Black-White Contrasts In Insulin Levels During Pubertal Development

The Bogalusa Heart Study

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Three hundred and seventy-seven children and adolescents aged 5–17 yr from the biracial (black-white) community of Bogalusa, Louisiana, were evaluated for Tanner stage of sexual development, plasma glucose, and insulin levels during an oral glucose tolerance test. Children of the two races were of similar age, weight, and height at each Tanner stage. Overall insulin response was compared by measuring the area under the insulin curve from the glucose tolerance test. Blacks, especially black females, had significantly higher insulin responses than their white counterparts. The insulin-glucose ratio at the initial t = 0 min baseline did not vary with race or sex throughout the Tanner stages. However, the 30 min postglucose data revealed clear differences between the races with blacks showing a higher insulin-glucose ratio. Ratios increased throughout puberty for both blacks and whites, boys and girls. The trends of racial contrasts seemed to be discernible even at the earliest stage of development. It is concluded that there is a clear difference between blacks and whites in insulin response to a glucose load early in childhood. These findings lead to the hypothesis that the greater prevalence of non-insulin-dependent diabetes mellitus seen in adult blacks, especially females, may be an expression of a difference in insulin secretion and related insulin resistance in early childhood. *Diabetes* 41:313–17, 1992

Blacks suffer disproportionately from non-insulin-dependent diabetes mellitus (NIDDM) (1). Whether this increased prevalence is due to exaggerated abnormalities in the release and/or action of insulin or to changes in related hormonal modulators of carbohydrate metabolism is unknown.

The Bogalusa Heart Study previously reported that differences in glucose tolerance can be demonstrated between blacks and whites in childhood (2). This suggests that a more detailed understanding of the factors regulating insulin and insulin resistance in these two groups of children may help delineate the increased prevalence of glucose intolerance of black adults.

It is established that insulin sensitivity decreases during puberty. Amiel et al. (3), using the euglycemic clamp technique, reported that glucose metabolism is 25–30% lower in pubertal children as compared to prepubertal controls at comparable insulin levels. Bloch et al. (4) found similar results. Others have used the hyperglycemic clamp technique to show that puberty is associated with an increased insulin response and postulated that this may reflect a compensatory response to a reduction in insulin sensitivity (5).

Although these studies suggest that insulin resistance changes during puberty, they do not reveal the stage of sexual maturation (Tanner stage) at which these changes in glucose tolerance begin. Further, details of whether pubertal stage modulates insulin secretion differently between blacks and whites has not as yet been investigated. The work in this paper was done to evaluate the pubertal stage at which changes in insulin levels occur and to examine whether there are sex or racial differences. The ultimate goal is to elucidate further the pathogenesis of decreased insulin sensitivity associated with puberty.

RESEARCH DESIGN AND METHODS

The children (n = 377) aged 5–17 yr in this study were selected from the biracial (65% white, 35% black) community of Bogalusa, Louisiana. A complete description of this population and how the specific subgroups were selected have been reported (6). As previously reported, on the basis of the average of two prior (1973–1974 and 1976–1977) determinations of very-low-density lipopro-

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TABLE 1
Anthropometric measurements and laboratory values of female children by race

