Obesity, Fasting Plasma Insulin, and C-Reactive Protein Levels in Healthy Children

Steven Shea,† Eve Aymong,* Patricia Zybert,‡ Harry Shamoon,§ Russell P. Tracy,¶ Richard J. Deckelbaum,** and Charles E. Basch‡*

Abstract

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Objective: Obesity is associated with hyperinsulinemia and increased level of C-reactive protein in older children and adults, but little is known about these relationships in very young children. We examined these relationships in healthy 2- to 3-year-old children.

Research Methods and Procedures: Analyses were performed on data from 491 healthy 2- to 3-year-old Hispanic children enrolled in a dietary study conducted in New York City, 1992 to 1995.

Results: Body mass index (BMI), ponderal index, and sum of four skinfolds were highly correlated ($r > 0.75$) in both boys and girls. Fasting insulin and glucose levels were only modestly correlated ($r = 0.37$ for boys and $r = 0.28$ for girls; $p < 0.001$ for both), but essentially all of the variability in a calculated index of insulin resistance was attributable to variability in fasting insulin level. The correlations of BMI with fasting insulin level were $r = 0.16$ ($p < 0.05$) in boys and $r = 0.14$ ($p < 0.05$) in girls. In separate multivariate regression analyses adjusting for age and sex, BMI and ponderal index were associated with fasting plasma insulin level ($p < 0.001$ for both obesity measures). In multivariate regression analyses adjusting simultaneously for age, sex, and either BMI or ponderal index, fasting insulin level, but not these obesity measures, was associated with C-reactive protein level.

Discussion: Obesity is associated with higher fasting insulin level, and fasting insulin is associated with C-reactive protein level, in healthy 2- to 3-year-old children.

Key words: children, C-reactive protein, insulin, body mass index, adipocity

Introduction

Recent research has shown the importance of hyperinsulinemia, insulin resistance, and impaired glucose tolerance in promoting atherosclerosis (1–3). It is also well established in adults that obesity is related to hyperinsulinemia (4–6) and insulin resistance (7), although the precise mechanism underlying this relationship remains controversial (8,9). In adults, obesity and hyperinsulinemia or insulin resistance are associated with dyslipidemia and higher blood pressure (10) even in the absence of diabetes. This cluster of metabolic characteristics has been termed Syndrome X, (11) the insulin resistance syndrome, (12), and the metabolic or multiple metabolic syndrome (13).

Obesity and the metabolic syndrome have also been associated with higher levels of systemic inflammatory factors, including C-reactive protein (CRP)[1] (14–18). Recent data implicate systemic inflammatory factors, including CRP, fibrinogen, and interleukin-6 as important risk factors for atherosclerosis and cardiovascular disease events (19–25). There is evidence of participation of inflammatory factors in the early stages of atherogenesis, including impairment of endothelial function (26) and the formation of fatty streaks and plaque (27–29), as well as in the thrombotic events that trigger myocardial infarction and some strokes (25). Two specific mechanisms involving CRP that

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*Division of General Medicine, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York; †Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York; ‡Department of Health and Behavior Studies, Teachers College, Columbia University, New York, New York; §Diabetes Research Center, Albert Einstein College of Medicine, Bronx, New York; ¶Departments of Pathology and Biochemistry, University of Vermont, Colchester, Vermont; **Institute of Human Nutrition and Department of Pediatrics, Columbia University, New York, New York.
Address correspondence to Steven Shea, M.D., Division of General Medicine, PH 9 East Room 105, 622 W. 168th Street, New York, NY 10032.
E-mail: ss35@columbia.edu

[1]Nonstandard abbreviations: CRP, C-reactive protein; BMI, body mass index.

have been described relate to monocyte activation (27,30) and to promotion of synthesis of adhesion molecules that recruit leukocytes to the endothelial surface, thereby amplifying the inflammatory process in the vascular endothelium (31). Interleukin-6, which stimulates hepatic production of fibrinogen and CRP, is synthesized in adipose tissue, and particularly by visceral adipose tissue (32,33). Synthesis of tumor necrosis factor-alpha, another proinflammatory cytokine, is also increased in obese subjects (34).

