0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(5):2218–2224

Contribution of Insulin Secretion and Clearance to Glucose-Induced Insulin Concentration in African-American and Caucasian Children

BARBARA A. GOWER, WESLEY M. GRANGER, FRANK FRANKLIN, RICHARD M. SHEWCHUK, AND MICHAEL I. GORAN

Department of Nutrition Sciences and Clinical Nutrition Research Center (B.A.G., F.F.), Department of Critical Care (W.M.G.), Department of Pediatrics (F.F.), and Department of Health Services Administration (R.M.S.), University of Alabama at Birmingham, Birmingham, Alabama 35294-3360; and Departments of Preventive Medicine and Physiology and Biophysics, University of Southern California, and Institute for Prevention Research (M.I.G.), Los Angeles, California 90033

Relative to Caucasians (C), African-American (AA) children and adults have lower indices of insulin sensitivity (S_i) and a higher acute insulin response to glucose (AIR_g). Among AA children, AIR_g is greater than that which would be predicted based on lower S_i. The objectives of the present study were 1) to determine whether insulin secretory parameters differ in AA *vs.* C children and adolescents using C-peptide modeling, 2) to determine whether hepatic insulin extraction differs with ethnicity/race using the C-peptide to insulin molar ratio, and 3) to determine whether the relatively greater AIR_g among African-Americans is due to greater insulin secretion or lesser clearance. Subjects (n = 76) were AA and C children (mean age, ~11 yr). A 3-h tolbutamide-modified iv glucose tolerance test and minimal modeling were used to determine S_i and AIR_g. First phase C-peptide/insulin secretion and basal, first, and second phase β-cell sensitivity to glucose were determined using C-peptide modeling with standard kinetic parameters developed in adults. The incremental C-peptide to insulin molar ratio over the 3-h test period, an index of hepatic insulin extraction, was calculated with the trapezoidal method. S_i was lower and AIR_g was higher in AA *vs.* C children. First phase C-peptide/insulin secretion and first phase β-cell sensitivity to glucose were approximately 2-fold greater in AA *vs.* C children ($P < 0.001$); there were no between-group differences in basal or second phase β-cell sensitivity to glucose. Hepatic insulin extraction was lower in AA *vs.* C (3.77 ± 1.78% *vs.* 5.99 ± 2.18%; $P < 0.001$). Multiple linear regression modeling indicated that first phase C-peptide/insulin secretion and hepatic insulin extraction contributed independently to AIR_g; however, it was only first phase C-peptide/insulin secretion that explained the significant independent contribution of ethnicity/race to AIR_g after adjusting for S_i. The results of this study suggest that greater AIR_g among AA is due to both greater insulin secretion and lesser hepatic insulin extraction, and that AIR_g above that predicted based on lower S_i is due to greater insulin secretion. The insulin secretion data await verification that the kinetic parameters used apply to children and AA. (*J Clin Endocrinol Metab* 87: 2218–2224, 2002)

THE ACUTE PHASE insulin concentration after a glucose challenge is greater among African-Americans (AA) compared with Caucasian-Americans (C) (1–5). Although this is attributed in part to ethnic/racial differences in insulin sensitivity (2, 3, 6–8) and associated compensatory mechanisms for maintaining hyperinsulinemia, the relative hyperinsulinemia among AA is greater than what would be expected based on differences in insulin sensitivity (9, 10). These observations imply that for any given degree of insulin sensitivity, either first phase insulin secretion is greater or hepatic insulin extraction is lesser among AA *vs.* C.

Differentiation of insulin secretion and clearance requires measurement of C-peptide. C-Peptide is secreted with insulin in equimolar amounts from the pancreas, but is not subject to hepatic extraction as is insulin and has a constant peripheral clearance. Thus, the relative amounts of C-peptide and insulin in the systemic circulation can be used to estimate hepatic insulin extraction (11). Insulin secretion can be estimated from mathematical modeling of C-peptide data during a frequently sampled iv glucose tolerance test. The minimal model of C-peptide kinetics proposed by Toffolo *et al.* (12) has been used to derive both an insulin secretion profile and several indices of β-cell function. By incorporating glucose concentration throughout the test, indices of β-cell sensitivity to glucose can be derived for basal, first phase, and second phase insulin secretion.

Few studies have used C-peptide measurements to address the possible physiological basis for the greater acute insulin response to glucose (AIR_g) among AA. Among adult men and women, greater postchallenge insulin among AA was attributed to lower hepatic insulin extraction, as reflected in the lower molar ratio of C-peptide to insulin in AA *vs.* C during a glucose tolerance test (13). Among adolescents, AA were found to have lower hepatic insulin clearance, based on the ratio of fasting C-peptide to fasting insulin, but also lower, rather than higher, insulin secretion, based on the measurement of fasting C-peptide concentration (14). Using iv glucose tolerance testing with measurements of insulin and C-peptide throughout, obese adolescent AA were found to have lower insulin sensitivity and greater insulin secretion than age-, sex-, and pubertal stage-matched obese C children (5). None of these studies determined whether the insulin concentration was disproportionate to insulin sensitivity in

Abbreviations: AA, African-American; AIR_g, acute insulin response to glucose; ANCOVA, analysis of covariance; C, Caucasian; CV, coefficient of variation; FSIGT, frequently sampled, iv glucose tolerance test; GCRC, General Clinical Research Center; S_i, insulin sensitivity.