	Tanner stage									
	1		2		3		4		5	
n (White/black)	31/12		16/13		25/13		21/16		13/16	
Age (yr)	8.6/8.3	(1.6/2.5)	12.1/11.3	(2.2/1.8)	13.3/13.0	(3.6/2.4)	15.4/14.0	(1.7/3.6)	16.3/16.4	(1.1/1.9)
Height (m)	1.27/1.30	(0.14/0.12)	1.49/1.42	(0.17/0.11)	1.56/1.53	(0.09/0.10)	1.59/1.56	(0.07/0.09)	1.61/1.60	(0.05/0.11)
Weight (kg)	25.2/27.6	(6.4/7.3)	38.3/37.7	(14.6/12.1)	46.2/46.1	(14.6/7.2)	49.4/49.9	(6.2/9.4)	56.7/50.3	(14.2/19.5)
Glucose (mM)										
t = 0	4.9/4.5	(0.5/0.9)	4.9/4.7	(0.6/0.4)	4.8/4.7	(0.2/0.4)	4.6/4.7	(0.6/0.8)	4.9/4.7	(0.4/0.3)
t = 30	7.4/6.4	(2.2/1.6)	7.0/6.6	(2.7/1.1)	7.5/5.9	(1.9/0.8)	6.8/6.5	(1.7/2.0)	6.6/6.0	(1.7/1.6)
t = 60	7.2/5.5	(3.8/2.0)	7.2/5.3	(1.7/1.4)	6.4/5.7	(2.0/1.5)	5.7/4.7	(2.3/2.6)	6.3/5.6	(3.4/2.4)
Insulin (pM)										
t = 0	93.3/136	(100/50)	71.8/107	(72/122)	129/129	(136/65)	144/179	(72/165)	129/154	(29/126)
t = 30	251/409	(222/391)	287/592	(344/505)	620/523	(560/552)	545/947	(481/610)	545/700	(322/538)
t = 60	373/377	(258/201)	337/466	(251/309)	517/509	(427/172)	488/700	(269/329)	502/509	(187/732)
Insulin/glucose										
t = 0	19.1/27.8	(16.5/14.3)	16.0/23.9	(12.6/22.7)	29.4/28.4	(26.0/10.7)	28.1/44.9	(17.1/36.4)	25.3/30.0	(5.9/26.5)
t = 30	32.3/72.8	(22.3/60.4)	46.2/77.7	(35.2/73.9)	87.2/84.9	(69.4/86.2)	88.0/125	(58.4/105)	74.9/118	(45.9/85.7)
t = 60	50.5/53.1	(34.0/36.6)	51.0/80.2	(40.1/46.5)	78.0/90.5	(65.4/41.4)	91.2/125	(59.9/70.4)	84.1/108	(49.2/106)

Values are medians with interquartile ranges in parentheses.

tein (VLDL) cholesterol and low-density lipoprotein (LDL) cholesterol concentrations, four groups of children were selected for a detailed study of serum lipoproteins in 1978. Group 1: both VLDL cholesterol and LDL cholesterol were in the lowest age-, race-, and sex-specific quintile; group 2: VLDL cholesterol was in the lowest quartile and VLDL cholesterol was in the highest quartile; group 3: both VLDL cholesterol and LDL cholesterol were in the highest quintile; group 4: VLDL cholesterol was in the highest quartile and LDL cholesterol was in the lowest quartile.

Each child was examined to determine the Tanner stage of pubertal development (7). In addition, weight and height were recorded. Each fasting child had an oral glucose tolerance test (1.75 g glucose/kg body wt with a maximum of 75 g) with an assessment of both glucose and insulin levels at 0, 30, and 60 min. All children were examined within a 6- to 8-wk period. Initially, 388 children were recruited into the study, however the results of 377 were used because of incomplete data on 11.

The analytical procedures used have been described, as well as the methods of physical examination (6). Plasma glucose was measured by an enzymatic method using the Beckman Instant Glucose Analyzer (Beckman, Palo Alto, CA). Insulin assays were conducted using a commercially available kit (Phadebus, Pharmacia, Piscataway, NJ).

Statistical analysis was carried out using SAS. Descriptive statistics such as median and interquartile range were obtained for each sex-, race-, and Tanner stage–specific group. Because of significant nonnormality, glucose at 30 and 60 min, insulin, insulin-glucose at 0, 30, and 60 min, and area under the curve for insulin were log-transformed and the resulting variables were not rejected for normality. Using the log-transformed data, race effects were evaluated for each sex-specific group. The effect of height, weight, and obesity (represented by wt/ht^3, ponderal index) were adjusted in a covariate analysis. Insulin was also tested for race effect after regressing on glucose.