The childhood origin of atherosclerosis has long been recognized (35–37), as has been the expression in childhood of characteristics that place individuals at increased risk for atherosclerosis later in life (37). Reports from the Bogalusa Heart Study and others have documented a relationship between obesity and fasting insulin levels in healthy children ranging in age from 5 to 23 years (38–50). One study in older children found a positive correlation between obesity and CRP level (51), and our own data from older children and young adults are consistent with this finding (52).

The data addressing these issues in very young children are sparse. Yajnik et al. studied Asian-Indian children 3.7 to 4.4 years of age and found associations of both low birth weight and higher current subscapular and triceps skinfold thickness with fasting plasma insulin level (53). Other studies of these relationships in this age group or in younger children have not been published to our knowledge. We examined the relationships of several measures of obesity to fasting plasma insulin and a calculated index of insulin resistance in healthy 2- to 3-year-old children. We also examined the relationship of obesity to CRP level. We are not aware of any published data addressing this relationship in children of this age. Our hypotheses were that relative obesity, even among very young non-obese children, would be associated with higher levels of fasting insulin and CRP.

Research Methods and Procedures

Study Population

Subjects were recruited at the Columbia-Presbyterian Medical Center's ambulatory general pediatrics practices and affiliated community-based practices in northern Manhattan, New York, between 1992 and 1995, for a randomized trial of a diet moderately reduced in saturated fat content. Before randomization, the 524 study children attended four visits over 6 months at which baseline measurements were obtained. Fasting blood samples were obtained at two of these four visits. All data reported here were obtained before randomization. Insulin and CRP levels were analyzed from the first blood specimen obtained from each child. The blood sample and the anthropometric data were collected on the same day for 368 children. For an additional 123 children, fasting insulin and CRP values were linked to anthropometric data obtained at a visit at which blood was not drawn but within 30 days of blood drawing. Thus, a total of 491 children were included in the analysis. The 33 children whose visits were more than 30 days apart were excluded from the analysis. The study was approved by the Institutional Review Boards at Columbia-Presbyterian Medical Center and Teachers College.

Measurement Procedures

Height was measured to the nearest centimeter using a rigid stadiometer. Weight was measured to the nearest 0.1 lb using a calibrated balance scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Ponderal index was calculated as weight in kilograms divided by height in meters cubed. Four skinfolds were measured with Lange calipers (Cambridge, MD) on the right side of the body as previously described: subscapular, triceps, waist (abdominal), and hip (suprailiac) (54). Each site was measured twice, and the mean value was used in the analysis. If the two values differed by more than 2 mm, a third measure was taken and the mean of the two closest measures was used. The values for the four sites were summed to provide a single score for obesity. Circumferences at the waist (level of the umbilicus) and hip (level of the maximum extension of the buttocks) were measured with a tape measure to the nearest 0.1 cm (55).

Biochemical Analyses

Subjects were instructed to fast after dinner (water was allowed) the night before the interview, and blood samples were obtained at the start of the clinical assessment. Plasma samples were drawn into EDTA tubes. Samples were stored for 3 to 5 years at –70 °C in a freezer with an alternative power source. Serum insulin levels were measured using a double antibody radioimmunoassay with cross-reactivity with pro-insulin (56). Serum glucose levels were measured using a standardized enzymatic procedure in a Hitachi 704 automated spectrophotometer (Hitachi, Tokyo, Japan). The fasting insulin resistance index was calculated as (fasting glucose [mM]) $\times$ (fasting insulin [μU/mL)])/22.5 (57,58). CRP levels were measured at the University of Vermont from citrated plasma using a highly sensitive enzyme-linked immunoabsorbent assay standardized according to the World Health Organization First International Reference Standard (59).

