Prevalence and Concomitants of Glucose Intolerance in European Obese Children and Adolescents

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OBJECTIVE — The worldwide increase in the prevalence of childhood obesity is reaching epidemic proportions and is associated with a dramatic rise in cases of type 2 diabetes. The prevalence of glucose intolerance and its determinants and the relation of cardiovascular risk factors with levels of glycemia and degree of obesity were studied in grossly obese children of European origin.

RESEARCH DESIGN AND METHODS — A total of 710 grossly obese Italian children (SD score [SDS] of BMI 3.8 ± 0.7) aged 6–18 years, including 345 male subjects, underwent an oral glucose tolerance test. Insulin resistance and insulin secretion were estimated using the homeostasis model assessment for insulin resistance and the insulinogenic index, respectively. Fibrinogen, C-reactive protein, lipids, and uric acid were measured. The 2-h postload glucose and degree of obesity, calculated as the SDS of weight/height^2, were used as dependent variables.

RESULTS — The prevalence of glucose intolerance was 4.5%. Insulin resistance ($P < 0.0001$), impaired insulin secretion ($P < 0.0001$), and diastolic blood pressure (BP) ($P < 0.05$) were significantly and independently related to 2-h postload glucose values. The degree of obesity did not relate to insulin resistance but was independently correlated with inflammatory proteins, uric acid, and systolic BP, variables that were often abnormal in this population.

CONCLUSIONS — In these grossly obese children, both insulin resistance and impaired insulin secretion contribute to the elevation of glycemia, and the degree of obesity is related to cardiovascular risk factors independently of insulin resistance.

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The prevalence of childhood obesity has more than doubled in the last 15 years in many regions of the world (1–4). This phenomenon is associated with a rapidly increasing trend in cases of type 2 diabetes in childhood. The close association between childhood obesity and diabetes has been reported mainly in ethnic groups at high risk for diabetes, such as American and Canadian Indians, African-Americans, Hispanics, Japanese, and Asian Indians (5), and more recently in multiethnic groups in the U.S. (6). In these populations, the evolution from normal to impaired glucose tolerance (IGT) is associated with insulin resistance and a failure of β-cell insulin secretory capacity, which deteriorates further as type 2 diabetes develops (7,8). However, the risk of progression to chronic hyperglycemia may also be related to constitutional factors because African-American children (9) and young Japanese with IGT (10) exhibit higher and lower insulin responses, respectively, to an acute elevation of glucose levels compared with Caucasians. The studies reporting the prevalence of IGT in obese children of entirely European origin are relatively few and are not conducted in large cohorts (11–15). Obesity in childhood also seems to harbor a number of risk factors for cardiovascular disease (CVD) in adult life, but is not yet clear whether these are determined by glycemia, degree of obesity, or other demographic, clinical, or biochemical features of the obese child.

We therefore investigated in a large cohort of grossly obese Italian children and adolescents, all of European origin, the prevalence of type 2 diabetes and IGT and their determinants. We also examined the relation between CVD risk factors and levels of glycemia and degree of obesity and studied the impact of puberty and birth weight on these variables.

RESEARCH DESIGN AND METHODS

— We studied a cohort of 710 obese children and adolescents of European origin by at least two generations. Subjects were referred by their general practitioner or their primary care pediatric consultant to the Istituto Auxologico Italiano, a specialized center for the study of obesity, between 1994 and 2001. They were admitted for metabolic evaluation and clinical management for 2 weeks. There were 345 male and 365 female subjects with ages ranging between 6 and 18 years. This article reports the baseline cross-sectional data of this population that is being followed-up for prospective evaluation of predictors of risk for metabolic and CVD. Patients with secondary obesity syndromes and acute illnesses were excluded from the study. Anthropometric measures were recorded. Duration of obesity, birth weight, and family history for obesity and diabetes were obtained by questionnaires filled in by the mother. Body weight was recorded to the

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Abbreviations: BG, blood glucose; BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; IGT, impaired glucose tolerance; SDS, SD score.