AA. Thus, questions remain about the nature of the relatively greater AIR_g among AA.

The objectives of the present study were 1) to determine whether insulin secretory parameters differ in AA *vs.* C children using C-peptide modeling, 2) to determine whether hepatic insulin extraction differs with ethnicity/race using the C-peptide to insulin molar ratio, and 3) to determine whether the greater AIR_g among African-Americans [in excess of that predicted based on lower insulin sensitivity (S_i)] is due to greater insulin secretion or lesser clearance.

Experimental Subjects

Subjects were 42 AA (19 males and 23 females) and 34 C (14 males and 20 females) children, aged 8–14 yr, who are taking part in an ongoing longitudinal study on body composition, body fat distribution, and disease risk factors. The present results were collected during the fall of 1999 and the winter/spring of 2000. All subjects were examined by a pediatrician, who determined pubertal status by the criteria of Tanner (15, 16). No child was taking medications known to affect body composition (*e.g.* ritalin or GH), had been diagnosed with syndromes or diseases known to affect body composition or fat distribution (*e.g.* Cushing's, Down's, or type 1 diabetes), or had been diagnosed with any major illness since birth. Ethnicity was determined by self-report. This study was approved by the institutional review board at University of Alabama at Birmingham, and parents provided informed consent before testing commenced.

Materials and Methods

Protocol

Subjects reported to the General Clinical Research Center (GCRC) at University of Alabama at Birmingham in the late afternoon for an overnight visit. They received a standard dinner and then fasted for 10–12 h until glucose tolerance testing the following morning. Body fat distribution was determined during the afternoon/evening of admission at the level of the umbilicus by single slice computed tomography scanning as previously described (8). Two weeks after the GCRC visit, body composition was determined at Department of Nutrition Sciences by dual energy x-ray absorptiometry (DPX-L, Lunar Corp., Madison, WI), as previously described (8).

Frequently sampled, iv glucose tolerance test (FSIGT)

At approximately 0600 h on the morning after GCRC admission, a topical anesthetic (Emla cream, AstraZeneca, Wilmington, DE) was applied to the antecubital space of both arms, and flexible iv catheters were placed. At time zero, glucose (25% dextrose; 11.4 g/m^2) was administered iv. Blood samples (2.0 ml) were collected at the following times relative to glucose administration at 0 min: −15, -5, -1, 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, insulin, and C-peptide.

Assays

Glucose was measured in 10 μl sera using an Ektachem DT II System (Johnson & Johnson, 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 a solid phase RIA (Diagnostic Products, Los Angeles, CA). In our laboratory this assay has a sensitivity of 11.4 pmol/liter, a mean intraassay CV of 5%, and a mean interassay CV of 6%. C-Peptide was measured in duplicate 25-μl aliquots with a double antibody RIA (Diagnostic Products). In our laboratory this assay has a sensitivity of 0.318 ng/ml, a mean intraassay CV of 3.57%, and a mean interassay CV of 5.59%.

Determination of insulin sensitivity and β-cell function

Glucose and insulin values were entered into the MINMOD computer program (version 3.0, Richard N. Bergman) for determination of S_i and AIR_g 17–19). First phase C-peptide/insulin secretion and basal, first phase, and second phase β-cell sensitivity to glucose were determined using the modeling equations reported by Toffolo *et al.* (12). First phase β-cell sensitivity to glucose is equal to first phase C-peptide/insulin secretion divided by the maximum increment in the serum glucose concentration. Thus, first phase β-cell sensitivity to glucose reflects the amount of hormone secreted normalized for the glucose load. Equations were programmed with SCIENTIST for Windows software (MicroMath Research, Salt Lake City, UT). The model rate constants were calculated based on age and obesity status using the regression equations of Van Cauter *et al.* (20) developed for adults. The model was fit to the C-peptide data with glucose as the forcing function, using the least squares algorithm and equal weighting for all data points. The C-peptide to insulin molar ratio was calculated using the incremental area under the curve (trapezoidal method) throughout the 180-min test period for each hormone as an index of hepatic insulin extraction. The highest C-peptide value measured for each subject during the first phase was used as peak first phase C-peptide concentration.

