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Longitudinal Changes in Body Fat in African American and Caucasian Children: Influence of Fasting Insulin and Insulin Sensitivity*

M. S. JOHNSON, R. FIGUEROA-COLON, T. T.-K. HUANG, J. H. DWYER, AND M. I. GORAN

Institute for Health Promotion and Disease Prevention Research, Department of Preventive Medicine, University of Southern California (M.S.J., T.T.-K.H., J.H.D., M.I.G.), Los Angeles, CA 90033; and Mead Johnson Nutritionals (R.F.-C.), Evansville, Indiana 47721

ABSTRACT

Obesity is associated with hyperinsulinemia and reduced insulin sensitivity, both risk factors for type 2 diabetes. However, it is not clear whether these risk factors occur as a result of obesity or whether they contribute to the development of obesity. The aims of this study were to determine whether baseline (first visit) or changes in insulin measures over time were associated with longitudinal changes in body fat mass during growth in children. The study group consisted of 137 children (83 Caucasian and 54 African American) with a mean age of 8.1 yr at baseline. The children returned for 3–6 annual visits for measurement of fasting insulin, insulin sensitivity (Si), and acute insulin response (AIR) from the tolbutamide-modified frequent sampling iv glucose tolerance test and for determination of body composition by dual energy x-ray absorptiometry. Data were analyzed using SAS Proc mixed growth models. Total fat mass increased with time by 15.6%/yr ($P = 0.013$), but the rate of increase was not significantly influenced by race, sex, or Tanner stage. However, fasting insulin (positive effect), Si (negative effect), and AIR (positive effect) were significantly associated with the rate of increase in fat mass. In conclusion, in this cohort of children, growth-related increases in body fat were significantly associated with increases in fasting insulin and AIR and decreases in Si. (*J Clin Endocrinol Metab* **86:** 3182–3187, 2001)

OBESITY IN CHILDREN has been shown to be associated with various risk factors for type 2 diabetes, including elevated levels of fasting insulin and glucose (1, 2) and reduced insulin sensitivity (3–5). However, the mechanisms relating increased fat to reduced insulin sensitivity are not known. Although it has been shown that obesity is associated with low insulin sensitivity, it is not clear whether increased fat mass causes lower insulin sensitivity or *vice versa*.

Weight loss, whether through exercise and/or diet, has been shown to result in decreased fasting insulin (2, 6–8), glucose (6, 7, 9), and improved insulin sensitivity (8, 10–12). However, the effect of weight gain on these risk factors is not clear. In two overfeeding studies in men, weight gain was associated with increased levels of fasting insulin and glucose (13, 14); however, this was not found in an overfeeding study of physically active people (15).

Both the overfeeding and weight loss studies have been intervention by design and have not addressed whether natural weight gain can be predicted by or is associated with differences in insulin or glucose levels. Studies of whether baseline insulin levels or insulin sensitivity can predict weight gain have been inconclusive. Baseline fasting insulin has been shown to be correlated with weight gain in overweight postmenopausal women (16), but not in middle-aged Caucasian men and women (17). In one previous prospective study in children, fasting insulin was correlated to the rate of weight gain over 9 yr in Pima Indian children (18). Whereas weight loss and cross-sectional studies have observed an increase in insulin sensitivity with weight loss, there has only been one study that has examined whether baseline insulin sensitivity predicts future weight gain. In this study Pima Indian adults with higher insulin sensitivity were found to be more likely to gain weight than those with lower insulin sensitivity (19). To our knowledge there have been no studies that have examined the relationship between fat gain and insulin sensitivity or acute insulin response during growth in children. Therefore, the aim of this study was to determine whether baseline levels of fasting insulin, insulin sensitivity, or acute insulin response predicted changes in total body fat, or whether changes in these insulin variables were only temporally associated with changes in total body fat in African American and Caucasian children.

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Address all correspondence and requests for reprints to: Dr. Michael I. Goran, Institute for Health Promotion and Disease Prevention Research, Department of Preventive Medicine, University of Southern California, 1540 Alcazar Street, Room 208, Los Angeles, California 90033. E-mail: goran@hsc.usc.edu.