Statistical Analyses

The distribution of fasting insulin values was skewed with long tail to the right, with measured values ranging from undetectable to 67 μU/mL. For statistical analyses, insulin values were transformed using the natural logarithm to bring the distribution closer to symmetry. Values for fasting insulin that were below the detection limit of the assay (1.0 μU/mL) were recoded as 1.0 μU/mL ($N = 85$). Another 28 children had values measured as 1.0 μU/mL, so

that a total of 113 children had values of 1.0 μU/mL for the analysis. Additional analyses were done imputing 0.5 μU/mL as the value for subjects with insulin levels below the assay detection limit, but the findings were not materially affected, and the analyses presented are based on imputation of 1.0 μU/mL for these subjects. Similarly, sum of skinfolds and CRP level were transformed with the natural logarithm for statistical analyses. Untransformed values are presented in the tables.

Children were classified into quintiles of BMI, ponderal index, and sum of skinfolds. Trends in mean transformed insulin values, glucose levels, and transformed CRP levels over quintiles were tested over obesity quintiles by regressing ln(insulin), glucose, and ln(CRP) on the ordinal values corresponding to quintiles. Sum of skinfolds values were transformed using the natural logarithm in these analyses. Relationships between these obesity measures and fasting insulin, glucose, and CRP levels were also summarized with Pearson correlations. Separate multivariate regression analyses were performed to test the independent relations of BMI or ponderal index to fasting insulin level after adjustment for age and sex. The high correlations among obesity measures precluded simultaneous inclusion of more than one obesity measure in a single regression model. Additional multivariate models were used to assess the independent relationships of the obesity measures and fasting insulin level to CRP.

Results

A total of 491 children were included in the analysis, 255 boys and 236 girls. All of the children in the study were of Hispanic background, and all were aged 2 to 3 years at the time of the study. Mean BMI was 17.2 kg/m^2 for boys and 17.1 kg/m^2 for girls (Table 1). Ponderal index also did not differ between boys and girls. Sum of skinfolds was available for 207 boys and 191 girls, 81.1% of the total sample, and was higher among the girls ($p < 0.01$). Mean fasting insulin level was lower among the boys (6.3 vs. 7.6 μU/mL; $p = 0.04$). The medians and interquartile ranges were 4 μU/mL (2,8) for boys and 5 μU/mL (2,9) for girls. Mean CRP levels did not differ significantly between boys and girls. The medians and interquartile ranges were 0.93 mg/L (0.70 to 1.36) for boys and 1.0 mg/L (0.78 to 1.34) for boys.

Table 1. Selected characteristics of 491 2- to 3-year-old children in the Hispanic Children's Health Study, New York, 1992 to 1995

Characteristic (units)	Boys ($N = 255$) [Mean (SD)]	Girls ($N = 236$) [Mean (SD)]	p Value
Age, years	2.7 (0.5)	2.8 (0.5)	0.04
Height, cm	93.2 (5.3)	92.7 (5.4)	0.36
Weight, kg	15.0 (2.4)	14.8 (2.7)	0.39
Body mass index, kg/m^2	17.2 (1.9)	17.1 (2.1)	0.65
Ponderal index, kg/m^3	18.5 (2.4)	18.5 (2.5)	0.98
Waist circumference, cm	50.3 (3.7)	50.3 (3.8)	0.94
Hip circumference, cm	53.0 (4.7)	54.0 (4.9)	0.03
Subscapular skinfold, mm	7.0 (2.2)	7.7 (2.9)	<0.01
Triceps skinfold, mm	9.7 (2.9)	10.1 (3.2)	0.20
Waist skinfold, mm	8.1 (3.3)	9.0 (4.1)	<0.01
Hip skinfold, mm	5.3 (1.9)	6.0 (2.7)	<0.01
Sum of skinfolds, mm	30.1 (9.2)	32.8 (12.1)	0.01
Fasting insulin, μU/mL*	6.3 (7.9)	7.6 (9.0)	0.04
Fasting glucose, mg/dL	79.2 (11.8)	77.4 (10.9)	0.07
Insulin resistance index†	1.3 (2.2)	1.5 (2.2)	0.36
C-reactive protein, mg/L	1.8 (3.6)	2.1 (4.4)	0.38

* p value based on t tests on log-transformed values.
† p calculated as (fasting glucose [mM/L]) (fasting insulin [μU/mL])/22.5.
Because of missing values, not all means are based on all subjects.