Statistical analyses

For all analyses variables were log-transformed to ensure normality of distribution. Two-way ANOVA, with ethnicity/race and gender as the class variables, was used to examine subject characteristics, derived variables from the FSIGT and minimal model, indices of β-cell function, and the C-peptide to insulin molar ratio. Multiple linear regression analysis was used to identify variables independently associated with AIR_g. The independent variables entered were ethnicity/race, those relevant variables that differed or tended to differ with ethnicity/race (S_i, Tanner stage, lean mass, and visceral fat), and indices of insulin secretion and clearance. A series of six models was conducted, with independent variables added sequentially to illustrate their relative contributions. Analysis of covariance (ANCOVA) was used to generate adjusted means for AIR_g. Due to a significant between-group difference in Tanner stage, analyses also were performed in a subset of the cohort group-matched for age and Tanner stage (n = 50; 27 AA and 23 C). ANOVA and regression modeling were conducted with SAS version 6.12 (SAS Institute, Inc., Cary, NC). Differences or effects were considered significant at $P < 0.05$.

Results

Descriptive data are shown in Table 1. The ethnicity/race term was not significant in two-way ANOVA models for age, fat mass, body weight, body mass index, or sc abdominal fat, but was significant for Tanner stage (AA > C). In addition, AA subjects tended to have greater lean body mass ($P = 0.08$) and less visceral fat ($P = 0.08$) than C subjects. The gender term was significant for Tanner stage (girls > boys). Computed tomography scan information (visceral fat and sc abdominal fat) was not available for five subjects (one AA male, two AA females, one C male, and one C female). According to the most recent data available on obesity classification in children (21), 24% of the AA children were obese, and 26% of the C children were obese.

Indices of insulin action and β-cell function are given in Table 2. Gender was not significant in any model; thus, data are shown by ethnicity/race. S_i was lower ($P < 0.01$), and AIR_g was greater ($P < 0.001$) in AA *vs.* C. Greater AIR_g among AA was significant even after statistically adjusting for S_i ($P < 0.001$; Fig. 1). Examination of fit indices from the C-peptide model showed that the mean coefficient of determination was 0.82 (range, 0.68–0.97), the mean correlation (between observed and calculated) was 0.91 (range, 0.83–0.96), and the mean r^2 was 0.97 (range, 0.91–0.99). First phase C-peptide/insulin secretion and first phase β-cell sensitivity to glucose were greater in AA *vs.* C ($P < 0.001$); there was no

TABLE 1. Descriptive statistics (mean ± SD)

	African-American (n = 42)		Caucasian (n = 34)	
	Male (n = 19)	Female (n = 23)	Male (n = 14)	Female (n = 20)
Age (yr)	10.9 ± 1.4	11.6 ± 1.8	11.4 ± 1.7	11.4 ± 1.6
Tanner stage[a]	3 ± 1	3 ± 1	2 ± 1	3 ± 1
Total fat mass (kg)	17.1 ± 14.8	18.4 ± 13.1	11.7 ± 8.0	15.8 ± 9.3
Total lean mass (kg)[b]	36.3 ± 9.5	35.4 ± 8.6	32.6 ± 10.0	31.6 ± 6.4
Weight (kg)	56.5 ± 22.2	57.6 ± 19.3	46.0 ± 13.6	50.0 ± 14.8
Body mass index (kg/m^2)	23.4 ± 6.1	23.2 ± 6.6	20.1 ± 4.3	21.9 ± 5.0
Visceral fat (cm^2)[b]	44.1 ± 36.8	33.3 ± 22.0	42.3 ± 16.0	44.4 ± 25.3
Subcutaneous abdominal fat (cm^2)	162.3 ± 169.2	183.8 ± 156.0	132.9 ± 109.6	170.4 ± 120.6

[a] $P < 0.01$ for ethnicity/race effect and $P < 0.05$ for gender effect, by two-way ANOVA.
[b] $P = 0.08$ for ethnicity/race effect by two-way ANOVA.

TABLE 2. Indices of insulin action and β-cell function (mean ± SD)

	African-Americans	Caucasians
S_i [$\times 10^{-5}$ min^{-1}/(pmol/liter)]	6.12 ± 3.82[a]	11.10 ± 7.00
AIR_g (pmol/liter) × 10 min)	11,766 ± 16,050[b]	3,516 ± 2,142
First-phase C-peptide/insulin secretion (pmol/liter)	3,549 ± 1,942[b]	1,734 ± 756
Basal β-cell sensitivity to glucose (10^9 min^{-1})	7.6 ± 3.8	7.5 ± 3.6
First-phase β-cell sensitivity to glucose (10^9)	325 ± 187[b]	159 ± 98
Second-phase β-cell sensitivity to glucose (10^9 min^{-1})	37.9 ± 21.9	32.5 ± 17.4
Glucose AUC (mmol/liter)	998 ± 68[a]	1,055 ± 98
C-peptide peak (nmol/liter)	3.4 ± 1.7[b]	2.0 ± 0.7
Hepatic insulin extraction (%)	3.77 ± 1.78[b]	5.99 ± 2.18

AUC, 180-min area under the curve.
[a] $P < 0.01$.
[b] $P < 0.001$.

