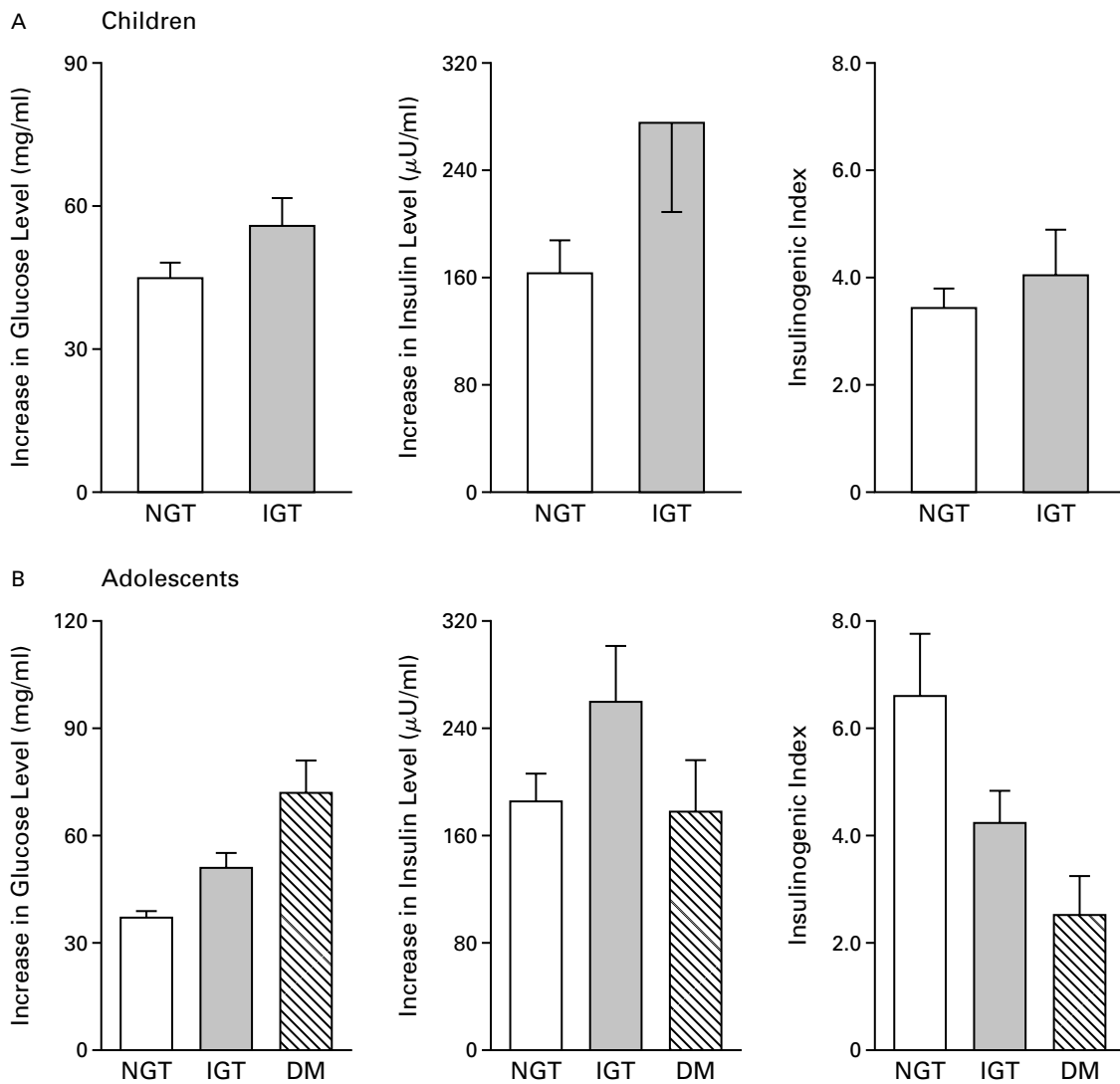


Figure 3. Mean (\pm SE) Changes from Base Line to 30 Minutes in Plasma Glucose and Insulin Levels and the Ratio of the Change in Insulin to the Change in Glucose (the Insulinogenic Index) in Obese Children and Adolescents with Normal Glucose Tolerance (NGT), Impaired Glucose Tolerance (IGT), or Type 2 Diabetes Mellitus (DM).

To convert values for glucose to millimoles per liter, multiply by 0.05551; to convert values for insulin to picomoles per liter, multiply by 6.

ly insulin resistance and hyperinsulinemia. Similar findings have been reported among adult Pima Indians²² and Mexican-American adults.²³ Although longitudinal studies are required to determine the sequence of events involved in the transitions from normal to impaired glucose tolerance and from glucose intolerance to diabetes, our study suggests that the onset of impaired glucose tolerance in obese children and adolescents is clearly associated with the development of severe insulin resistance while normal beta-cell function is still relatively preserved. In the presence of overt diabetes, insulin secretion declines, as demonstrated by

the lower insulin levels during the oral glucose-tolerance test in the adolescents with type 2 diabetes.