RESULTS

Tables 1 and 2 present the number, age, weight, height, glucose, and insulin values of the children studied. Although there are more whites (229) than blacks (148), reflecting the composition of the population, there are significant numbers of both in all categories; the smallest number in any sex-, race-, and Tanner stage–specific group is 12. The ages for the two races are not statistically different at comparable Tanner stages except at stage four for the girls. At this one point there was a statistically significant difference in the ages between the races ($P = 0.004$). The weights and heights between the two races at comparable Tanner stages were not statistically different.

Figure 1 shows the area under the curve using the 0, 30, and 60 min insulin values for the two sexes and two races at each Tanner stage for all the children in the study. This value is a reflection of the overall insulin response to the standard glucose challenge. In both sexes there are clear trends toward higher insulin values in late puberty as compared to early puberty. Furthermore, at nearly each stage, blacks tend to have higher values than whites. This is especially noticeable in late puberty for black females; their area under the curve of insulin levels is above that of their white counterparts. This relative hyperinsulinemia is not caused by more obesity (as measured by ponderal index, wt/ht^3) because the black females are slightly (but not significantly) lighter than their white counterparts while being of similar heights (Table 1).

Although inspection of these curves show differences between blacks and whites, there was a large variability at each point. However, analysis of variance for the entire study group revealed that race had a significant effect on

TABLE 2
Anthropometric measurements and laboratory values of male children by race

	Tanner stage									
	1		2		3		4		5	
n (White/black)	43/16		16/16		18/12		19/14		27/20	
Age (yr)	8.6/8.4	(3.2/1.4)	12.0/11.9	(2.2/1.5)	13.3/13.5	(2.1/1.6)	15.2/15.2	(1.8/1.6)	16.3/16.1	(1.3/2.6)
Height (m)	1.33/1.32	(0.20/0.12)	1.52/1.53	(0.12/0.07)	1.59/1.52	(0.12/0.13)	1.69/1.69	(0.08/0.19)	1.74/1.71	(0.09/0.12)
Weight (kg)	29.3/30.2	(10.7/9.6)	41.5/40.2	(11.6/14.1)	44.8/40.5	(22.1/19.0)	62.7/55.0	(19.5/12.1)	72.5/63.0	(19.2/16.7)
Glucose (mM)										
t = 0	4.9/4.9	(0.4/0.6)	5.0/4.8	(0.5/0.6)	5.1/4.7	(0.4/0.4)	4.9/4.7	(0.2/0.7)	5.1/4.7	(0.5/0.4)
t = 30	6.8/7.7	(2.4/1.3)	8.4/7.8	(2.8/1.6)	7.7/7.4	(1.4/0.8)	7.2/6.9	(1.4/1.7)	7.6/7.4	(1.9/1.3)
t = 60)	6.1/5.9	(3.0/1.3)	6.6/5.6	(2.3/1.9)	6.4/6.4	(1.9/1.6)	5.8/5.7	(2.4/1.8)	6.1/6.1	(0.9/1.6)
Insulin (pM)										
t = 0	78.9/86.1	(50.2/100)	111/89.7	(111/133)	108/78.9	(78.9/104)	100/122	(78.9/78.9)	122/126	(115/64.6)
t = 30	273/391	(201/355)	452/595	(215/387)	431/523	(351/452)	517/627	(330/330)	596/559	(473/596)
t = 60	273/265	(230/323)	463/423	(294/448)	496/431	(337/323)	531/545	(423/222)	613/488	(366/373)
Insulin/glucose										
t = 0	16.0/18.8	(9.8/20.7)	22.2/18.6	(21.6/27.5)	21.3/16.2	(14.2/20.8)	20.9/22.5	(12.3/19.7)	24.0/27.2	(18.9/14.2)
t = 30	37.3/55.3	(26.7/44.8)	47.9/75.3	(35.3/71.1)	57.2/72.8	(35.9/64.2)	64.7/93.6	(36.2/43.3)	73.1/85.4	(52.2/97.6)
t = 60	43.6/43.5	(24.1/44.3)	55.2/60.9	(38.1/77.9)	70.3/69.6	(51.7/46.9)	80.5/93.1	(55.1/58.6)	105/91.4	(61.8/52.1)