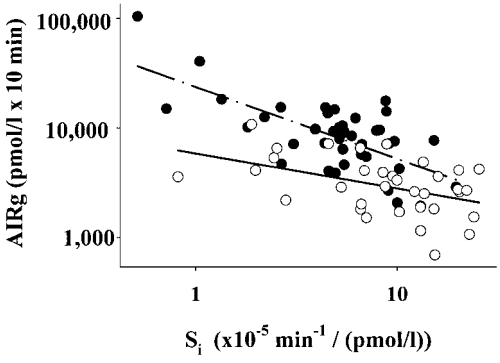

FIG. 1. AIR_g *vs.* S_i in AA (●) and C (○) subjects ($P < 0.001$ for difference between groups, by ANCOVA).

between-group difference in basal β-cell sensitivity to glucose or second phase β-cell sensitivity to glucose. The C-peptide to insulin molar ratio was greater in C ($P < 0.001$). Plots of mean glucose, C-peptide, and insulin concentrations during the FSIGT are shown in Fig. 2, A, B, and C, respectively. When expressed as the area under the curve for the entire 180-min test, glucose was significantly lower in AA *vs.* C ($P < 0.01$). The peak C-peptide concentration during the first phase was significantly higher in AA *vs.* C ($P < 0.001$).

In a series of multiple regression analyses for the dependent variable AIR_g (Table 3), it was shown first that, as expected, AIR_g was strongly related to S_i (model 1). Subsequently, it was determined that ethnicity/race was independently associated with AIR_g after adjusting for S_i (model 2) and for S_i, Tanner stage, lean mass, and visceral fat (model 3). However, adding the additional variable first phase C-peptide/insulin secretion eliminated the independent relationship between ethnicity/race and AIR_g (model 4, Fig. 3). Although independently related to AIR_g, hepatic insulin extraction did not eliminate the significant contribution of ethnicity/race (model 5). When both first phase C-peptide/insulin secretion and hepatic insulin extraction were in the model, both contributed independently to AIR_g (model 6). Results did not differ if AA subjects with AIR_g greater than 2 SD above the mean (four individuals) were eliminated from the analyses.

In the subset of subjects matched for age and Tanner stage, AA and C did not differ with respect to age (11.4 ± 1.7 for AA and 11.0 ± 1.4 for C), Tanner stage (2.8 ± 1.2 for AA and 2.2 ± 1.1 for C), body composition, or body fat distribution. As with the complete cohort, within the matched subset, the two groups differed with respect to S_i, AIR_g, first phase C-peptide/insulin secretion, first phase β-cell sensitivity to glucose, and the incremental C-peptide to insulin molar ratio (Table 4). Multiple linear regression analysis for the dependent variable AIR_g indicated that ethnicity/race was no longer a significant determinant when S_i, lean mass, visceral fat, and first phase C-peptide/insulin secretion were placed in the model (Table 5) or when S_i, lean mass, visceral fat, first phase C-peptide/insulin secretion, and hepatic insulin extraction were in the model; these results agree with those obtained with the complete cohort.

Discussion

The present study was conducted to determine whether insulin secretion or hepatic insulin extraction differed in AA *vs.* C children, and whether differences in insulin secretion, extraction, or both explained the higher absolute and S_i-adjusted AIR_g among AA. The C-peptide modeling results