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Subjects and Methods

Subjects

This study consisted of 137 children, 83 Caucasian (23 boys and 60 girls) and 54 African American (23 boys and 31 girls), aged 8.1 ± 1.6 yr at baseline. All children returned annually for follow-up visits over 3–6 yr for a total of 591 study visits. The children were recruited from Birmingham, AL, and had been free of any major illnesses since birth (20). Some cross-sectional data from these children have been reported

previously (3, 21). Studies were performed during the school year (fall and spring). The nature, purpose, and possible risks of the study were carefully explained to the parents and children before consent was obtained. This study was approved by the institutional review board at the University of Alabama at Birmingham. All measurements were performed at the General Clinical Research Center (GCRC) and the Department of Nutritional Sciences at the University of Alabama at Birmingham between 1994 and 1999.

Protocol

At each annual visit, children were admitted to the GCRC in the late afternoon for an overnight visit. Anthropometric measurements, including the state of sexual maturation, were obtained. After 2000 h only water and energy-free, noncaffeinated beverages were permitted until after the morning testing. On the following morning after an overnight fast, blood was collected for hormone analyses, and a tolbutamide-modified, frequently sampled, iv glucose tolerance test was performed. Two weeks later body composition was determined by dual energy x-ray absorptiometry (DXA) in the morning after an overnight fast.

Assessment of sexual maturation

Tanner's criteria were used to estimate sexual maturation on the scale of 1–5, with stage 1 being prepubertal and 5 being adult. The same qualified pediatrician (R.F.) assessed Tanner stage in all the children.

Assessment of body composition

Body composition was measured by DXA using a Lunar Corp. (Madison, WI) DPX-L densitometer that we have previously validated in the pediatric body weight range (22, 23). DXA scans were performed and analyzed using pediatric software (version 1.5e; Lunar Corp.) (22, 23).

Tolbutamide-modified frequently sampled iv glucose tolerance test

At 0600 h on the morning after GCRC admission, a topical anesthetic (Emla cream; Astra Pharmaceuticals L.P., Wayne, PA) was applied to the antecubital space of both arms, and at 0700 h, flexible iv catheters were placed. Three blood samples (2 mL) were drawn for determination of basal glucose and insulin. At time zero, glucose (25% dextrose; 11.4 g/m^2) was administered iv. Blood samples (2 mL) were then collected at the following times relative to glucose administration at 0 min: 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 min. Tolbutamide (125 mg/m^2) was injected iv at 20 min. Sera were analyzed for glucose and insulin, and values were entered into the MINMOD computer program (version 3.0) for determination of insulin sensitivity (24–26). The acute insulin response, based on the area above baseline insulin concentration, was calculated by trapezoidal method during 0–10 min (27).

Assay of glucose and insulin

Glucose was measured in 10 μL serum using an Ektachem DT II System (Johnson & Johnson Clinical Diagnostics, Rochester, NY). In our laboratory, this analysis has a mean intraassay coefficient of variation (CV) of 0.61% and a mean interassay CV of 1.45%.

Insulin was assayed in duplicate 200-μL aliquots with Coat-A-Count kits (Diagnostic Products, Los Angeles, CA). According to the supplier, the cross-reactivity of this assay with proinsulin is 40% at midcurve; C peptide is not detected. In our laboratory, this assay has a sensitivity of 11.4 pmol/L (1.9 μIU/mL), a mean intraassay CV of 5%, and a mean interassay CV of 6%. Commercial quality control sera of low, medium, and high insulin concentrations (Lyphochek, Bio-Rad Laboratories, Inc., Anaheim, CA) were included in every assay to monitor variation over time.

Statistics

Total fat mass, lean mass, fasting insulin, insulin sensitivity (Si), and acute insulin response (AIR) were not normally distributed and were log transformed before analysis. Random coefficients mixed models were used to determine the overall growth rate of body fat and the influence of each hormone variable (fasting insulin, Si, and AIR) on this growth rate. Mixed models were used to account for intraperson correlations among repeated measures (mean of 4.3 measures/child). Between- and within-subjects degrees of freedom were used, and the covariance structure of the random effects was unstructured.

The following specifications were made for the model for the overall growth rate for fat.

