Temporal Association Between Obesity and Hyperinsulinemia in Children, Adolescents, and Young Adults: The Bogalusa Heart Study

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Obesity is generally associated with hyperinsulinemia. However, whether obesity precedes or follows hyperinsulinemia is not clear. The present study examined the temporal nature of the association between obesity and hyperinsulinemia in a biracial (black-white) community-based population enrolled in the Bogalusa Heart Study. Three longitudinal cohorts of children (n = 427; baseline age, 5 to 7 years), adolescents (n = 674; baseline age, 12 to 14 years), and young adults (n = 396; baseline age, 20 to 24 years) were selected retrospectively, with a follow-up period of approximately 3 years. In general, longitudinal changes in the mean body mass index (kilograms per meter squared), an indicator of adiposity, and fasting insulin level did not parallel each other. In a bivariate analysis, baseline insulin levels correlated significantly with the follow-up body mass index in adolescents and adults, but not in children. On the other hand, the baseline body mass index correlated significantly with follow-up insulin levels in all cases. Logistic regression analysis showed that the proportion of subjects who developed obesity (body mass index >75th percentile, specific for age, race, gender, and survey year) at follow-up study increased significantly across baseline quintiles (specific for age, race, gender, and survey year) of insulin only among adolescents, irrespective of race and gender. This relationship disappeared after adjusting for the baseline body mass index. By contrast, a significant positive trend between baseline quintiles of the body mass index and incidence of hyperinsulinemia (>75th percentile) at follow-up study was noted among all age groups independent of race, gender, and baseline insulin levels. Further, in a multiple stepwise regression model, the best predictor of the follow-up insulin level was the baseline body mass index in children and adults and the baseline insulin in adolescents. The baseline body mass index was the best predictor of the follow-up body mass index in all three age groups. These results, by showing the temporal nature of the relation between obesity and hyperinsulinemia beginning in childhood, support the role of obesity in the development of hyperinsulinemia.

OBESITY and hyperinsulinemia/insulin resistance are known risk factors for type 2 diabetes, atherosclerotic cardiovascular disease, and hypertension.[1-8] Further, obesity is commonly associated with insulin resistance and the attendant hyperinsulinemia.[2,3] However, whether obesity precedes or follows hyperinsulinemia is uncertain.[9,10] Conceptually, potential mechanisms have been proposed to explain the causality either way.[11-15]

Some but not all studies in adults observed a lesser degree of body weight gain in individuals with higher fasting insulin and insulin resistance at baseline.[16-21] Evidence was also presented for both temporal sequences in middle-aged and older men.[22] The only study that addressed this issue in children found fasting hyperinsulinemia in Pima Indians to be a predictor of development of obesity.[23] Since the subjects examined in some of these studies were from high-risk populations genetically predisposed to obesity and type 2 diabetes, these findings may not be generalizable to other populations.

The genesis of adult obesity is thought to begin in childhood.[24-28] The fat mass and fat pattern, as well as insulin sensitivity, change markedly during periods of growth and maturation.[29-36] Longitudinal data from the Bogalusa Heart Study, a community-based study of cardiovascular risk factors beginning in childhood,[37] provide an opportunity to examine the temporal nature of the association between obesity and hyperinsulinemia during childhood, adolescence, and young adulthood.

SUBJECTS AND METHODS

Population

The biracial (65% white and 35% black) population of the Bogalusa Heart Study consists of all children and eligible young adults living in Bogalusa, LA. Between 1973 and 1993, seven cross-sectional surveys of schoolchildren aged 5 to 17 years and four surveys of young adults aged 18 to 32 years examined previously as children were conducted at approximately every 3-year period. The participation rate was approximately 80% for schoolchildren and approximately 60% for the young adult cohort.

Because plasma insulin levels were measured beginning in 1981, subjects examined between 1981 and 1993 were eligible for this study. Three longitudinal cohorts of children (n = 427; baseline age, 5 to 7 years), adolescents (n = 674; baseline age, 12 to 14 years), and young adults (n = 396; baseline age, 20 to 24 years) were selected retrospectively, with a follow-up period of approximately 3 years. The distribution of sample size, age, race, and gender is shown in Table 1.