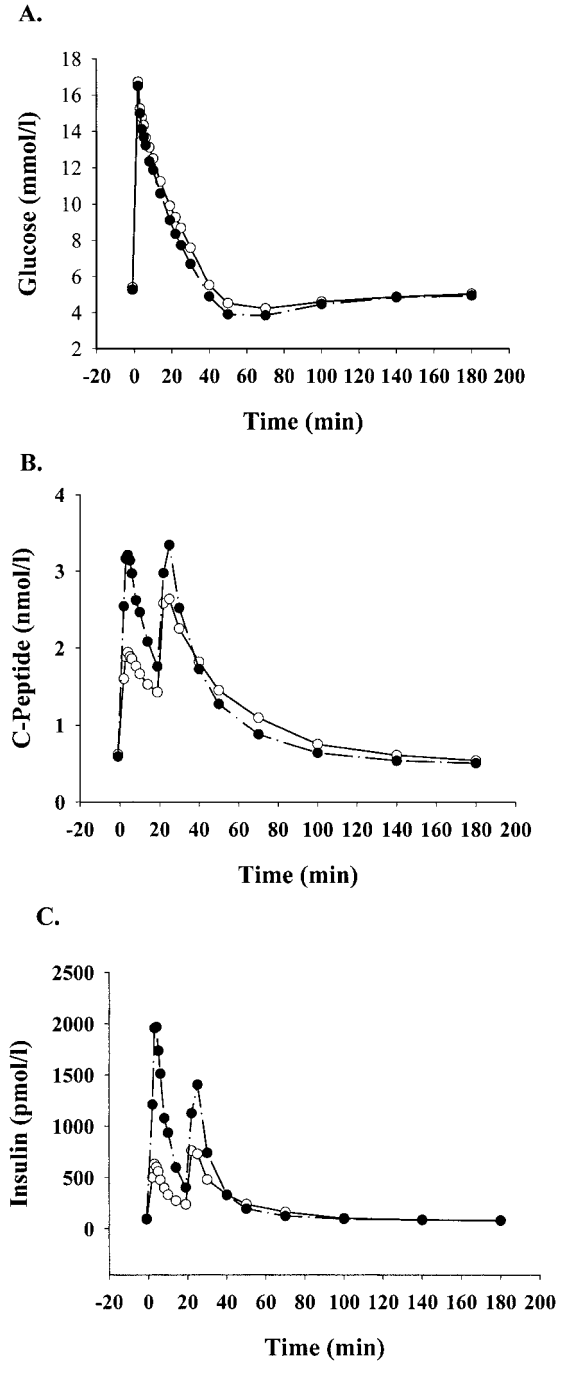

FIG. 2. Glucose (A), C-peptide (B), and insulin (C) *vs.* time in AA (●) and C (○) subjects during the iv glucose tolerance test. Significant between-group differences were detected in glucose area under the curve ($P < 0.01$), first phase C-peptide peak ($P < 0.001$), and AIR_g ($P < 0.001$).

suggested that both first phase C-peptide/insulin secretion and β-cell sensitivity to glucose were higher among AA; however, these results were derived using adult C-peptide kinetic parameters and need to be verified. In contrast, hepatic insulin extraction, determined from the C-peptide to insulin molar ratio, was lower among AA. Thus, the greater AIR_g among AA may have been due to both greater insulin secretion and lesser insulin clearance. Multiple regression analysis suggested that greater AIR_g in AA, after adjusting for S_i, was due to greater insulin secretion.

Previous studies have shown that postglucose challenge insulin concentrations are higher among AA *vs.* C individuals (1–3, 5). This is true in adults, adolescents, and children. Although AA are also more insulin resistant (2, 3, 6–8), the relative hyperinsulinemia among AA is apparent in prepubertal children even after adjusting for S_i (9, 10). Likewise, in the present study scatterplots of AIR_g *vs.* S_i clearly reveal that at any given degree of S_i, AA have greater AIR_g.

The source of greater AIR_g among AA could be either greater insulin secretion or lesser hepatic insulin extraction. Results from C-peptide modeling suggested that both first phase C-peptide/insulin secretion and first phase β-cell sensitivity to glucose were higher among AA. First phase C-peptide/insulin secretion presumably reflects the quantity of insulin that is synthesized and transported into a pool of hormone that is released immediately upon stimulation by glucose. First phase β-cell sensitivity to glucose reflects the amount of hormone secreted normalized for the glucose load. The present results suggest that the pancreas in an AA subject is synthesizing and storing more insulin in an immediately available pool, and that this larger amount of hormone is released in response to a uniform glucose stimulus. For this reason, the AA group appears to have a greater first phase sensitivity to glucose.

We also examined the contribution of hepatic insulin extraction to AIR_g, using the molar ratio of C-peptide to insulin throughout the 180-min FSIGT as an index of hepatic insulin extraction. Concern has been raised that the use of this ratio can lead to misinterpretation of data due to differences in the circulatory half-life and distribution space of the two hormones (11). However, after 180 min both C-peptide and insulin have returned to baseline concentrations. Thus, the ratio of C-peptide to insulin incremental area under the curve over the 180-min test period may be a reasonable reflection of hepatic insulin extraction (11). Lower hepatic insulin extraction appears to be responsible for greater AIR_g among AA *vs.* C adults (13).

Similarly, the present results suggested that hepatic insulin extraction was approximately 37% lower in the AA *vs.* C children. Thus, a lesser degree of hepatic insulin extraction probably contributed to the greater AIR_g in the AA group. The reason for lower hepatic insulin extraction among AA *vs.* C children is not known. Truncal lean body mass, as determined by dual energy x-ray absorptiometry, is 12.2% lower in AA *vs.* C, suggesting that organ mass may be lower in the former (22). It has been suggested that liver mass plays a significant role in determining the quantity of insulin extracted by the liver (23). Therefore, lower liver mass among AA *vs.* C may contribute to less hepatic insulin extraction.