The loss of the first phase of insulin secretion has important pathogenic consequences, since it plays a key part in priming insulin action in target tissues that are responsible for normal glucose homeostasis.^{24,25} As a marker of early beta-cell response, we used the insulinogenic index, which was partially preserved in the adolescents with impaired glucose tolerance, whereas it was significantly reduced in the presence of frank diabetes. To further evaluate beta-cell function early in the prediabetic stage in obese children,

we measured proinsulin levels and calculated the ratios of proinsulin to insulin. Disproportionate hyperproinsulinemia is a clear marker of beta-cell dysfunction in overt type 2 diabetes.^{8,9,26} In Japanese-American men,²⁷ Mexicans,²⁸ and elderly white persons,²⁹ increased proinsulin levels have been found to predict the development of type 2 diabetes. In this study, fasting proinsulin levels were increased in children with impaired glucose tolerance, but their proinsulin-to-insulin ratios did not differ significantly from the ratios among those with normal glucose tolerance. Thus, in the very early stages of glucose intolerance in children and adolescents, despite the increased demand for beta-cell secretion, the hyperproinsulinemia is proportional to the hyperinsulinemia. The vigorous hyperinsulinemic response to glucose found in the pre-diabetic stage in obese children and adolescents may reflect an up-regulation of beta-cell function caused by chronic severe insulin resistance. Such a degree of hyperinsulinemia is not present in adults with impaired glucose tolerance.³⁰ It is conceivable that advanced age, together with changes in the size and mass of beta cells, the accumulation of amyloid in the islets, or both may contribute to the phenotypic expression of impaired insulin secretion that is found in some adults with impaired glucose tolerance.^{8,24}

The oral glucose-tolerance test is a labor-intensive method for studying carbohydrate metabolism. Unquestionably, the fasting plasma glucose level is easier and faster to measure, and its measurement is more acceptable to patients than an oral glucose-tolerance test. In our cohort of obese children and adolescents with impaired glucose tolerance, the prevalence of impaired fasting glucose levels (more than 110 mg per deciliter or 6 mmol per liter) was extremely low (less than 0.08 percent), whereas all four adolescents with diabetes had impaired fasting glucose levels. This suggests that fasting hyperglycemia is indicative of a more advanced stage of clinical diabetes, and the determination of its presence represents a very insensitive method for detecting impaired glucose tolerance. Similar findings on the low prevalence of impaired fasting glucose levels in adolescents have recently been reported by Fagot-Compagna et al.³¹ Our study suggests that the oral glucose-tolerance test can reliably establish a diagnosis of impaired glucose tolerance, since the intraperson variation was low in obese children and adolescents. This test may be required for the early detection of impaired glucose tolerance as well as of silent type 2 diabetes in patients with severe childhood obesity.

In summary, this cross-sectional study suggests that insulin resistance, initially associated with hyperinsulinemia and hyperproinsulinemia, is the most important risk factor linked to the development of impaired glucose tolerance in severe childhood obesity. In the

presence of established diabetes, beta-cell failure becomes fully manifest.

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CORRECTION

Prevalence of Impaired Glucose Tolerance among Children and Adolescents with Marked Obesity

Prevalence of Impaired Glucose Tolerance among Children and Adolescents with Marked Obesity . On line 2 of the Methods section of the Abstract, the dose of glucose should have been "1.75 g of glucose per kilogram of body weight," rather than "1.75 mg." In the first line of the legend to Figure 1, the dose of glucose should also have been "1.75 g per kilogram," rather than "1.75 mg."

CORRECTION

Impaired Glucose Tolerance in Obese Children and Adolescents

To the Editor: The report by Sinha et al. (March 14 issue)¹ provides important and timely information about the association between impaired glucose tolerance and obesity in children. However, it is important to note that the study sample was derived from a clinic population that may not be the most representative sample suitable for deriving prevalence estimates. Moreover, it is interesting to note that in 1968 Paulsen et al.² reported a very similar finding. Using the same criteria of the American Diabetes Association (ADA) used by Sinha et al. in 2002, Paulsen et al. reported that 17 percent of the 66 obese children they studied had impaired glucose tolerance, and 6 percent met the criteria for type 2 diabetes.

Thus, the association of obesity with impaired glucose tolerance and type 2 diabetes in children may not be a new phenomenon. However, the number of obese children is increasing rapidly, especially in some ethnic groups.³ Thus, the absolute number of children in the population who have impaired glucose tolerance and type 2 diabetes is increasing because of the increased numbers of obese children. Future research should focus on why an accumulation of excess body fat becomes detrimental to health. Public health efforts should focus on reducing the prevalence of obesity among children, since this factor alone is likely to have a major effect on the current and future risk of type 2 diabetes.