The time interval required to detect a temporal relation between obesity and hyperinsulinemia is not established. In the current study, a 3-year follow-up period was chosen to examine the temporal relationship during the developmental periods of childhood, adolescence, and young adulthood.

General Examinations

Identical protocols were used by trained examiners across all surveys.[37] Subjects were instructed to fast for 12 hours before venipuncture, and compliance was determined by interview on the morning of the examination.

Height and weight were measured in triplicate to the nearest 0.1 cm and 0.1 kg, respectively, and the mean values were used in analyses. As a measure of overall adiposity, the body mass index (weight in kilograms divided by the square of the height in meters) was used.

The reproducibility of anthropometric measurements was assessed in

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Table 1. Sample Size, Age, Race, and Gender Distribution of Study Cohorts: The Bogalusa Heart Study

Group	Sample Size (n)					Age, yr (mean ± SD)	
	Total	White Males	Black Males	White Females	Black Females	Baseline	Follow-up
Children	427	137	71	140	79	6.5 ± 0.5	9.7 ± 0.7
Adolescents	674	215	143	188	139	13.0 ± 0.8	15.9 ± 0.8
Adults	396	123	31	178	64	22.0 ± 1.4	25.4 ± 1.5

a 10% random sample in each survey, and the intraclass (within-observer) correlation coefficients were greater than .99 for the height, weight, and body mass index.

Insulin Assay

Plasma immunoreactive insulin levels were measured by a commercial radioimmunoassay kit (Phadebas; Pharmacia Diagnostics, Piscataway, NJ). According to the manufacturer, the detection limit is less than 2 μU/mL; the antibody has 41% (by weight) cross-reactivity with proinsulin, which is disproportionately low in nondiabetics. The reproducibility in terms of the intraclass correlation between blind duplicate values was .94 to .98.

Statistical Analyses

All analyses were performed using SAS software.[38] Race and gender differences in the body mass index and insulin level were examined by an ANOVA model that included race and gender main effects and race-by-gender interactions. Changes in study variables over time were evaluated using repeated-measure ANOVA methods. Spearman correlation coefficients were computed to assess bivariate relationships between insulin and the body mass index.

Logistic regression models were used to test whether the baseline status of one factor (quintile of insulin or body mass index) was significantly associated with the incidence of the other factor (obesity or hyperinsulinemia) at follow-up study. For each cross-sectional study, gender-, race-, and age-specific percentiles were computed for the body mass index and insulin. Obesity and hyperinsulinemia were defined at levels above the 75th percentile (specific for survey year, race, age, and gender). Only subjects free of obesity or hyperinsulinemia (as already defined) at baseline were included in this analysis. Baseline values for the predicted variables were included in adjusted models. A significance level of P less than .05 was used as a criterion for inclusion in the model.

A multiple stepwise linear regression procedure was used to predict the follow-up insulin level or body mass index from independent variables that included baseline insulin, baseline body mass index, gender (0, male; 1, female), race (0, white; 1, black), and baseline age. Again, a significance level for inclusion in the model was specified at P less than .05.

RESULTS

The baseline and follow-up body mass index in children, adolescents, and adults is shown in Fig 1 by race and gender. There was no race or gender difference in the body mass index among children at the baseline and follow-up periods. As adolescents, black females showed a higher body mass index than black males at baseline ($P = .002$). As adults, females showed a race difference (blacks > whites) at the baseline ($P = .013$) and follow-up ($P = .012$) periods and whites showed a gender difference (males > females) at the baseline ($P = .009$) and follow-up ($P = .009$) periods. The body mass index at follow-up study increased significantly in all age-race-gender groups.

With respect to fasting plasma insulin levels, shown in Fig 2, a gender difference (females > males) was noted in children ($P = .005$) and adolescents ($P = .002$) at baseline; at follow-up study, black females as children ($P = .023$) and adolescents ($P = .047$) had higher values than all other race-gender groups. There was neither a race nor a gender difference in adults. Insulin levels at follow-up study increased significantly during childhood only in black females, and decreased significantly during adolescence only in white females. There were no significant longitudinal changes among the race-gender groups during adulthood. A comparison of longitudinal changes in the mean body mass index versus insulin level showed that in general, changes in these two variables did not parallel each other (Figs 1 and 2).