Relations of Obesity Measures with Fasting Insulin Level

Pearson correlations among measures of obesity were high in both boys and girls (Table 2). The Pearson correlation coefficients relating BMI to ln(insulin) were 0.16 ($p < 0.05$) in boys and 0.14 ($p < 0.05$) in girls. For ponderal index and sum of skinfolds, these correlation coefficients were 0.14 ($p < 0.05$) and 0.18 ($p < 0.01$) in boys and 0.06 (p = not significant) and 0.18 ($p < 0.05$) in girls. There were 12 children in the study, 7 boys and 5 girls, with BMI >22 kg/m^2. With these children excluded, the correlations relating BMI to ln(insulin) were 0.15 ($p < 0.05$) in boys and 0.05 (p = not significant) in girls; those relating ponderal index to ln(insulin) were 0.13 ($p < 0.05$) in boys and –0.01 (p = not significant) in girls; and those relating sum of skinfolds to ln(insulin) were 0.20 ($p < 0.01$) in boys and 0.09 (p = not significant) in girls. These results indicate that the associations of the obesity measures with fasting insulin level were partly but not wholly accounted for by the 12 children with BMI >22 kg/m^2.

Table 2. Pearson correlations and numbers of subjects for measures of obesity, fasting insulin, insulin resistance index, and CRP in 491 2- to 3-year-old children

	Boys							
	Weight	**BMI**	**Ponderal index**	**Sum of skinfolds**	**Waist circumference**	**Fasting insulin**	**Insulin resistance index**	**C-reactive protein**
Weight	—	0.69* (n = 255)	0.30* (n = 255)	0.64* (n = 207)	0.84* (n = 252)	0.11 (n = 255)	−0.02 (n = 255)	0.04 (n = 237)
BMI		—	0.89* (n = 255)	0.78* (n = 207)	0.77* (n = 252)	0.16† (n = 255)	0.02 (n = 255)	0.08 (n = 237)
Ponderal index			—	0.60* (n = 207)	0.50* (n = 252)	0.14† (n = 255)	0.03 (n = 255)	0.09 (n = 237)
Sum of skinfolds				—	0.72* (n = 207)	0.18‡ (n = 207)	0.02 (n = 207)	0.07 (n = 192)
Waist circumference					—	0.13† (n = 252)	0.01 (n = 252)	0.06 (n = 234)
Fasting insulin						—	0.72* (n = 255)	0.07 (n = 237)
Insulin resistance index							—	0.06 (n = 237)
CRP								—

	Girls							
	Weight	**BMI**	**Ponderal index**	**Sum of skinfolds**	**Waist circumference**	**Fasting insulin**	**Insulin resistance index**	**C-reactive protein**
Weight	—	0.75* (n = 236)	0.37* (n = 236)	0.78* (n = 191)	0.85* (n = 232)	0.19‡ (n = 236)	0.16† (n = 236)	0.07 (n = 217)
BMI		—	0.89* (n = 236)	0.80* (n = 191)	0.80* (n = 232)	0.14† (n = 236)	0.14† (n = 236)	0.10 (n = 217)
Ponderal index			—	0.59* (n = 191)	0.54* (n = 232)	0.06 (n = 236)	0.08 (n = 236)	0.09 (n = 217)
Sum of skinfolds				—	0.81* (n = 191)	0.18† (n = 191)	0.13 (n = 191)	0.12 (n = 174)
Waist circumference					—	0.22* (n = 232)	0.20 (n = 232)	0.09 (n = 214)
Fasting insulin						—	0.72* (n = 236)	0.25* (n = 217)
Insulin resistance index							—	0.22‡ (n = 217)
CRP								—

* $p < 0.001$.
† $p < 0.05$.
‡ $p < 0.01$.