Dependent variable: log fat mass

Class variable. Visit number (no. 0–5) was used in the repeated statement to account for missing data.

Fixed effects. Initial age, initial fat mass, race (0 for Caucasian, 1 for African American), and sex (0 for boys and 1 for girls) were used as fixed covariates.

Random effects. Tanner stage (no. 1–5), time (years) since initial visit, and intercept (defined at baseline) were the random effects.

Interactions. The interaction between time and other variables in the model was used to interpret whether a particular variable had a significant effect on the change in fat over time. For example, the time $\times$ race interaction represented the effect of race on the rate of change of fat over time. Two-way interactions between time and the fixed variables were included in the model.

The same model was used to examine the influence of each of the three hormone variables on the overall growth rate for fat, with the addition of initial hormone level and rate of change in the hormone level included as additional fixed effects. These were obtained by regressing the hormone variable against time and saving the slopes (change in hormone) and intercepts (initial hormone level). Three-way interactions were also included among time, the hormone variables, race, sex, and Tanner stage. Data were analyzed using SAS statistical software version 7.0 (SAS Institute, Inc., Carey, NC), with a significance level of $P < 0.05$.

Results

The baseline descriptive statistics of the children are shown in Table 1 together with the number of subjects that had data for three, four, five, and six repeated visits.

Fat growth model (Table 2)

There was a significant increase in fat mass over time (β= 0.063; $P = 0.013$), which represented an increase of 15.6%/yr [95% confidence interval (CI), 9.1–22.5%] even after adjusting

TABLE 1. Baseline values of the variables used in the analysis together with the number of subjects with three, four, five, and six visits

	Baseline (visit 0)	Subjects with 3 visits	Subjects with 4 visits	Subjects with 5 visits	Subjects with 6 visits	Total subjects	Total visits
Age (yr)	8.1 ± 1.6						
Total fat mass (kg)	9.5 ± 6.1	31	46	46	14	137	591
Total lean mass (kg)	20.8 ± 5.1	31	46	46	14	137	591
Fasting insulin (U/dL)	12.0 ± 11.1	40	54	30	11	132	552
Si ($\times 10^{-5}$ min/μU·dL)	5.9 ± 4.7	47	24	0	0	71	237
AIR (μU/dl·min)	957.1 ± 553.6	47	24	0	0	71	237

TABLE 2. Results of the Proc mixed growth model for change in log fat mass

	β ± SE	P
Time (yr)	**0.063 ± 0.025**	**0.013**
Initial age (yr)	0.0002 ± 0.003	0.956
Initial fat (kg)	**1.010 ± 0.017**	**<0.0001**
Race (0 = C, 1 = AA)	0.001 ± 0.009	0.898
Sex (0 = M, 1 = F)	0.001 ± 0.009	0.943
Tanner stage	0.003 ± 0.010	0.756
Time × initial age	−0.004 ± 0.003	0.197
Time × race	0.002 ± 0.009	0.814
Time × sex	0.013 ± 0.010	0.195
Time × tanner stage	0.002 ± 0.003	0.370

Significant model factors are shown in *bold*. C, Caucasian; AA, African American.

for the amount of fat mass at baseline. This increase in fat mass over time was not significantly different between Caucasian and African American children (time × race, $P = 0.8$), between boys and girls (time × sex, $P = 0.2$), or with increasing sexual maturation (time × Tanner, $P = 0.4$). However, it should be noted that at 94.3% of the visits children were at Tanner 3 or below. As these two-way interactions were not significant in the fat growth model, they were not included in the models that examined the hormonal influence on the change in body fat. Including lean mass in the model did not change any of the results.

Influence of fasting insulin on the change in fat mass over time (Table 3)

The initial level of fasting insulin was significantly and positively related to the increase in fat mass over time ($\beta = 0.116$; $P < 0.0001$). The higher the fasting insulin of the children at baseline, the greater the increase in fat mass, even after adjusting for the amount of fat mass at baseline. The change in fasting insulin was also significantly and positively related to the increase in fat mass over time ($\beta = 0.319$; $P = 0.022$). The children with the greatest change in insulin per yr also had the greatest increase in fat mass per yr. In this study a 20% increase in the initial level or the change in fasting insulin per yr resulted in 2.1% (95% CI, 1.7–2.6%) and 6.0% (95% CI, 3.3–8.7%) increases in fat mass per yr, respectively. These relationships were not significantly influenced by race, sex, or Tanner stage ($P > 0.3$) and remained unchanged after including lean mass in the model.