Interrelationships of the baseline versus follow-up body mass index and insulin level are listed in Table 2 by race and gender. In general, irrespective of race and gender, the baseline insulin level correlated poorly with the follow-up body mass index and insulin level in children and moderately in adolescents and adults. On the other hand, the baseline body mass index correlated moderately with the follow-up insulin level in all race-gender-age groups and strongly with the follow-up body mass index in all cases.

The relationship of the baseline insulin level (age-, race-, and gender-specific quintiles) to the incidence of obesity (>age-, race-, and gender-specific 75th percentile for body mass index) at follow-up study in children, adolescents, and adults is shown in Fig 3. Since there was no evidence of an interaction between insulin and race or gender, the race-gender groups were combined to increase statistical power. The proportion of

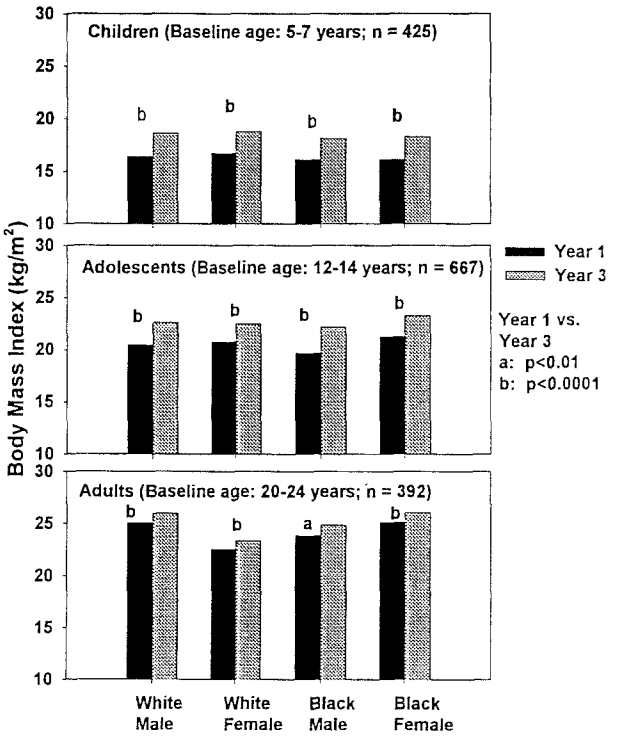

Fig 1. Longitudinal changes in body mass index in children, adolescents, and adults by race and gender: the Bogalusa Heart Study.

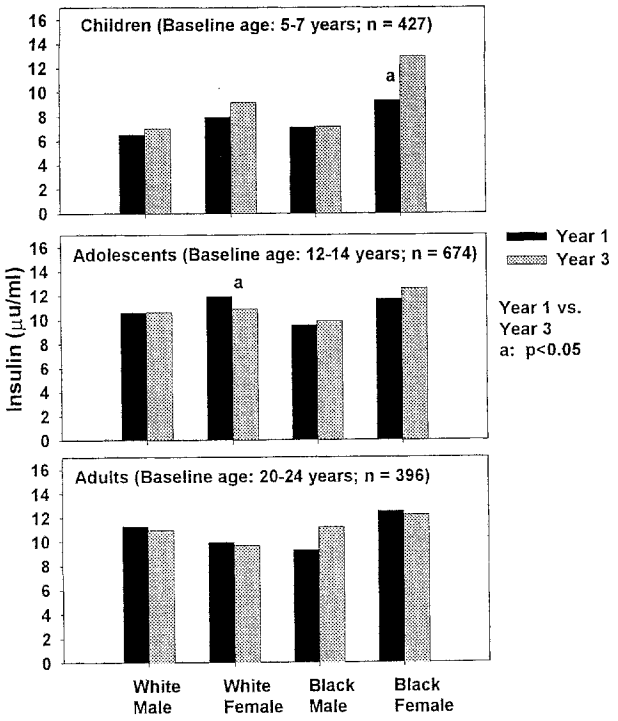

Fig 2. Longitudinal changes in fasting plasma insulin in children, adolescents, and adults by race and gender: the Bogalusa Heart Study.

subjects who developed obesity at follow-up study increased significantly across baseline quintiles of insulin only among adolescents. Compared with adolescents in the lowest baseline quintile of insulin, those in the highest quintile were 3.4 times more likely to develop obesity at follow-up study (Table 3).