Results from multiple regression modeling indicated that both insulin secretion and hepatic insulin extraction were significant independent determinants of AIR_g in this group of children. However, when both first phase C-peptide/insulin secretion and hepatic insulin extraction were sequentially placed in a model for AIR_g, only first phase C-peptide/insulin secretion eliminated the significant contribution of

TABLE 3. Multiple linear regression analysis for the dependent variable AIR_g

Model	Independent variable	Parameter estimate ± SEE	*P*	Model R^2
1	Intercept	3.31 ± 0.06	<0.001	0.40
	Log S_i	−0.64 ± 0.09	<0.001	
2	Intercept	3.37 ± 0.05	<0.001	0.58
	Log S_i	−0.49 ± 0.08	<0.001	
	Ethnicity/race	−0.33 ± 0.06	<0.001	
3	Intercept	3.11 ± 1.95	0.115	0.59
	Log S_i	−0.38 ± 0.12	<0.010	
	Ethnicity/race	−0.40 ± 0.07	<0.001	
	Tanner stage	0.006 ± 0.045	0.889	
	Log lean mass	−0.04 ± 0.47	0.939	
	Log visceral fat	0.24 ± 0.18	0.184	
4	Intercept	−0.79 ± 0.92	0.394	0.92
	Log S_i	−0.21 ± 0.06	<0.001	
	Ethnicity/race	−0.04 ± 0.04	0.264	
	Tanner stage	−0.01 ± 0.02	0.542	
	Log lean mass	−0.008 ± 0.213	0.971	
	Log visceral fat	0.03 ± 0.02	0.743	
	Log first-phase C-peptide/insulin secretion	1.16 ± 0.07	<0.001	
5	Intercept	3.56 ± 1.33	0.010	0.81
	Log S_i	−0.001 ± 0.094	0.988	
	Ethnicity/race	−0.20 ± 0.05	<0.001	
	Tanner stage	0.003 ± 0.03	0.917	
	Log lean mass	0.04 ± 0.32	0.901	
	Log visceral fat	0.06 ± 0.12	0.651	
	Log hepatic insulin extraction	−1.280.15	<0.001	
6	Intercept	0.28 ± 0.71	0.698	0.95
	Log S_i	−0.06 ± 0.05	0.203	
	Ethnicity/race	−0.02 ± 0.03	0.424	
	Tanner	−0.01 ± 0.02	0.517	
	Log lean mass	0.02 ± 0.16	0.885	
	Log visceral fat	−0.016 ± 0.062	0.791	
	Log first-phase C-peptide/insulin secretion	0.91 ± 0.06	<0.001	
	Log hepatic insulin extraction	−0.62 ± 0.09	<0.001	

Six models are presented; each of the first five has an additional independent variable(s) added to illustrate their relative contributions; model 6 shows all variables. The independent contribution of ethnicity/race to AIR_g is absent only in models containing first-phase C-peptide/insulin secretion (models 4 and 6).

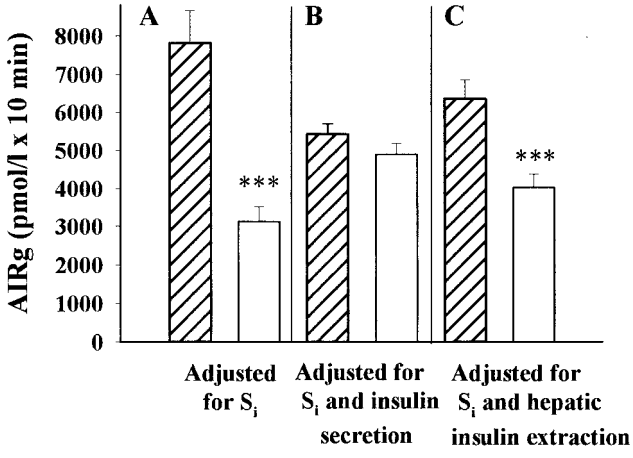

FIG. 3. AIR_g in AA (▨) and C (□) subjects. All means are adjusted for Tanner stage, lean mass, and visceral fat. In addition, means in A are adjusted for S_i, means in B are adjusted for S_i and first phase C-peptide/insulin secretion, and means in C are adjusted for S_i and hepatic insulin extraction. ***, $P < 0.001$ for difference between groups (by ANCOVA).

ethnicity/race to the model, after adjusting for S_i. Thus, the relatively greater AIR_g among AA (AIR_g adjusted for S_i) appeared to be due to greater insulin secretion.

In the present study Tanner stage did not play a role in determining AIR_g. Although Tanner stage was placed in the regression models to account for the difference in Tanner stage between the two ethnic/racial groups, Tanner stage was not independently related to AIR_g in any of the models. In addition, the data analyzed with the subset of children matched for Tanner stage produced results similar to those obtained with the entire sample. Thus, although S_i decreases transiently during midpuberty (24, 25), this change did not influence the determinants of the ethnic/racial difference in AIR_g investigated in this study.