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To the Editor: Sinha et al. report that the prevalence of impaired glucose tolerance was 25 percent in children (4 to 10 years old), which was similar to the prevalence in the group of adolescents studied, who should also have had insulin resistance of puberty,¹ making impaired

glucose tolerance more likely. Although the purpose of this study was not only to determine the prevalence of impaired glucose tolerance, these prevalence data were given prominence in the abstract and discussion. We suggest that the unexpectedly high prevalence of impaired glucose tolerance in the group of children who were 4 to 10 years old may be due to referral bias in favor of extremely overweight children, who may have already had evidence of dysmetabolic syndrome X.

We evaluated glucose tolerance in substantially overweight black children and white children (6 to 11 years old) who were recruited from the local community and whose parents were not seeking treatment for the weight problem. The prevalence of impaired glucose tolerance was much lower in this group of children (4.1 percent; 95 percent confidence interval, 2 to 9 percent), even though they had significantly greater insulin resistance and a significantly higher index of beta-cell function than did children who were not overweight (Table 1). An evaluation of children in our cohort who had a mean (\pm SD) body-mass index of 32 ± 5 (calculated as the weight in kilograms divided by the square of the height in meters), which was similar to the mean value in the cohort described by Sinha et al., showed that only 3 of 48 children had impaired glucose tolerance (6.3 percent; 95 percent confidence interval, 1 to 17 percent).

Table 1. Results of Metabolic Studies in Overweight Children and Children of Normal Weight Who Were Recruited from the Community.

TABLE 1. RESULTS OF METABOLIC STUDIES IN OVERWEIGHT CHILDREN AND CHILDREN OF NORMAL WEIGHT WHO WERE RECRUITED FROM THE COMMUNITY.*

VARIABLE	OVERWEIGHT (N=121)	NOT OVERWEIGHT (N=104)
Race — no.		
Black	52	30
White	69	74
Sex — no.		
Male	54	42
Female	67	62
Impaired fasting glucose — no. (%)†	0	0
Impaired glucose tolerance — no. (%)†	5 (4.1)	0
Age — yr	8.4±1.5	8.6±1.3
BMI		
Mean	27.0±5.8	17.0±1.7‡
Range	17–46	13–23
Standard-deviation score for BMI	4.3±2.5	1.2±1.4‡
Insulin-resistance index§	3.4±2.7	1.5±0.8‡
Insulin sensitivity¶	0.33±0.03	0.38±0.04‡
Insulinogenic index	0.17±0.14	0.07±0.04‡

*Children were recruited from the community for metabolic studies at the National Institutes of Health. Children were classified as overweight if they had a body-mass index (BMI), calculated as the weight in kilograms divided by the square of the height in meters, at or above the 95th percentile for age, sex, and race; children were classified as not overweight if they had a BMI between the 5th and 95th percentiles.² Plus-minus values are means ±SD.

†Impaired fasting glucose and impaired glucose tolerance were defined according to the criteria of the American Diabetes Association, as described by Sinha et al.³

‡P<0.05 by the t-test.

§The insulin-resistance index was calculated with the use of homeostatic model assessment; values are on a scale from approximately 1 to 15, with higher values indicating greater insulin resistance.⁴

¶[Insulin sensitivity was calculated with the use of the quantitative insulin-sensitivity check index (QUICKI); values are on a scale from approximately 0.25 to 0.40, with higher values indicating greater sensitivity to insulin.⁴

||The insulinogenic index indicates pancreatic beta-cell function.⁵

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To the Editor: We have recently studied the prevalence of impaired glucose tolerance and the relation between cardiovascular risk factors and levels of glycemia in 710 grossly obese Italian children and adolescents (age range, 6 to 18 years; mean age, 14 years; standard-deviation score for body-mass index, 3.8±0.7), all of whom were of European origin for at least two generations. The frequency of impaired glucose tolerance and of type 2 diabetes was 4.5 percent and 0.1 percent, respectively — figures that are consistently lower than those reported by Sinha et al. in their cohort of obese American children. The obese Italian children had considerably lower values for insulin resistance, calculated by homeostatic model assessment, than their American counterparts. In a multivariate analysis, glucose values measured two hours after an oral glucose dose (1.75 g per kilogram) were significantly and independently related to insulin resistance (P<0.001) and to insulin secretion, measured as the insulinogenic index (P<0.001), suggesting that both an impaired insulin response and reduced insulin sensitivity contributed to the hyperglycemia in the Italian children. We believe that differences in ethnic background and in lifestyle and dietary habits may account for the striking disparity in the prevalence of impaired glucose tolerance between these two cohorts of obese children.