Table 2. Interrelationships of Baseline Versus Follow-up Body Mass Index and Insulin Level in Children, Adolescents, and Adults by Race and Gender: The Bogalusa Heart Study

	Follow-up Study					
	Children		Adolescents		Adults	
Group	Insulin	BMI	Insulin	BMI	Insulin	BMI
White males	(n = 137)		(n = 215)		(n = 123)	
Baseline insulin	−.02	.13	.35§	.45§	.34§	.43§
Baseline BMI	.33§	.81§	.35§	.88§	.45§	.91§
White females	(n = 140)		(n = 188)		(n = 178)	
Baseline insulin	.06	.10	.35§	.33§	.28§	.25§
Baseline BMI	.52§	.89§	.34§	.87§	.30§	.86§
Black males	(n = 71)		(n = 132)		(n = 31)	
Baseline insulin	.09	.08	.31‡	.29‡	.39*	.27
Baseline BMI	.56§	.88§	.17*	.91§	.63§	.91§
Black females	(n = 79)		(n = 139)		(n = 64)	
Baseline insulin	.11	.08	.24†	.23†	.45‡	.54§
Baseline BMI	.25*	.83§	.36§	.92§	.43‡	.90§

NOTE. Values are Spearman correlation coefficients.
Abbreviation: BMI, body mass index.
*$P < .05$.
†$P < .01$.
‡$P < .001$.
§$P < .0001$.

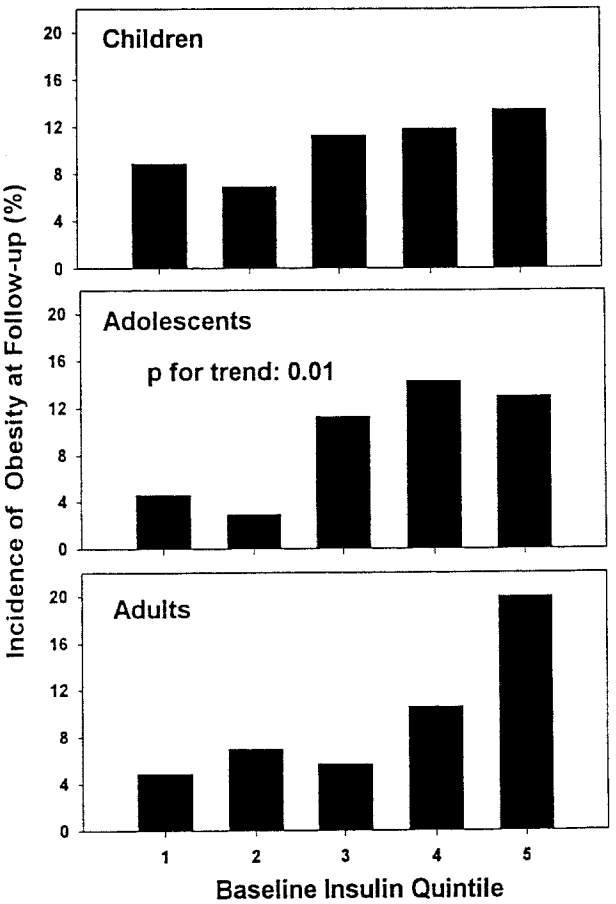

Fig 3. Incidence of obesity (body mass index > 75th percentile, specific for age, race, gender, and survey year) at follow-up study in children, adolescents, and adults by insulin quintiles (specific for age, race, gender, and survey year) at baseline: the Bogalusa Heart Study.

However, this relationship disappeared after adjusting for the baseline body mass index.