Values are medians with interquartile ranges in parentheses.

the values ($P = 0.0004$). Even after adjusting for other parameters that could affect insulin levels (weight, height, age, ponderal index, and Tanner stage) analysis of variance shows that there is a very significant race effect on area under the insulin curve for both boys ($P = 0.01$) and girls ($P = 0.003$). Hence, after allowing for any differences in body size, age, and sexual development of the participants, black children were found to have higher insulin levels for the same glucose load as their white counterparts. In general, this trend is noticeable at each stage of puberty.

The ratio of insulin to glucose at the 0, 30, and 60 min data points were compared (Tables 1 and 2). Results for this ratio at each Tanner stage at time 0 min for both boys and girls and blacks and whites are comparable and low and unaffected by pubertal stage. On the other hand, this ratio at 30 and 60 min shows a clear rise through puberty. For boys this increase appears to form a gradual stepwise increase as puberty progresses. However, in girls it tends to increase rapidly in the middle of sexual development. These increases in insulin-glucose ratio during puberty are not caused by a progressive decrease in glucose values. Although there is a slight trend toward lower serum glucose values at 30 min as puberty progresses (Tables 1 and 2), the magnitude of this fall is insufficient to cause the near doubling of the insulin-glucose ratio seen as puberty goes from stage 1 to 5. Instead, the increased insulin to glucose ratio is a reflection of the higher peripheral insulin levels seen as puberty advances.

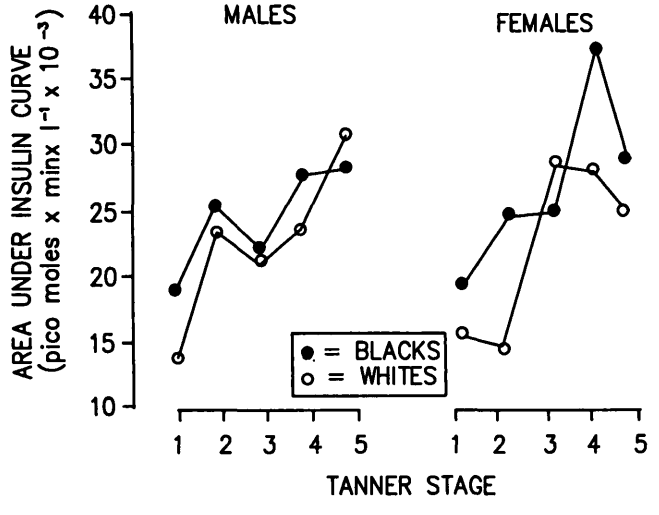

FIG. 1. Postglucose insulin response of children by race, sex, and Tanner stage. Each child received a glucose tolerance test with measurement of insulin values at 0, 30, and 60 min. Each child's value was used to determine the area under the curve for those insulin values plotted against time. The median values for these areas are plotted against the Tanner stage.

At each Tanner stage blacks of both sexes tend to have higher insulin-glucose ratios at 30 and 60 min than whites. Analysis of variance for the entire population showed that race had a significant effect on the mean of insulin-glucose values for both boys ($P = 0.0001$) and girls ($P = 0.0001$). Furthermore, even after adjusting for height, weight, ponderal index, age, and Tanner stage, there was a statistically significant racial difference for boys ($P = 0.0001$) and girls ($P = 0.0001$). Racial differences were still seen after the insulin levels were adjusted for the glucose values, with blacks having higher values. At 60 min the difference between the races was no longer significant for males but was still significant for females.

When the children were stratified by lipoprotein classification similar results were found; blacks had higher insulin-glucose ratios. However, the smaller number of individuals in each cell precluded rigorous statistical verification for each lipid group.