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

Table 1—*Demographic, clinical, and biochemical features of a cohort of 710 obese children and adolescents*

Variable	Boys	Girls	Whole group
n	345	365	710
Age (years)	14 (6–18)	14 (7–18)	14 (6–18)
Height (cm)	161.0 ± 12.0*	156.1 ± 10.6	158.8 ± 11.5
Weight (kg)	93.5 ± 25.7*	85.6 ± 20.3	88.9 ± 23.6
SDS-BMI	4.1 ± 0.7*	3.6 ± 0.6	3.8 ± 0.7
BMI (kg/m^2)	35.2 ± 6.1	34.8 ± 5.8	35.0 ± 6.0
Waist (cm)	104.1 ± 5.3†	95.5 ± 7.6	98.3 ± 7.9
Duration of obesity (year)	7.1 ± 3.6	6.7 ± 3.6	6.8 ± 3.5
Obesity in family (%)	58	63	61
Diabetes in family (%)	53	55	54
Birth weight (g)	3423 ± 511.6	3411 ± 571.3	3417 ± 542.3
LDL cholesterol (mmol/l)	2.7 ± 0.8	2.6 ± 0.7	2.6 ± 0.8
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3
Triglycerides (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3
Uric acid (μmol/l)	382.6 ± 116*	347 ± 102	364.2 ± 110.6
Fibrinogen (mg/dl)	377.7 ± 73.4†	392.3 ± 77.9	385.5 ± 76.1
CRP (mg/dl)	0.5 ± 0.7	0.5 ± 0.5	0.5 ± 0.6
Systolic BP (mmHg)	128 ± 14*	124 ± 14	126 ± 14
Diastolic BP (mmHg)	77 ± 9	77 ± 10	76 ± 10

Data are expressed as mean (range), mean ± SD, and %. *$P < 0.0001$, †$P < 0.01$ vs. girls.

nearest 0.1 kg using a standard beam balance scale, with the subjects wearing light indoor clothing and no shoes. Height was recorded to the nearest 0.5 cm using a standardized wall-mounted height board. The degree of obesity was quantified using Cole's least mean square method, which normalizes the BMI skewed distribution and expresses BMI as an SD score (SDS). This measure gives ages and sex-specific estimates of the distribution median (M), coefficient of variation (S), and the degree of skewness (L) by a maximum-likelihood fitting technique (16). Visceral obesity was assessed by waist circumference measured at the level of the umbilicus and the superior iliac crest. The measurement was made at the end of a normal expiration while the subjects were in a standing position. Pubertal development was assessed by physical examination according to the criteria of Tanner (17). Diastolic and systolic blood pressure (BP) were measured to the nearest 2 mmHg in the supine position after 5 min rest, using a standard mercury sphygmomanometer with an appropriately sized cuff (18). The average of six measurements obtained on different days during admission was used in the analysis.

After a 12-h overnight fast, subjects underwent an oral glucose tolerance test (1.75 g/kg, up to a maximum of 75 g glucose in 250 ml of water). Plasma samples were drawn at baseline and after 30 and 120 min for determination of plasma glucose and insulin concentration, and categorization of glucose tolerance status was made using the World Health Organization criteria (19).

Insulin resistance was estimated using the homeostasis model assessment for insulin resistance ($HOMA_{IR}$; fasting insulin × fasting glucose/22.5) (20). β-Cell function was determined by the insulinogenic index ($\Delta I30/\Delta G30$), expressed as the ratio of the incremental (0–30 min) insulin and glucose response after commencement of oral glucose intake during the oral glucose tolerance test (21). Fasting blood samples were taken for lipids, uric acid, fibrinogen, and C-reactive protein (CRP) measurements.