The physiological significance of greater AIR_g among AA children is unclear. Impaired, rather than excessive, first phase insulin secretion is associated with subsequent development of glucose intolerance and type 2 diabetes (26). Thus, AA children would eventually have to experience a decline in β-cell function for the disease to develop. Higher AIR_g among AA could result in a more rapid rate of glucose disposal and may be responsible for the lower glucose AUC observed among AA in the present study. In addition, greater glucose-stimulated insulin concentrations among AA and C children are inversely associated with circulating free fatty acids, suggesting that hyperinsulinemia among AA suppresses lipolysis (27), which is lower among AA children (28). Chronically suppressed lipolysis may contribute to lower circulating triglycerides among AA *vs.* C (29). Whether insulin-mediated suppression of lipid mobilization contrib-

TABLE 4. Indices of insulin action and β-cell function (mean ± SD) in a subset of the cohort matched for age and Tanner stage

	African-Americans (n = 27)	Caucasians (n = 23)
S_i [$\times 10^{-5}$ min^{-1}/(pmol/liter)]	6.73 ± 4.33[a]	12.00 ± 6.57
AIR_g (pmol/liter × 10 min)	12,138 ± 18,984[b]	3,360 ± 2,220
First-phase C-peptide/insulin secretion (pmol/liter)	3,533 ± 2247[b]	1,712 ± 738
Basal β-cell sensitivity to glucose (10^9 min^{-1})	7.6 ± 4.0	7.1 ± 3.2
First-phase β-cell sensitivity to glucose (10^9)	306 ± 204[b]	152 ± 87
Second-phase β-cell sensitivity to glucose (10^9 min^{-1})	36.3 ± 24.4	31.3 ± 16.3
Hepatic insulin extraction (%)	3.99 ± 1.98[b]	6.35 ± 1.87

AUC, 180-min area under the curve.
[a] $P < 0.01$.
[b] $P < 0.001$.

TABLE 5. Multiple linear regression analysis for the dependent variable AIR_g in a subset of the cohort matched for age and Tanner stage; model $R^2 = 0.94$

	Parameter estimate ± SEE	*P*
Intercept	−0.47 ± 0.71	0.508
Ethnicity/race	−0.06 ± 0.04	0.151
Log S_i	−0.18 ± 0.06	<0.010
Log lean mass	−0.01 ± 0.15	0.511
Log visceral fat	0.09 ± 0.08	0.258
Log first-phase C-peptide/ insulin secretion	1.15 ± 0.07	<0.001

utes to greater obesity among AA (30) remains to be determined.

A limitation of this study is the use of C-peptide kinetic parameters that were developed for C adults; similar kinetic data are not available for AA or for children. It is possible that renal clearance of C-peptide differs with ethnicity/race or age. Thus, there is risk in assuming that the published kinetic data apply to this study population, and results regarding insulin secretion should be considered tentative.

In conclusion, the present results suggest that greater AIR_g among AA is due to both greater insulin secretion and lesser hepatic insulin extraction, and that AIR_g above that predicted based on S_i is due to greater insulin secretion. These results warrant confirmation with more robust indices of hepatic insulin extraction, *e.g.* indices obtained by mathematical modeling (31), and the use of ethnicity/race- and child-specific C-peptide kinetic parameters. Longitudinal studies are needed to determine whether and how greater AIR_g early in life is related to risk for development of type 2 diabetes among AA.

Acknowledgments

The assistance of study coordinator Tena Hilario and the staff of the GCRC and the participation of the children and their families are gratefully acknowledged.

Received September 24, 2001. Accepted January 18, 2002.

Address all correspondence and requests for reprints to: Dr. Barbara A. Gower, Department of Nutrition Sciences and Clinical Nutrition Research Center, University of Alabama at Birmingham, Birmingham, Alabama 35294-3360. E-mail: bgower@uab.edu.

This work was supported by NICHHD Grants R29-HD-32668 and R01-HD/HL-33064 (to M.I.G.), NIDDK Grant R01-DK-58278 (to B.A.G.), Clinical Nutrition Research Center Grant P30-DK-56336, and General Clinical Research Center Grant M01-RR-00032.