Influence of Si on the change in fat mass over time (Table 4)

Both initial Si ($\beta = -0.057$; $P = 0.031$) and the change in Si per yr ($\beta = -0.358$; $P = 0.003$) were significantly and negatively associated with the increase in fat mass over time, even after adjusting for initial fat mass. Lower Si at baseline and greater decreases in Si were related to greater increases in fat mass. The magnitude of these effects were as follows. A 20% decrease in initial Si would result in a 1.0% (95% CI, 0.6–1.5%) increase in fat mass per yr, and a 20% decrease in the change in Si per yr would result in a 6.7% (95% CI, 4.5–9.1%) increase in fat mass per yr. These relatively small changes in Si would increase the yearly gain in fat mass from 15.6% to 16.6% and 22.3%, respectively. In addition, the relationship between initial Si and the increase in fat mass over time was significantly influenced by race ($\beta = -0.048$; $P = 0.021$). For a given difference in initial Si, the resulting change in fat mass was greater in Caucasian than African American children. Neither sex ($P = 0.6$) nor Tanner stage ($P = 0.8$) influenced the relationship between initial Si and the change in fat mass. In addition, the relationship between the change in Si and the change in fat mass was not significantly influenced by race ($P = 0.5$), sex ($P = 0.1$), or Tanner stage ($P = 0.3$). When lean mass was included in the model, none of the relationships changed.

TABLE 3. Results of the Proc mixed model to examine whether fasting insulin is associated with the rate of acquisition of fat mass

	β ± SE	P
Time (yr)	−0.030 ± 0.028	0.279
Initial age (yr)	0.001 ± 0.003	0.847
Initial fat (kg)	**0.988 ± 0.022**	**<0.0001**
Race (0 = C, 1 = AA)	0.00002 ± 0.010	0.999
Sex (0 = M, 1 = F)	0.0002 ± 0.009	0.987
Tanner stage	0.005 ± 0.010	0.633
Log initial insulin	0.010 ± 0.030	0.724
Δ log insulin	−0.010 ± 0.073	0.896
Time × initial age	**−0.007 ± 0.003**	**0.011**
Time × initial insulin	**0.116 ± 0.025**	**<0.0001**
Time × Δ log insulin	**0.319 ± 0.139**	**0.022**

Significant model factors are shown in *bold*. C, Caucasian; AA, African American; Δ log insulin, change in log fasting insulin during the study.

None of the three-way interactions with race, sex, and Tanner stage were significant, and they are not shown.

TABLE 4. Results of the Proc mixed model to examine whether insulin sensitivity (Si) is associated with the rate of acquisition of fat mass

	β ± SE	P
Time (yr)	**0.157 ± 0.040**	**0.0001**
Initial age (yr)	0.002 ± 0.005	0.622
Initial fat (kg)	**0.997 ± 0.031**	**<0.0001**
Race (0 = C, 1 = AA)	0.007 ± 0.016	0.641
Sex (0 = M, 1 = F)	0.002 ± 0.014	0.892
Tanner stage	−0.011 ± 0.013	0.413
Log initial Si	0.010 ± 0.034	0.774
Δ log Si	0.029 ± 0.091	0.756
Time × initial age	**−0.009 ± 0.004**	**0.036**
Time × log initial Si	**−0.057 ± 0.026**	**0.031**
Time × Δ log Si	**−0.358 ± 0.118**	**0.003**
Time × log initial Si × race	**−0.048 ± 0.021**	**0.021**

Significant model factors are shown in *bold*. C, Caucasian; AA, African American; Δ log Si, change in log insulin sensitivity during the study.