Trend analyses for fasting insulin level across quintiles of obesity measures for boys and girls combined were $p = 0.01$ for BMI, $p = 0.09$ for ponderal index, $p < 0.01$ for sum of skinfolds, and $p < 0.01$ for waist circumference. Trend tests for boys and girls separately are shown in Figures 1 to 3. These tests were statistically significant in the boys for BMI, sum of skinfolds, and ponderal index, and for waist circumference in the girls.

The ratio of central to peripheral obesity, using either the ratio of waist to triceps skinfold or the ratio of waist to hip

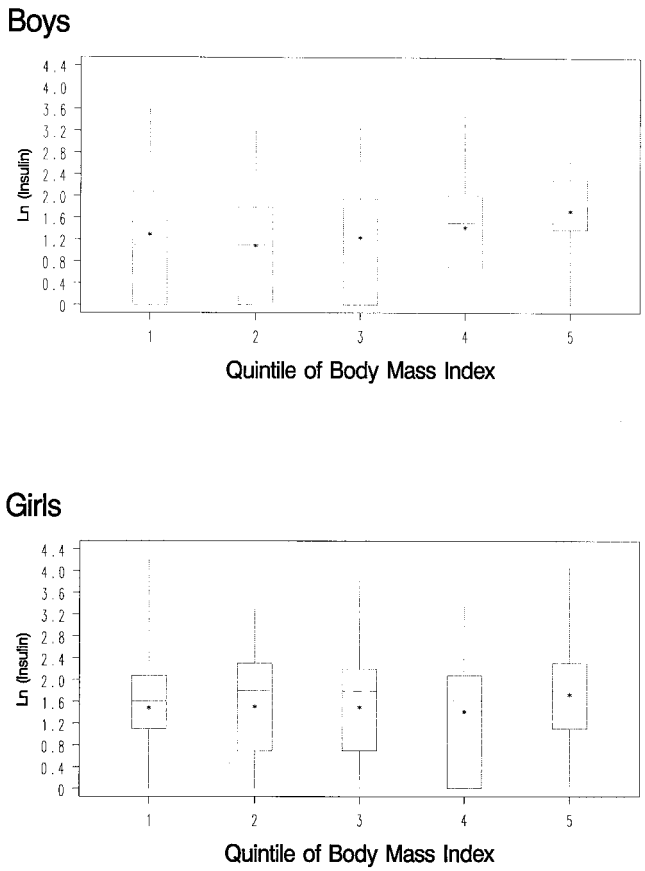

Figure 1: Box plot of ln(insulin) by quintile of BMI in boys (top) and girls (bottom). Asterisk, mean; middle line, median; box edges, 1 QR = 75th to 25th percentiles; whiskers, range.