DISCUSSION

This paper reports a detailed study of insulin and glucose values during a glucose tolerance test in black and white

children categorized by sexual development. Others have conducted similar studies looking at children (8), black children (9) or a comparative study of the two sexes (10), but this is the largest report comparing the two races and sexes at each Tanner stage. It shows a definite difference between the two races that is present in both sexes. An understanding of the genesis of this difference may delineate why adult blacks have a higher prevalence of diabetes and more hypertension than whites.

Although the children in this study were not randomly selected, the results are likely to be applicable to the general population. All children were free living and healthy. They were selected for intense observation because of their serum VLDL cholesterol and LDL cholesterol values. They were all at the upper or lower 20–25th percentile of the distribution of the total population of children. Because race-sex and age-specific cutoff points were used in the sample selection, the race-sex composition of the sample was similar to that of the population of Bogalusa. Race-sex differences in fasting levels of lipoproteins, insulin, and glucose levels were similar to that of the entire population of children. Furthermore, when the comparison was conducted within each lipoprotein subgroup, the trend was unchanged. Blacks had higher insulin levels and insulin-glucose ratios at both the 30 and 60 min time points. Thus, because of these facts and the finding that the lipoprotein profile did not influence the racial difference, these data are applicable to the general population.

Differences in insulin levels between the races are not caused by differences in the course of sexual development. The fact that the ages, heights, and weights of the black and white children are comparable at each Tanner stage suggests that sexual development proceeds along similar lines.

In this analysis insulin response to the glucose tolerance test rose through puberty. This is consistent with a response to an increase in insulin resistance seen during puberty using insulin clamp techniques (3–5). In this study, insulin levels adjusted for glucose values are higher in both black boys and girls at the 30 min time point and at the 60 min point for black females, suggesting that blacks may be more insulin resistant than whites even during childhood.

The cause of the pubertal increase in insulin resistance is not clear. Some have suggested that growth hormone may mediate this effect (11). There is certainly a relationship between insulin, insulin resistance and growth hormone, and/or insulinlike growth factor (IGF) levels during puberty (3,4,12,13). On the other hand, several steroid hormones rise dramatically during puberty and others have suggested that changes in this class of hormones may be pivotal (4,14). Although it is tempting to propose relationships with gonadal steroid hormones for the changes in pubertal insulin resistance, note that Billiar et al. (15) found that neither the chronic administration of androgens nor estrogens is associated with abnormalities in glucose tolerance in rhesus monkeys. Another possible steroid candidate is dehydroepiandrosterone (DHEA), an adrenal steroid that increases during puberty. This hormone has been shown to improve glucose metabolism in rodent diabetic models (16,17). One of us (F.S.) has evidence that DHEA is an antagonist of glucocorticoid action (18). Whether relative changes of this hormone mediate changes in pubertal insulin sensitivity is not known.

The coexistence of obesity, hypertension, hyperlipidemia, and insulin resistance in adults is common and suggests a shared pathogenesis (19). The higher prevalence and expression of diabetes in adult blacks over whites may have multiple etiologies: obesity, for example, may be more prevalent in black adults. Fat distribution may be different. The results in this study suggest an additional explanation. Even at an early age, blacks compared to whites show a relatively higher insulin level adjusted for the glucose value. This suggests that even the nondiabetic black population may have more insulin resistance than whites. Whether increased insulin secretion in blacks during adolescence preceeds obesity and related morbid conditions later in life is not known. In an earlier publication we speculated that since black children had lower fasting and postglucose glucose values, the possibility exists that black children, especially black girls, may have increased insulin response due to increase secretion related to some other unknown mechanism (2). Clearly all the factors influencing insulin levels and insulin resistance are yet to be elucidated.

Other observations of the Bogalusa Heart Study have shown significant correlations between insulin and glucose levels with central obesity, blood pressure levels and serum lipoproteins. A careful delineation of the factors controlling insulin resistance in very young children might lead to insight into the mechanisms of adult non-insulin-dependent diabetes mellitus.

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