Influence of AIR on the change in fat mass over time (Table 5)

Initial AIR ($\beta = 0.068$; $P = 0.023$) and the change in AIR ($\beta = 0.232$; $P = 0.047$) were both significantly and positively related to the change in fat mass even after adjusting for the initial level of fat mass. Higher AIR at baseline and greater changes in AIR were related to increased changes in fat mass. A 20% increase in the initial AIR or the change in AIR per yr resulted in a 1.2% (95% CI, 0.7–1.8%) and 4.3% (95% CI, 2.1–6.6%) increase in fat mass per yr, respectively. As with Si, race was found to be a significant modifying factor in the

TABLE 5. Results of the Proc mixed model to examine whether the acute insulin response (AIR) is associated with the rate of acquisition of fat mass

	$\beta \pm$ SE	P
Time (years)	−0.096 ± 0.082	0.241
Initial age (years)	0.0005 ± 0.005	0.917
Initial fat (kg)	**1.000 ± 0.025**	**<0.0001**
Race (0 = C, 1 = AA)	0.002 ± 0.020	0.899
Sex (0 = M, 1 = F)	−0.001 ± 0.014	0.951
Tanner	0.003 ± 0.014	0.837
Log initial AIR	−0.0002 ± 0.033	0.997
Δ Log AIR	−0.002 ± 0.091	0.986
Time × initial age	−0.005 ± 0.004	0.177
Time × log initial AIR	**0.068 ± 0.030**	**0.023**
Time × Δ log AIR	**0.232 ± 0.117**	**0.047**
Time × log initial AIR × race	**−0.013 ± 0.006**	**0.031**

Significant model factors are shown in *bold*. C, Caucasian; AA, African American; Δ log AIR, change in log acute insulin response during the study.

relationship between initial AIR and the change in fat (β = −0.013; P = 0.031). For any given difference in initial AIR, Caucasian children had a greater change in fat mass during the study. Neither sex (P = 0.5) nor Tanner stage (P = 0.7) influenced the relationship between initial AIR and the change in fat mass. The relationship between change in AIR and change in fat mass was not influenced by race (P = 0.4), sex (P = 0.1), or Tanner stage (P = 0.8). None of the relationships changed after adjusting for lean mass.

Discussion

This study represents the first longitudinal assessment of the relationship between fasting levels of insulin, in addition to Si and AIR, and changes in body fat during growth in children. High initial fasting levels of insulin and AIR and low Si were associated with increased rates of fat gain in this cohort, even after adjusting for initial fat mass. In addition, differences in initial AIR and Si had greater effects on fat gain in Caucasian compared with African American children. Changes in fasting insulin, AIR, and Si during the study were also associated with changes in body fat, with increases in fasting insulin, AIR, and decreases in Si being related to increased fat gain.

The finding that high initial fasting insulin predicted greater fat gain supports the findings of the only other longitudinal study in children (Pima Indians) (18) and one in postmenopausal women (16), which found that baseline fasting insulin was correlated with rate of weight gain. We extended this general observation by showing that changes in fasting insulin over time were associated with changes in fat mass over time, and this effect was independent of baseline insulin. However, in other studies of Caucasian adults (17) and white and black young adults (28), no relationship was found between fasting insulin and weight gain once the data were adjusted for baseline weight. Although cross-sectionally, African American prepubertal children (21, 29) and adolescents (29, 30) have been shown to have higher fasting insulin levels than Caucasians, we found that the effect of fasting insulin on the rate of fat gain was the same in both African Americans and Caucasians. However, the higher fasting insulin generally observed among African Americans places them at higher risk for fat gain over time.