The effect of the baseline body mass index on the development of hyperinsulinemia (>age-, race-, and gender-specific 75th percentile for insulin) at follow-up study in children, adolescents, and adults is shown in Fig 4. The interaction terms race × body mass index and gender × body mass index were not significant in any age groups. A significant positive trend between baseline quintiles of the body mass index and incidence of hyperinsulinemia at follow-up study was noted among all age groups. This significant trend persisted after controlling for race and gender. Children, adolescents, and adults in the highest quintile of the body mass index versus those in the lowest quintile at baseline were 3.7 to 8.4 times more likely to develop hyperinsulinemia at follow-up study (Table 4). After adjusting for baseline insulin, a high body mass index at baseline remained significantly associated with the incidence of hyperinsulinemia at follow-up study.

Predictor variables that were related independently to the follow-up body mass index and insulin level in children, adolescents, and adults are presented in Table 5. The best predictor of follow-up insulin was the baseline body mass index in children and adults and baseline insulin in adolescents.

Gender and race were additional independent correlates, ranked in that order, in children; the baseline body mass index and baseline age in adolescents; and the baseline insulin in adults. The best predictor of the follow-up body mass index was the baseline body mass index in all three age groups. Additional independent correlates of the follow-up body mass index included gender and baseline age in adolescents, and none in children and adults. The percent variability explained (R^2) was higher for the body mass index than for insulin in all three age groups.

DISCUSSION

The present community-based study demonstrates a significant positive association between the degree of baseline obesity and the incidence of hyperinsulinemia at follow-up study in children, adolescents, and young adults alike. This association, which was independent of race, gender, and the baseline insulin level, suggests that obesity may precede hyperinsulinemia beginning in childhood. To our knowledge, no comparable data describing simultaneously the temporal association between obesity and hyperinsulinemia during childhood, adolescence, and young adulthood are available to establish this relationship in the general population.

In the present study, the body mass index was used as an indicator of adiposity, although this relative weight index reflects bone and muscle mass, as well as fat mass. Earlier observations from this population showed a high correlation between the body mass index and skinfold thicknesses and the ratio of subscapular to triceps skinfold thickness, measures of fat mass and fat distribution.[27,39] Information on insulin resistance measured by a hyperinsulinemic-euglycemic clamp test could be of interest for the present study. However, the fasting insulin level can be considered a reasonably good measure of insulin resistance in epidemiologic studies.[40,41]

The temporal relation between obesity and hyperinsulinemia found during childhood is of particular interest. During childhood, the baseline insulin level correlated poorly with the follow-up body mass index, whereas the baseline body mass index was significantly related to the follow-up insulin level in this age group. Importantly, in a multivariate analysis, the baseline body mass index was the best predictor of insulin levels at follow-up study in children. This is consistent with the observed adverse effect of baseline obesity on the development of hyperinsulinemia at follow-up study during childhood.