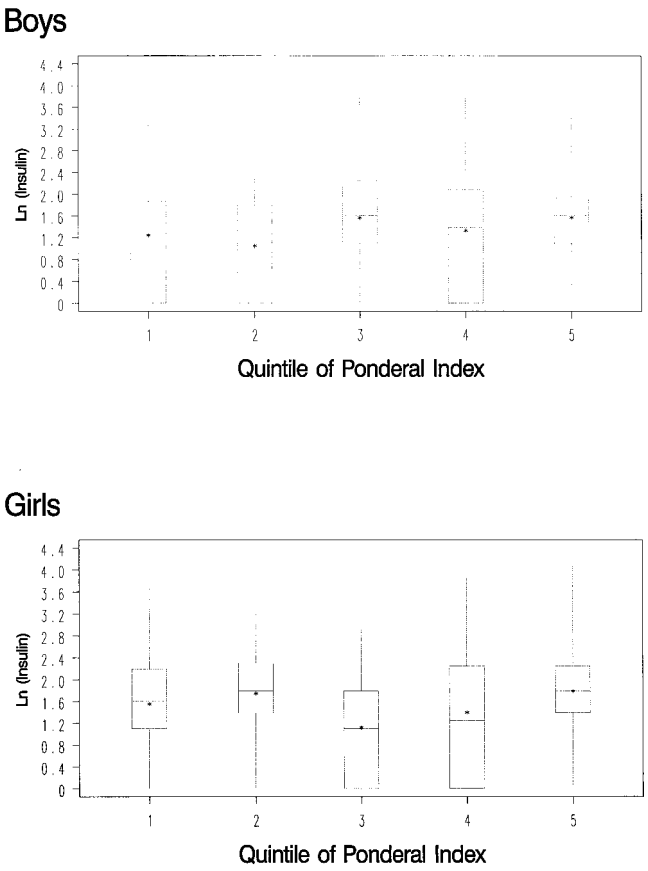

Figure 2: Box plot of ln(insulin) by quintile of ponderal index in boys (top) and girls (bottom). Asterisk, mean; middle line, median; box edges, 1 QR = 75th to 25th percentiles; whiskers, range.

circumference, showed no independent relationship to fasting insulin level after adjustment for BMI or sum of skinfolds in either boys or girls separately. In the sample as a whole, the triceps to waist ratio was marginally significant ($p = 0.048$) after adjustment for BMI but not after adjustment for ponderal index. Waist-to-hip ratio was not significant in the sample as a whole.

The correlations between ln(insulin) and glucose level were 0.32 ($p < 0.001$) for the sample as a whole, 0.37 for boys, and 0.28 for girls ($p < 0.001$ for both). Despite these correlations, there were no significant differences or linear trends in glucose levels across quintiles of BMI, sum of skinfolds, or waist circumference for boys or girls. Analyses using calculated insulin resistance as the dependent variable were fully consistent with the analyses using fasting insulin. This was to be expected because essentially all of the variability in calculated insulin resistance in our sample was attributable to the variability in fasting insulin level and very little to fasting glucose level.

Regression analyses relating BMI and ponderal index to fasting insulin level, after adjustment for age and sex, were significant ($p < 0.001$; Table 3).

Relations of Obesity Measures and Fasting Insulin with CRP Level

The correlations of obesity measures with CRP were low and not statistically significant in either boys or girls (Table 2) or in the sample as a whole. None of the trend tests for CRP in relation to BMI, ponderal index, or sum of skinfolds was significant, either in the sample as a whole or in the boys and girls considered separately. In regression analyses, the associations of BMI ($p = 0.051$) and ponderal index ($p = 0.04$) with CRP were of borderline statistical significance (Table 4) after adjustment for age and sex.

The correlations between fasting insulin and CRP were 0.16 ($p < 0.001$) in the sample as a whole ($N = 454$) and 0.07 ($p =$ not significant) in the boys and 0.25 ($p < 0.001$) in the girls (Table 2). Regression analyses showed significant relations between fasting insulin level and CRP after adjustment for age, sex, and either BMI or ponderal index (Table 4). In these analyses, in which the obesity measures and fasting insulin level were simultaneously included, fasting insulin level was significantly related to CRP ($p = 0.001$ and $p = 0.002$, respectively), but BMI and ponderal index were not.