In previous cross-sectional studies, insulin sensitivity has been shown to be lower in overweight adults and children, compared with that in subjects of normal weight (3–5), and also lower in African Americans compared with Caucasians, independent of differences in body fat (3, 29). However, few studies have addressed whether insulin sensitivity is associated with longitudinal changes in fatness, especially in children. Our results indicate that low initial insulin sensitivity and a decrease in insulin sensitivity during the study were associated with increased fat gain over time. In addition, increased initial insulin sensitivity appears to reduce the gain in fat mass more in Caucasians than in African Americans. Therefore, in addition to already having a lower insulin sensitivity than Caucasians, which by itself would lead to greater increases in fat mass, African Americans appear to be more resistant to the apparent beneficial effect of an increased insulin sensitivity. Our findings are in contrast with those from the only other longitudinal study, which found a positive relationship between insulin sensitivity and weight gain in nondiabetic adult Pima Indians (31). It has been assumed that insulin resistance develops over the years as an individual becomes obese and is thought to be protective against further weight gain (18, 31). It is hypothesized that a low sensitivity of adipose tissue to insulin will prevent further fat deposition. Our results conflict with this general hypothesis, as we found that low insulin sensitivity had the opposite effect and resulted in increased fat gain. Our results could be explained by skeletal muscle becoming resistant, whereas the adipose tissue remained insulin sensitive. Skeletal muscle accounts for a large proportion of total body mass, and if this was to become insulin resistant, our whole body estimate of insulin sensitivity would be lower. Reduced sensitivity of the muscle mass would lead to a compensatory increase in insulin, which would increase the stimulation of the still insulin-sensitive adipose tissue to deposit fat. One mechanism by which muscle, but not fat, could become insulin resistant is through the accumulation of lipid within the muscle cells. Increased levels of intramyocellular lipid have been shown to be related to insulin resistance in the muscle tissue (32–34), and this may cause skeletal muscle to become insulin resistant before any changes in the sensitivity of adipose tissue. In mice, the inactivation of insulin receptors in muscle leads to the muscle becoming insulin resistant, whereas the adipose tissue actually becomes more sensitive (35). These mice also show increased adiposity compared with control mice. This animal model indicates that muscle can become insulin resistant, whereas fat stays insulin sensitive, and this results in increased adiposity.

There are very few studies that have looked at the relationship between AIR and weight gain, and to our knowledge no longitudinal studies in children have been performed. High AIR at the start of the study and increases in AIR during the study were both related to increased fat gain. As with insulin sensitivity, differences in AIR were found to have greater effects on the change in fat mass in Caucasians than in African Americans. As suggested above, it appears

that the change in fat mass in African Americans is more resistant to changes in insulin secretion.

Increased insulin secretion occurs as a response to decreased sensitivity to insulin; therefore, African Americans who have a lower insulin sensitivity than Caucasians also have a higher AIR (29, 36, 37). It is possible that the relationships observed in this study between AIR and fat gain are the result of changes in insulin sensitivity, and that those children with decreased insulin sensitivity and hence increased AIR, will have increased fat gain. Although both insulin sensitivity and the AIR were significant predictors of increased fat gain, when a further model was run to examine the influence of disposition index (insulin secretion corrected for the degree of insulin resistance) (24) on changes in fat mass, neither the initial disposition index nor the change in the disposition index was predictive of changes in fat mass. This suggests that the relationship between insulin secretion (AIR) and increased fat mass is a consequence of its relationship to insulin sensitivity.

Although the magnitude of the hormone effects on the rate of fat gain appear small (a 20% difference in hormone levels resulted in changes of between 1.0–6.7% in the rate of increase in fat mass), these effects still result in significant increases in fat. For example, a 3% increase in the gain in fat mass would result in a child gaining an extra 0.86 kg of fat over 3 yr (based on the average baseline fat of 9.49 kg). These magnitudes are based on a difference of 20% in the insulin measures, which is well within the range of this data for all insulin measures (*e.g.* range, 3.2–52 for fasting insulin and 1.69–16.16 for insulin sensitivity) and are likely to be conservative estimates of the effect on fat gain.

The major strengths of this study include the utilization of advanced methodological techniques for the accurate measurement of body composition, Si, and AIR and the incorporation of repeated measurements of body fat and the hormone variables. Many longitudinal studies have been prospective in design and have only examined whether baseline hormone concentrations influence the increase in weight/fat. However, hormone concentrations are not static and may also change over time. In this study we have shown significant independent effects of both baseline values and changes in insulin measures on the change in fat mass.

In conclusion, our results indicate that increases in fasting insulin and AIR and decreases in Si are associated with gain in fat mass during pubertal growth. Therefore, preventing further increases in fasting insulin and decreases in insulin sensitivity by diet and exercise (2, 6, 7, 38, 39) may also help to prevent further fat gain during this critical period of development.

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