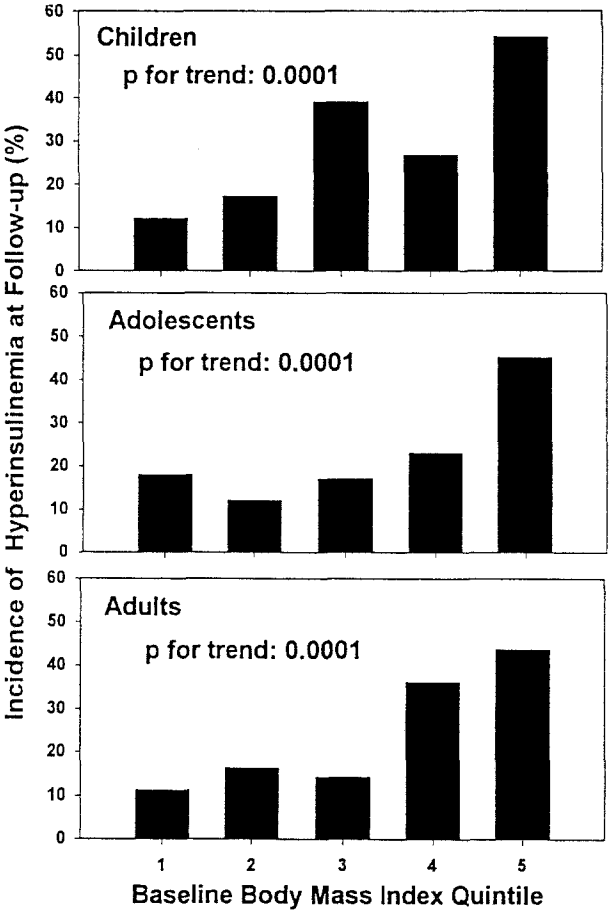

Fig 4. Incidence of hyperinsulinemia (insulin >75th percentile, specific for age, race, gender, and survey year) at follow-up study in children, adolescents, and adults by body mass index quintiles (specific for age, race, gender, and survey year) at baseline: the Bogalusa Heart Study.

Table 3. Incidence of Obesity at Follow-up Study in Children, Adolescents, and Adults According to 1st and 5th Quintiles of Insulin at Baseline: The Bogalusa Heart Study

Group*	No. of Subjects	Incidence (%) Total	Baseline Insulin Quintile† 1	5	Odds Ratio	95% Confidence Interval	P
Children	308‡	10.1	8.9	13.5	1.6	0.5-5.1	.4308
					1.3§	0.4-4.6	.6978
Adolescents	496	8.3	4.6	13.0	3.4	1.3-9.7	.0538
					1.0§	0.3-3.9	.9996
Adults	278	7.9	4.9	20.0	4.9	1.2-19.8	.0770
					1.7§	0.3-8.4	.5129

NOTE. Obesity is defined as a body mass index >75% percentile, specific for age, gender, race, and survey year.

*Baseline age: children, 5-7 years; adolescents, 12-14 years; adults, 20-24 years.

†Age-, race-, gender-, and survey year–specific.

‡Subjects who were not obese at baseline.

§Adjusted for baseline body mass index.

Contrary to the present findings, previous studies in Pima Indian children found hyperinsulinemia to be a predictor of the development of obesity.[23] However, Pima Indians represent a distinct high-risk ethnic group with a strong genetic predisposition to hyperinsulinemia/insulin resistance, obesity, and type 2 diabetes.[42,43] It has been hypothesized that populations genetically highly susceptible to type 2 diabetes are endowed with the thrifty genotype, which was intended to facilitate efficient fat storage in times of food abundance through a high insulin response to provide an energy buffer in times of scarcity.[44] Obesity and type 2 diabetes ensue in non-westernized populations when a rapid transition occurs from a traditional subsistence lifestyle to a Western diet and low-activity lifestyle.[45] In this context, hyperinsulinemia may be an early expression of the thrifty genotype preceding obesity, as envisaged in the case of

Table 4. Incidence of Hyperinsulinemia at Follow-up Study in Children, Adolescents, and Adults According to 1st and 5th Quintiles of Body Mass Index at Baseline: The Bogalusa Heart Study

Group*	No. of Subjects	Incidence (%) Total	Baseline BMI Quintile† 1	5	Odds Ratio	95% Confidence Interval	P
Children	293‡	27.6	12.3	54.2	8.4	3.4-20.7	.0001
					8.2§	3.3-20.4	.0001
Adolescents	492	21.1	18.1	45.3	3.7	1.9-7.3	.0001
					3.6§	1.8-7.0	.0003
Adults	278	21.9	11.3	43.8	6.1	2.2-16.9	.0005
					5.3§	1.9-14.7	.0016

NOTE. Hyperinsulinemia is defined as a insulin levels >75th percentile, specific for age, gender, race, and survey year.

Abbreviation: BMI, body mass index.

*Baseline age: children, 5-7 years; adolescents, 12-14 years; adults, 20-24 years.

†Age-, race-, gender-, and survey year–specific.

‡Subjects who were not hyperinsulinemic at baseline.

§Adjusted for baseline insulin.

Pima Indian children.[23] However, the thrifty genotype metabolic sequelae may not be applicable to the entire population.