Plasma glucose was measured by the glucose oxidase method, and total cholesterol, HDL cholesterol, triglycerides, and uric acid concentrations were measured by a colorimetric method on an automated analyzer (Roche Diagnostics, Mannheim, Germany). CRP concentrations were measured by an immunoturbidimetric assay (Roche Diagnostics), with a sensitivity of 0.2 mg/dl and intra- and interassay CVs of 1.5 and 7.2%, respectively. The normal range of CRP using this method in our laboratory is 0–1 mg/dl. Fibrinogen was measured in citrate plasma with a clot-rate assay using the ACL 200/IL instrument (Instrumentation Laboratory, Milan, Italy). The sensitivity of the assay was 7.5 mg/dl, and the intra- and interassay CVs were 4.8 and 5.2%, respectively, at a concentration of 275 mg/dl. Serum insulin was measured in duplicate by a chemiluminescent assay (DPC, Los Angeles, CA), with a sensitivity of 14.3 pmol/l and intra- and interassay CVs of 3.7 and 6.7%, respectively, at a concentration of 380 pmol/l.

Statistical analysis

Differences between groups and univariate regression analyses were calculated using both parametric and nonparametric tests depending on the distribution of the variables. Multivariate analysis was performed using variables statistically significant at the 5% level in univariate analysis. Closely interrelated variables were entered separately in these models. The 2-h postload glucose and SDS-BMI, as a measure of the degree of obesity, were the dependent variables in this analysis. To assess the effect of puberty on inflammatory and CVD markers, the population was divided into the five Tanner stages, and ANCOVA was performed using SDS-BMI and age as covariates. Between-group differences were assessed by the post hoc least significant difference test for multiple comparisons. A probability value <0.05 was considered significant. Data are given as the means ± SD unless otherwise stated. SPSS version 10.1 (SPSS, Chicago, IL) was used for analysis.

RESULTS — The demographic, clinical, and biochemical characteristics of the 710 obese children and adolescents are summarized in Table 1. The duration of obesity was apparently 7 years. Of the obese children, 61% had a positive family history for obesity and 54% for diabetes, with no differences between sexes. Compared with girls, boys were more obese but had similar birth weights. Lipid profiles and CRP were similar between the sexes, whereas uric acid was significantly higher in boys and fibrinogen in girls.

A substantial proportion of these obese children had abnormal parameters for their age (Table 2). Systolic BP was significantly higher in boys than in girls and was above the age-related 95th percentile adjusted for height in 29% of girls and 25% of boys. Diastolic BP exceeded

Table 2—*Percentage of obese children and adolescents with values of lipids and inflammatory markers above (or below for HDL cholesterol) the age-adjusted normal ranges*

	Boys	Girls	Whole group
Triglycerides	14	21	17.5
HDL cholesterol	12	22	17
LDL cholesterol	21	16	18.5
CRP	12	11	11.5
Fibrinogen	35*	44	39.5
Uric acid	28†	44	36

Data are %. Normal ranges for lipids and uric acid are derived from *The Clinical Guide to Laboratory Test.* Tietz NW, Ed. W.B. Saunders, 1990. *$P <$ 0.05, †$P < 0.0001$ vs. girls.

the 95th percentile for height in 13% of boys and 17% of girls (Fig. 1).

When cutoff values for the adult populations were used, as published by recent Adult Treatment Panel III clinical guidelines (22), the percentage of abnormality was 10% for triglycerides, 52% for HDL cholesterol, and 15% for BP.

Glucose intolerance

Of the obese children, 1 had diabetes, 30 had IGT, and 3 had impaired fasting glucose, 2 of whom also had IGT, to give an overall prevalence of glucose intolerance of 4.5%. Compared with children with normal glucose tolerance, children with IGT had significantly higher fasting blood glucose (BG; 4.8 ± 0.67 vs. 4.5 ± 0.43 mmol/l, $P < 0.0001$) and 2-h postload insulin levels (median [interquartile range] 711.4 pmol/l [546–906] vs. 414.0 pmol/l [270–576], $P < 0.0001$). Family history for diabetes and obesity were also more frequent in glucose-intolerant children, but not significantly so (62 vs. 53% and 71 vs. 61%, respectively; NS). The male-to-female ratio, age, fasting insulin levels, $HOMA_{IR}$, lipids, fibrinogen, CRP, BP, SDS-BMI, and birth weight were similar between the two groups. The proportion of children at Tanner II–IV stages was also comparable between glucose-intolerant and glucose-tolerant children (22 vs. 37%, NS). When 2-h BG was considered as a continuous variable in the whole population of obese children, it was found to be positively correlated, in univariate analysis, with $HOMA_{IR}$ ($r = 0.141$, $P < 0.0001$) and negatively with $\Delta I30/\Delta G30$ ($r = -0.159$, $P < 0.0001$). A weak relationship was also found with diastolic BP ($r = 0.097$, $P < 0.01$) and triglycerides ($r = 0.081$, $P < 0.05$) (Table 3), but there was no association with SDS-BMI and birth weight. In a multivariate regression analysis with 2-h postload glucose values as the dependent variable, only $\Delta I30/\Delta G30$, $HOMA_{IR}$, and diastolic BP remained significantly and independently related (Table 4). Of the obese children, 64% had an $HOMA_{IR} > 2.5$, which is the cutoff level to distinguish normal from impaired insulin sensitivity in adults (20). $HOMA_{IR}$ was univariately correlated with lipids, BP, 2-h BG and $\Delta I30/\Delta G30$, SDS-BMI, and uric acid (Table 3).