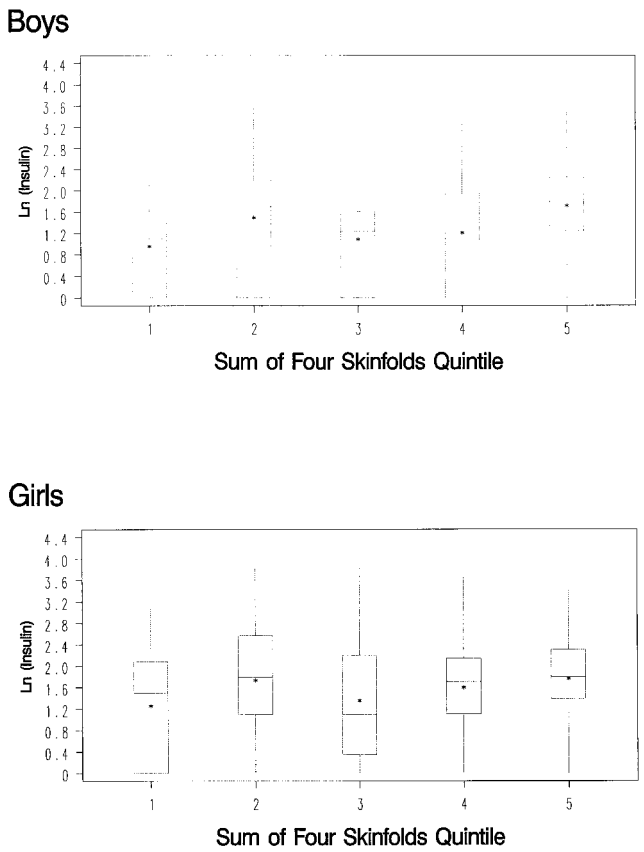

Figure 3: Box plot of ln(insulin) by quintile of sum of skinfolds in boys (top) and girls (bottom). Asterisk, mean; middle line, median; box edges, 1 QR = 75th to 25th percentiles; whiskers, range.

Discussion

The main finding of this study is that relative obesity is positively related to fasting insulin level in healthy, nonobese children as young as 2 to 3 years of age. We found relations of only borderline statistical significance between these measures of obesity and CRP level, contrary to reports in older children of a positive association (51,52), but we did find a significant relationship of fasting insulin to CRP level after adjustment for obesity measures. These relationships have not previously been reported in healthy, nonobese children of this age.

The mean height and weight of the children in our study was well within normal range for healthy children in the United States (60). Mean height and weight for boys in our study were 93.2 cm and 15.0 kg, respectively, compared with medians for 3-year-old boys of 96 cm and 14.3 kg, respectively. Mean height and weight for girls in our study were 92.7 cm and 14.8 kg, respectively, compared with medians for 3-year-old girls of 95 cm and 13.8 kg, respectively. These comparisons suggest that the children in our study were slightly more obese than national averages. The children in our study were recruited following procedures designed to obtain a sample of normal, healthy children who were free of chronic diseases and who lived in the community surrounding our site. Thus, the relationships we observed between measures of obesity and fasting insulin level seem to be present in normal, healthy children at a very early age.

There was no observable relation of fasting glucose level with BMI, ponderal index, sum of skinfolds, or waist cir-

Table 3. Results of multivariate regression analyses with fasting insulin level (μU/mL) as the dependent variable in 491 2- to 3-year-old children

Variable	β (SE)	p Value
Age, months	0.02 (0.007)	<0.01
Sex	0.16 (0.09)	NS
BMI, kg/m^2	0.08 (0.02)	<0.001
Age, months	0.03 (0.008)	<0.001
Sex	0.14 (0.09)	NS
Ponderal index, kg/m^3	0.08 (0.02)	<0.001

NS, not significant.