In the present study, the proportion of individuals who developed obesity at follow-up study increased with baseline insulin levels (quintiles) only among adolescents, irrespective of race and gender. However, this association disappeared after adjusting for the baseline body mass index. It should be noted that the best predictor of the follow-up body mass index was the baseline body mass index, not baseline insulin, in all three age groups. In adolescents, unlike children and adults, the nature of the association between obesity and hyperinsulinemia may be complicated because puberty per se is associated with impaired insulin sensitivity and related hyperinsulinemia.[32-36]

The present observation that baseline obesity was associated with the development of hyperinsulinemia in young adults differs from previous studies in adults.[16-22] Studies in middle-aged to elderly adult males found evidence for the temporal sequence of obesity and hyperinsulinemia to occur in both directions.[22] Higher insulin levels predicted greater weight gain in postmenopausal women predisposed to obesity.[16] A higher baseline insulin level was associated with lower weight gain in black and white subjects aged 45 to 64 years, but not in those aged 18 to 30 years.[17] Among Pima Indian adults, who are generally obese, lesser insulin resistance and reduced insulin secretion predicted greater weight gain.[18,19] Whether factors such as the age at baseline, duration of follow-up study, postmenopausal hormonal status, and genetic susceptibility for obesity of the subjects examined in these prior studies could account for the divergent findings is not clear.

Table 5. Predictors of Follow-up Body Mass Index and Insulin Level in Children, Adolescents, and Adults: The Bogalusa Heart Study

Follow-up Variable	Predictor Variable* Children (n = 425)	Adolescents (n = 667)	Adults (n = 392)
Insulin	Baseline BMI§	Baseline insulin§	Baseline BMI§
	Gender§	Baseline BMI§	Baseline insulin§
	Race‡	Baseline age†	
	R^2 = .19	R^2 = .23	R^2 = .34
BMI	Baseline BMI§	Baseline BMI§	Baseline BMI§
		Gender†	
		Baseline age†	
	R^2 = .79	R^2 = .81	R^2 = .84

NOTE. R^2 is the amount of variability in the follow-up level explained by the variable listed.

Abbreviation: BMI, body mass index.

*Ranked according to the strength of the association.

†$P < .01$.

‡$P < .001$.

§$P < .0001$.

A number of putative mechanisms that underlie the temporal sequence of obesity and hyperinsulinemia in either direction have been suggested. Increases in body fat, especially visceral fat, mobilize excess free fatty acids (FFAs) in the portal circulation, which in turn reduces hepatic clearance of insulin, causing peripheral hyperinsulinemia.[11-13] Utilization of excess FFAs by muscle at the expense of glucose may contribute to the peripheral insulin resistance in obesity.[46,47] Further, increased secretion of tumor necrosis factor alpha and leptin by adipose tissue in obesity has been invoked in insulin resistance.[48,49] Increases in insulin secretion as a compensation for insulin resistance are known to follow obesity in general.[50] Conversely, hyperinsulinemia per se is thought to promote accumulation of body fat in experimental obesity by preferential oxidation of carbohydrate over fat.[14] An increased response of adipose tissue lipoprotein lipase to hyperinsulinemia may drive the excess uptake and storage of FFAs, resulting in obesity.[15] It should be emphasized that the pathophysiologic mechanism(s) underlying the temporal sequence of obesity and hyperinsulinemia is complicated, since other neuroendocrine factors such as the sex hormones, adrenocorticosteroid axis, and sympathetic nervous system are intimately involved in this relationship.[11,12,51,52] The current observational study, although longitudinal in nature, cannot prove causality. However, by showing the temporal nature of the relation between obesity and hyperinsulinemia beginning in childhood, this study indicates a role of obesity in the development of hyperinsulinemia.

The proposition that the adverse effect of obesity on the development of hyperinsulinemia begins in childhood suggests that the continuation of obesity over time results in prolonged insulin resistance and the related metabolic syndrome characterized by dyslipidemia, hypertension, and glucose intolerance.[2,3] Irrespective of the putative cause(s) in terms of whether obesity drives hyperinsulinemia or vice versa, overnutrition characterized by positive energy balance is considered to play a major role in the development of obesity.[13,51] Therefore, a prudent diet and exercise, if undertaken beginning in childhood, may have a salutory effect in preventing obesity and the related morbidity and mortality.

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