Obesity

The degree of obesity expressed as SDS-BMI was related, in univariate analysis, with inflammatory markers, lipids, BP,

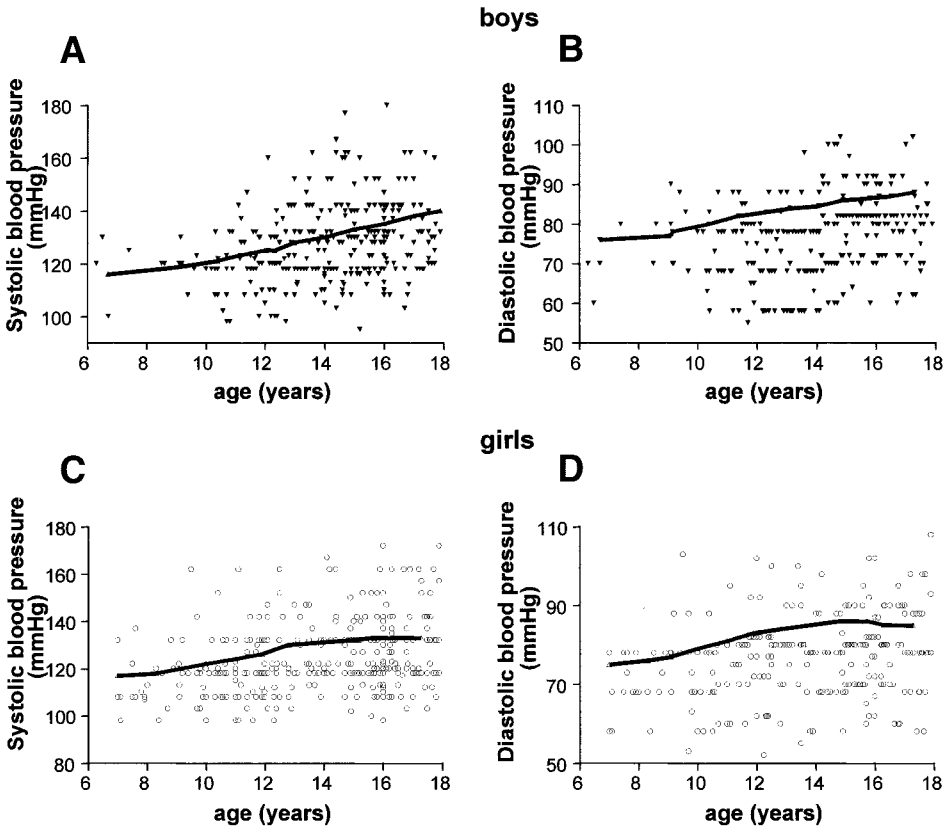

Figure 1—*BP at different ages in boys (A and B) and girls (C and D) in 710 obese children. The solid line represents the age- and sex-related 95th percentile of BP (18).*

Table 3—*Relationship between obesity, postload glucose, and insulin resistance with cardiovascular risk factors in 710 obese children and adolescents*