Table 4. Results of multivariate regression analyses with CRP (mg/L) as the dependent variable in 491 2- to 3-year-old children

Variable	β (SE)	p Value
Age (months)	0.003 (0.006)	NS
Sex	0.07 (0.08)	NS
BMI (kg/m^2)	0.04 (0.02)	0.051
Age (months)	0.007 (0.007)	NS
Sex	0.06 (0.07)	NS
Ponderal index (kg/m^3)	0.04 (0.02)	0.04
Age (months)	−0.0003 (0.006)	NS
Sex	0.05 (0.07)	NS
BMI (kg/m^2)	0.03 (0.02)	NS
Fasting insulin level (μU/mL)	0.12 (0.04)	0.001
Age (months)	0.003 (0.007)	NS
Sex	0.05 (0.07)	NS
Ponderal index (kg/m^3)	0.03 (0.02)	0.13
Fasting insulin level (μU/mL)	0.12 (0.04)	0.002

NS, not significant.

cumference in the children in our study, indicating that glucose homeostasis was maintained despite higher fasting insulin levels among the children of relatively greater obesity. This is consistent with the established pattern of onset in middle and late adulthood of glucose intolerance (61) and the temporal sequence in adults, whereby hyperinsulinemia precedes glucose intolerance (62,63). Our observations indicate that relative hyperinsulinemia begins much earlier in life than has previously been appreciated. Long-term longitudinal data will be needed to test whether relative hyperinsulinemia in early childhood is maintained through subsequent growth and development and whether it is a precursor of absolute hyperinsulinemia or glucose intolerance later in life.

The relations between obesity measures and C-reactive protein level were of borderline statistical significance in regression models without fasting insulin level and were not significant after further adjustment for fasting insulin. These observations are unlikely to reflect measurement error in the measures of obesity, because relationships with the obesity measures were observed for fasting insulin level. It is also unlikely that there were problems with frozen specimens or measurement error in CRP level, because we found relationships between CRP and obesity and physical fitness in older children using specimens handled in similar fashion and assayed in the same laboratory (52) and between fasting insulin level and CRP in this study. It is possible that abnormalities in fasting insulin level precede the low-grade elevation of CRP seen with obesity in older children and adults (8,19–24,64), either temporally or pathophysiologically.

Several potential limitations may affect the interpretation of our findings. First, the study children were not randomly sampled. However, it is highly unlikely that selection bias arising from nonrandom sampling or from subject characteristics associated with study participation influenced the observed associations between measures of obesity and fasting insulin level. The Hispanic families in our study originated almost entirely from the Caribbean basin. Additional studies in very young children of other race/ethnicity would be useful in confirming the relationships we observed. Second, it is possible that prolonged freezing may have affected the samples used for the insulin analyses, thereby contributing to the undetectable insulin levels in 85 of the children. We do not think this is likely, in that these samples were stable for other assays. Rather, we believe that these undetectable fasting insulin levels represent part of the normal range. Third, direct measurement of insulin resistance was not a feature of the study protocol. However, fasting insulin level has been shown in adults to correlate well with direct measurement of insulin resistance in normoglycemic subjects (65). Direct verification that the children fasted for 12 hours before phlebotomy was not feasible. Even overnight hospitalization would not have guaranteed complete fasting without continuous observation of the children and their mothers. We confirmed at the time of the phlebotomy that the mothers understood the instruction for the child to fast except for water, and also that the instruction had been followed. Nonfasting before phlebotomy would stimulate insulin secretion and increase plasma insulin level. Random nonfasting would have resulted in nondifferential misclassification of fasting insulin values and tended to mask the associations between measures of obesity and fasting insulin level (66).

In summary, in healthy 2- to 3-year-old children, relative obesity is associated with increased fasting plasma insulin level and a calculated index of insulin resistance. These associations have been extensively documented in adults and older children. While the correlations were modest in magnitude, these associations have not been previously documented in children this young. The relative insulin elevations we observed in relation to BMI, sum of skinfolds, and waist circumference were not associated with discernibly higher plasma glucose level. Our data are observational and do not establish whether relative obesity causes hyperinsulinemia or whether hyperinsulinemia itself, arising on some other basis, contributes to obesity and central obesity. There is evidence supporting both mechanisms (4,8,9). We also found a relationship between fasting insulin and CRP levels in these children. These findings indicate that an increased level of fasting insulin is associated even with modest relative obesity and is biochemically detectable before age 3 in healthy children.

Acknowledgments

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