References

1. **Arslanian S, Suprasongsin C, Janosky JE** 1997 Insulin secretion and sensitivity in black vs. white prepubertal healthy children. J Clin Endocrinol Metab 82:1923–1927
2. **Arslanian S, Suprasongsin C** 1996 Differences in the in vivo insulin secretion and sensitivity of healthy black versus white adolescents. J Pediatr 129:440–443
3. **Haffner SM, D'Agostino RJ, Saad MF, Rewers M, Mykkanen L, Selby J, Howard G, Savage PJ, Hamman RF, Wagenkneckt L, Bergman RN** 1996 Increased insulin resistance and insulin secretion in non-diabetic African-Americans and Hispanics compared to non-Hispanic whites: The Insulin Resistance Atherosclerosis Study. Diabetes 45:742–748
4. **Svec F, Nastasi K, Hilton C, Bao W, Srinivasan SR, Berenson GS** 1992 Black-white contrasts in insulin levels during pubertal development. The Bogalusa Heart Study. Diabetes 41:131–317
5. **Schuster DP, Kien CL, Osei K** 1998 Differential impact of obesity on glucose metabolism in black and white American adolescents Am J Med Sci 316: 361–367
6. **Lovejoy JC, de la Bretonne J, Klemperer M, Tulley R** 1996 Abdominal fat distribution and metabolic risk factors: effects of race. Metabolism 45:1119–1124
7. **Osei K, Schuser DP** 1996 Effects of race and ethnicity on insulin sensitivity, blood pressure, and heart rate in three ethnic populations. Am J Hypertension 9:1157–1164
8. **Gower BA, Nagy TR, Goran MI** 1999 Visceral fat, insulin sensitivity, and lipids in prepubertal children. Diabetes 48:1515–1521
9. **Gower BA, Goran MI** 2000 Immunoreactive insulin, specific insulin, and proinsulin in African-American and Caucasian children. Diabetes 49(Suppl 1):A297
10. **Lindquist CH, Gower BA, Goran MI** 2000 The role of dietary factors in ethnic differences in early risk of cardiovascular disease and type 2 diabetes. Am J Clin Nutr 71:725–732
11. **Polonsky KS, Rubenstein AH** 1984 C-Peptide as a measure of the secretion and hepatic extraction of insulin. Pitfalls and limitations. Diabetes 33:486–494
12. **Toffolo G, De Grandi F, Cobelli C** 1995 Estimation of β-cell sensitivity from intravenous glucose tolerance test C-peptide data. Knowledge of the kinetics avoids errors in modeling the secretion. Diabetes 44:845–854
13. **Osei K, Schuster DP** 1994 Ethnic differences in secretion, sensitivity, and hepatic extraction of insulin in black and white Americans. Diabet Med 11: 755–762
14. **Jiang X, Srinivasan SR, Radhakrishnamurthy B, Dalferes ERJ, Berenson GS** 1996 Racial (Black-White) differences in insulin secretion and clearance in adolescents: the Bogalusa Heart Study. Pediatrics 97:357–360
15. **Marshall WA, Tanner JM** 1969 Variations in pattern of pubertal changes in girls. Arch Dis Child 44:291–303
16. **Marshall WA, Tanner JM** 1970 Variations in the pattern of pubertal changes in boys. Arch Dis Child 45:13–23
17. **Bergman RN, Phillips LS, Cobelli C** 1981 Physiologic evaluation of factors controlling glucose tolerance in man. Measurement of insulin sensitivity and β-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 68:1456–1467
18. **Pacini G, Bergman RN** 1986 MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Comput Methods Progr Biomed 23:113–122
19. **Yang YJ, Youn JH, Bergman RN** 1987 Modified protocols improve insulin sensitivity estimation using the minimal model Am J Physiol 253:E595–E602
20. **Van Cauter E, Mestrez F, Sturis J, Polonsky KS** 1992 Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. Diabetes 41:368–377
21. **Cole TJ, Bellizzi MC, Flegal KM, Dietz WH** 2000 Establishing a standard definition for child overweight and obesity worldwide: international survey. Br Med J 320:1–6
22. **Hunter GR, Weinsier RL, Darnell BE, Zuckerman PA, Goran MI** 2000 Racial

differences in energy expenditure and aerobic fitness in premenopausal women. Am J Clin Nutr 71:500–506
23. **Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G** 1997 Insulin resistance and hypersecretion in obesity. J Clin Invest 100:1166–1173
24. **Bloch CA, Clemons P, Sperling MA** 1987 Puberty decreases insulin sensitivity. J Pediatr 110:481–487
25. **Amiel SA, Caprio S, Sherwin RS, Plewe G, Haymond MW, Tamborlane WV** 1991 Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism. J Clin Endocrinol Metab 72:277–282
26. **Del Prato S, Tiengo A** 2001 The importance of first-phase insulin secretion: implications for the therapy of type 2 diabetes mellitus. Diabetes Metab Res Rev 17:164–174
27. **Gower BA, Herd SL, Goran MI** 2001 Anti-lipolytic effects of insulin in African American and white prepubertal boys. Obes Res 9:224–228
28. **Danadian K, Lewy V, Janosky JJ, Arslanian S** 2001 Lipolysis in African-American children: is it a metabolic risk factor predisposing to obesity? J Clin Endocrinol Metab 86:3022–3026
29. **Srinivasan SR, Wattigney MS, Webber LS, Berenson GS** 1991 Race and gender differences in serum lipoproteins of children and adolescents, and young adults - emergence of an adverse lipoprotein pattern in white males: The Bogalusa Heart Study. Prev Med 20:671–684
30. **Dawson DA** 1988 Ethnic differences in female overweight: data from the 1985 National Health Interview Survey. Am J Public Health 78:1326–1329
31. **Toffolo G, Arduini A, De Zanche N, Avogaro A, Cobelli C,** A minimal model of insulin during insulin modified IVGTT: assessment of hepatic insulin extraction. Proc 3rd IFAC Symposium on Modeling and Control in Biomedical Systems, Elsevier, Amsterdam, Warwick, UK, 1997, 91–95 (Abstract)