Variable	Regression coefficient	*P* value
SDS-BMI		
CRP	0.207	0.000
Fibrinogen	0.179	0.000
HDL cholesterol	−0.190	0.000
Triglycerides	0.126	0.001
Systolic BP	0.167	0.000
Diastolic BP	0.120	0.002
$HOMA_{IR}$	0.114	0.003
ΔI30/ΔG30	0.091	0.010
Birth weight	0.098	0.027
Uric acid	0.260	0.000
$HOMA_{IR}$		
Triglycerides	0.221	0.000
HDL cholesterol	−0.120	0.001
Systolic BP	0.109	0.005
Diastolic BP	0.157	0.000
2-h BG	0.141	0.001
ΔI30/ΔG30	0.178	0.000
SDS-BMI	0.114	0.003
Uric acid	0.089	0.029
2-h BG		
ΔI30/ΔG30	−0.159	0.000
$HOMA_{IR}$	0.141	0.001
Diastolic BP	0.097	0.003
Triglycerides	0.081	0.050

ΔI30/ΔG30, insulinogenic index.

$HOMA_{IR}$, ΔI30/ΔG30, birth weight, and uric acid (Table 3). There was no correlation between SDS-BMI and 2-h BG.

In a multivariate regression analysis with SDS-BMI as the dependent variable, triglycerides, $HOMA_{IR}$, and diastolic BP were excluded. (Table 4). The variables independently correlated with SDS-BMI together explained 19% of the variance.

Puberty

Of the obese children, 20, 29, and 51% were at Tanner stages I, II–IV, and V, respectively. After adjustment for SDS-BMI and age, the degree of insulin resistance progressively increased from Tanner I to Tanner IV pubertal stage and subsequently decreased at Tanner stage V. HDL cholesterol, triglycerides, and systolic BP showed a pattern of change consistent with that of the degree of insulin sensitivity (Fig. 2), whereas diastolic BP and uric acid tended to progressively increase and total cholesterol decrease throughout puberty (Tanner stage I to V: 73.9 ± 1.0 to 78.5 ± 0.80 mmHg, $P < 0.01$; 340 ± 15.60 to 370.2 ± 9.0 μmol/l, NS; 4.7 ± 0.10 to 4.1 ± 0.06 mmol/l, $P < 0.0001$; respectively). Fibrinogen and CRP remained stable throughout (data not shown).

CONCLUSIONS — This study describes the clinical, metabolic, and biochemical features of a large, recent cohort of grossly obese children, all of European origin. Boys were more obese than girls, in line with the observation that the prevalence of obesity among U.S. adolescents has increased more among boys than among girls (23). A positive family history for obesity and diabetes was present in more than half of the children, as was also reported in a smaller group of obese children (24), and the prevalence of insulin resistance was high. IGT was present in 4.5% of these children, a prevalence that is lower than that previously reported by other authors in obese children of Caucasian origin (11–15). The reasons for these differences are not entirely clear, but methodological and calendar effects could be important. A number of previous reports used a different definition of IGT, which would favor detection of higher prevalences (25), and some observations date back several decades (11–13). The prevalence of IGT in our study was also significantly lower than the >20% recently reported in American obese children and adolescents from a multiethnic background (6). The frequency of diabetes in that population was 4% among the adolescents, which contrasted with 0.2% in our subgroup of 609 adolescents (11–18 years of age). Racial differences, lifestyle, and dietary habits may account for the disparity of results between our present cohort and the obese American children. In our cohort of grossly obese children, postload BG levels were independently correlated with a decrease in both insulin sensitivity and insulin secretion. This means that even before the development of IGT, both insulin resistance and insulin secretory dysfunction contribute to raised glucose levels. Two longitudinal studies, in Mexican-American and Pima Indians, have found that primary defects in both insulin action and secretion are responsible for the transition from normal glucose tolerance to IGT and from IGT to overt diabetes (7,8). We observed that similar defects are present in obese children of an ethnic group at significantly lower risk for type 2 diabetes. The recent report by Sinha et al. (6) in the obese American children and adolescents found a slightly smaller contribution of β-cell dysfunction. Furthermore, the children in our study showed a positive and independent correlation between postchallenge glucose and some CVD risk factors, such as diastolic BP, confirming in obese children the increasing cardiovascular risk with increasing glycemia observed in adults (26,27).