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To the Editor: It would be helpful if Sinha and colleagues would comment on the usefulness of screening 22 million obese children worldwide with an oral glucose-tolerance test rather than a simpler and less expensive method. Table 2 of their report shows a significant difference in the fasting insulin level between obese children and adolescents with normal glucose tolerance and those with impaired glucose tolerance. If this difference is consistent and reproducible, why not use the insulin-resistance index as a screening tool?

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To the Editor: The findings reported by Sinha et al. provide strong evidence that, even in childhood, obesity with its associated conditions represents an epidemic with substantial effects on public health. In the accompanying editorial by Rocchini,¹ the final paragraph, on effective strategies to combat obesity-related diabetes, contains a statement that concerns me. Rocchini notes that the prevention of obesity is an obvious strategy but states that “despite all our best efforts, prevention of childhood obesity eludes our grasp.” Rocchini suggests that a more effective strategy would be to identify obese children who are at high risk for diabetes on the basis of oral glucose-tolerance testing and to target them for intensive weight-loss treatment.

In my opinion, the solution to the obesity epidemic must be based on much broader public health and clinical strategies. The time has come to develop comprehensive national obesity-prevention programs that include educational, behavioral, and environmental components analogous to those already in place for tobacco use. Examples of effective prevention programs that focus on children and adolescents are school-based interventions designed to increase physical activity and consumption of healthier foods and home-based interventions designed to reduce television viewing.^{2,3} Physicians and other health care professionals, elected officials, educators, and parents need to recognize the impact of this major health problem and have the will and energy to correct it through preventive approaches.

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Dr. Caprio replies:

To the Editor: I agree with Dr. Goran that prevalence rates are best derived from non-clinic-based samples. Of note is the recent school-based study by Grey et al.,¹ involving 42 obese adolescents whose parents were not seeking treatment. In this group, the prevalence of impaired glucose tolerance was 21.4 percent, and the prevalence of type 2 diabetes was 4.6 percent — findings that are very similar to

ours. I disagree with Dr. Goran's statement that our findings were very similar to those reported by Paulsen et al. in 1968; they did not use the same ADA definitions that we used. When we recalculated the prevalence of impaired glucose tolerance in their study using the ADA criteria that we had used in our study, impaired glucose tolerance was present in 11 percent of the children, and 6 percent had type 2 diabetes mellitus.

The low prevalence of impaired glucose tolerance (6.3 percent) reported by Uwaifo et al. in obese children recruited from the community is probably due to a low insulin-resistance index. In fact, the mean insulin-resistance index in their obese children was 3.4 ± 2.7 , whereas in our children it was 5 ± 0.6 in children with normal glucose tolerance and 7.2 ± 1 in those with impaired glucose tolerance.

Interestingly, Invitti et al. report that the cohort of children they studied, although grossly obese, had a considerably lower insulin-resistance index than our obese American cohort. As in our study, insulin resistance was found to be strongly and independently related to the glucose level at two hours. However, in contrast to our findings, the insulinogenic index was related to the glucose level at two hours. It is conceivable that our cohort was not large enough for us to detect differences in beta-cell function in patients with impaired glucose tolerance. We concur that differences in insulin resistance related to ethnic background and lifestyle may explain the striking disparity in the prevalence of impaired glucose tolerance between the two cohorts.

In response to Dr. Speiser's two important questions: we suggest that children with marked obesity undergo screening for fasting hyperinsulinemia and other features of the metabolic syndrome. The reproducibility of the insulin-resistance index (determined by homeostatic model assessment) is not known and varies greatly according to the method used to measure insulin and glucose levels. Furthermore, its predictive value in children needs to be determined.

We would also like to note that in our report, the values for proinsulin and for the ratio of proinsulin to insulin on page 806 and in Figure 2 are incorrect. All reported values for proinsulin and for the ratio of proinsulin to insulin should be divided by a factor of 10. In addition, the second part of the last sentence of the legend to Figure 2 should read, “to convert values for proinsulin to picomoles per liter, divide by 0.00939.”

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The editorialist replies:

To the Editor: There are two commonly used strategies to combat a major public health problem such as adolescent obesity. One is a population-based strategy, as suggested by Dr. Gaenzer. The other strategy is to identify persons at high medical risk (e.g., obese adolescents with impaired glucose tolerance) and target them for disease-specific therapy. The population-based strategy works well when the program is both effective in preventing or curing the problem and low in cost. An excellent example of an outstanding population-based strategy is the use of vaccinations to prevent childhood diseases. However, there is no effective low-cost treatment for childhood obesity. I agree with Dr. Gaenzer that the time has come to develop comprehensive national obesity-prevention programs similar to programs aimed at tobacco use. However, until we have a prevention program that has been proved to reduce the incidence of childhood obesity significantly, I stand by my recommendation to identify obese children who are at high risk for diabetes and target them for intensive weight-loss treatment.

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