A substantial proportion of children had abnormal values for lipids, uric acid, CRP, fibrinogen, and BP, factors that are often interrelated. The true significance of these abnormal frequencies is limited by the use of literature-derived normal ranges (28). A significant percentage of abnormalities, however, were found even when cutoff values for adults were used.

Table 4—*Variables independently associated, in an age- and sex-adjusted stepwise multiple linear regression analysis, with the dependent variables 2-h blood glucose and SDS-BMI in 710 obese children and adolescents*

Dependent variable	Independent variable	β coefficient	*P* value
2-h BG	ΔI30/ΔG30	−0.186	0.000
	$HOMA_{IR}$	0.158	0.000
	Diastolic BP	0.094	0.018
SDS-BMI	Fibrinogen	0.141	0.003
	CRP	0.143	0.000
	Uric acid	0.168	0.000
	HDL cholesterol	−0.171	0.000
	Systolic BP	0.118	0.009
	ΔI30/ΔG30	0.135	0.002
	Birth weight	0.102	0.002

ΔI30/ΔG30, insulinogenic index.

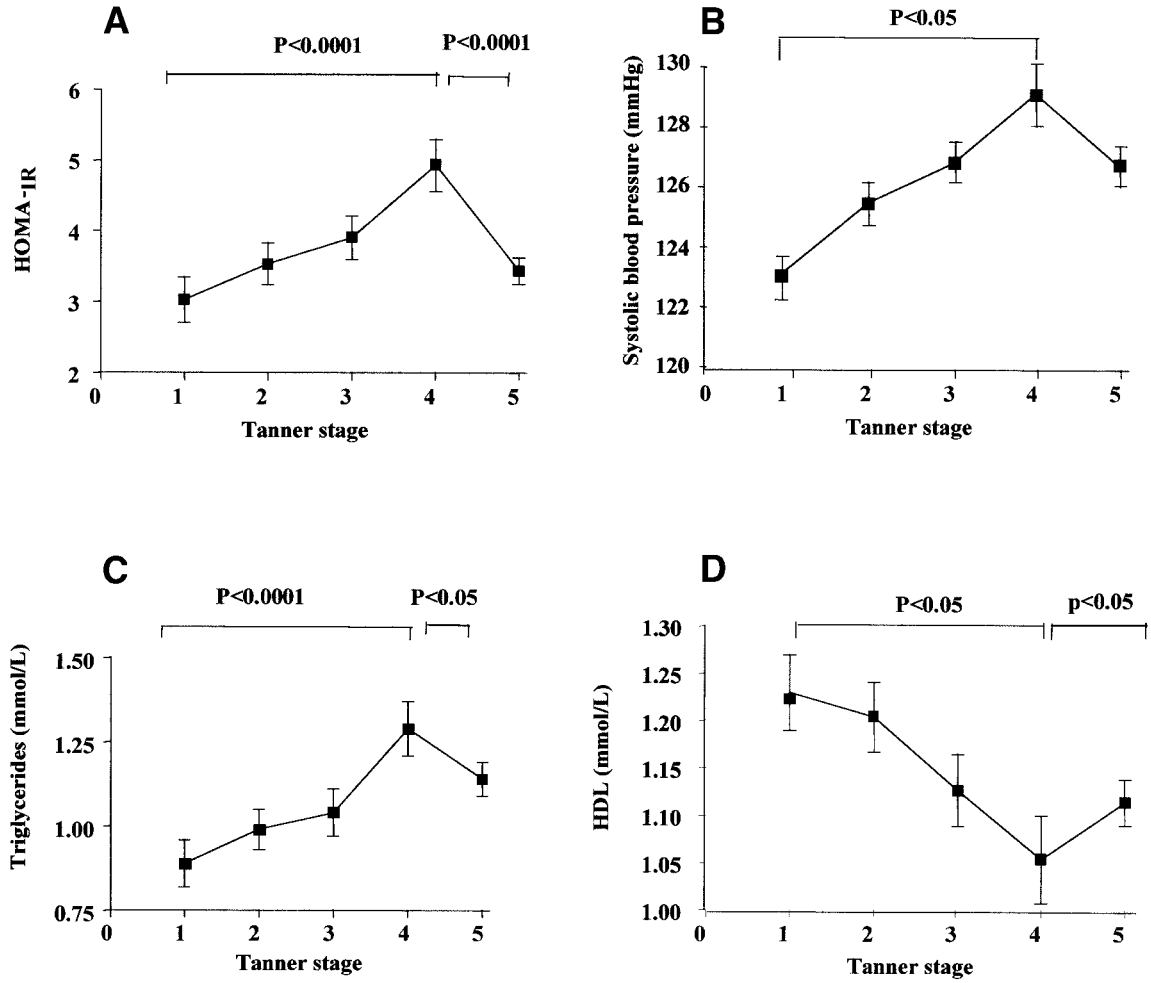

Figure 2—*Pattern of $HOMA_{IR}$ (A), systolic BP (B), triglycerides (C), and HDL cholesterol (D) during the different pubertal stages in 710 obese children. Results are expressed as the means ± SE adjusted for SDS-BMI and age.*

These results are in accord with previous smaller observations (29–35) and, for the first time in a large cohort with a wide age range, indicate that many obese children have, like obese adults, elevated levels of CRP and uric acid, factors that, in adulthood, are related to an increased risk of CVD and diabetes (36–41).

In the present study, 25% of boys and 29% of girls had elevated values of systolic BP, and ~15% showed elevated levels of diastolic pressure, a prevalence that is lower than that of 40% previously reported in a Hungarian group of obese children (15). The independent relationship of systolic BP with the degree of obesity and of diastolic BP with 2-h glycemia suggests that the level of BP in the obese child is affected by factors that may have differential effects on either systolic or diastolic BP.

In univariate analysis, $HOMA_{IR}$ and obesity were interrelated and were in turn associated with a variety of other cardiovascular risk factors. However, the relationship of the degree of obesity with cardiovascular risk factors was independent of and not affected by $HOMA_{IR}$ (or 2-h BG), strongly suggesting that obesity per se, separately from insulin sensitivity or glucose intolerance, impacts on CVD risk.

A low birth weight, particularly if followed by a rapid weight gain, has been associated with an increased risk of insulin resistance, type 2 diabetes, hypertension, and atherosclerosis in adult life (42). This does not seem to be the case in grossly obese children, because those who developed glucose intolerance had similar birth weights compared with those who did not. Furthermore, birth weights were positively correlated with the degree of obesity. This finding agrees with the results of recent epidemiological studies that have shown that the incidence of obesity rises with increasing birth weight (43) and that adolescent BMI is predicted by birth weight (44).

The changes in insulin sensitivity during progression through puberty were independent of the degree of obesity and associated with parallel and consistent changes in triglycerides, HDL cholesterol, and systolic BP, whereas uric acid and diastolic BP showed a physiological age-dependent increase. The pattern of change in insulin sensitivity and lipids was similar to that reported in normal-weight children (45,46), and the changes in systolic BP are first described here. It was interesting to note that at Tanner stage IV, 12.2% of subjects had triglyceride levels above the 95th percentile of distribution. This percentage fell to 6.9% at Tanner stage V. The prognostic signifi-

cance of this observation remains to be established.

From a cross-sectional study, we cannot tell whether the abnormalities seen in these obese children will impact on their long-term health; however, many of the variables measured in this study track with age and are likely to increase the risk for metabolic and CVDs in adulthood. The few studies that have examined the long-term effects of childhood or adolescent obesity on adult morbidity and mortality have observed an increased occurrence of CVDs and digestive and metabolic diseases among those subjects who were obese during adolescence (47–49).

In conclusion, we have found, in a large cohort of grossly obese children of European origin, that the prevalence of glucose intolerance is low compared with that observed in the U.S., and CVD risk factors were independently related to the level of postload glycemia and the degree of obesity, but they were not associated with low birth weight.

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