A Family History of Diabetes Is Related to Abnormal Insulin Sensitivity in African-Caribbean Girls of Low Birth Weight: Is Catch-up Weight Important?

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This retrospective cohort study examined the relationship of birth weight, family history of diabetes (FamHx), and current weight to insulin resistance in Black girls and boys on the Caribbean island of Barbados. A cohort of 56 low birth weight (LBW) and 120 normal birth weight (NBW) adolescents born between January 1, 1986, and December 31, 1988, were recruited for study participation in 2002. FamHx was ascertained by questionnaire. Body mass index (BMI) and waist circumference (WC) were used to assess fat distribution. Fasting blood glucose and insulin were measured from blood samples drawn from each adolescent participant. Insulin resistance was estimated by the homeostasis model assessment (HOMA) technique. These data show that only among LBW girls was a positive (+) FamHx associated with higher HOMA (FamHx ''Yes''=1.22 ± 0.298 vs ''No''=0.811 ± 0.452; P=.032). No significant relationships were observed among boys. Further analyses revealed that compared to their NBW counterparts, LBW girls without FamHx, had a smaller WC (69.70 ± 9.88cm vs 76.70 ± 15.64cm, respectively; P=.055). In contrast, LBW girls with a (+) FamHx had similar mean WC (77.71 ± 16.46cm) to those of NBW girls with (+) FamHx (WC=71.50 ± 10.38cm; P=.405). These data indicate that along with a family history of diabetes, catch-up weight may be important in assessing diabetes risk in Black Caribbean LBW adolescent girls. (*Ethn Dis*. 2005;15:424–428)

Key Words: Diabetes, Low Birthweight, Insulin Resistance

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Introduction

A positive family history of diabetes increases an individual's risk for developing type 2 diabetes in their lifetime.[1] Studies have shown that adolescents with a parent or grandparent with diabetes are less sensitive to insulin than those without a family history of diabetes.[2,3] Among African-American youth this relationship is more profound[4] and may be compounded by the increased risk of low birth weight (LBW) in this population.

Although the relationship between birth weight and insulin resistance in youth is unclear, evidence suggests that those born with a weight <2500 g are at increased risk for developing diabetes and other metabolic abnormalities as adults.[5] Among children, the association of LBW with metabolic abnormalities is greatest for LBW individuals who experience weight gain that allows them to "catch-up" in body weight to their normal birth weight (NBW) counterparts.[6,7] The underlying genetic contribution to the ability to "catch-up" in body weight or to diabetes risk among LBW individuals is not well understood.

The epidemic of childhood obesity in the United States which disproportionately affects Blacks[8] has implications for earlier onset of type 2 diabetes and greater disease burden in the African-American population. To address this problem studies to elucidate the interrelationship of birth weight, childhood weight, family history of diabetes, and biological markers of metabolic health risk are needed. Moreover, these concerns also extend to Black Caribbean populations that are experiencing economic development, an increase in sedentary lifestyle, and growing rates of childhood obesity.[9,10] This report presents the results of a study designed to examine the relationship of family history of diabetes, birth weight, and current body size in adolescence to insulin resistance in African Caribbean adolescent boys and girls age 14–16 years on the island of Barbados.

Methods

The current retrospective study was conducted between June 2002 and February 2003 on the island of Barbados in the Caribbean. The study sample consisted of 176 adolescents age 14–16 years, including 56 persons who were born with LBW and 120 persons who were of NBW. Recruitment of the study sample entailed a list, generated with the assistance of local physicians, of women who gave birth to a singleton at the Queen Elizabeth Hospital on the island of Barbados. All women who gave birth on any date between January 1, 1986, and December 31, 1988, were eligible for the study. A letter about the study was subsequently mailed to the homes of potential participants from a health-care provider familiar to them. Women and their eligible children who agreed to participate were asked to contact the study center to set-up a time for data collection. If a woman had multiple births during the reference period, one child was randomly selected for inclusion in the study. Of those contacted, 90% agreed to participate in the study. The medical records department of the Queen Elizabeth Hospital estimates an

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Table 1. Characteristics of study corresponds by family history of diabetes

	FamHx (+) (*N*=26) % or Mean (SD)	FamHx (−) (*N*=150) % or Mean (SD)	*P* Value
Age (years)	15.30 (0.78)	15.24 (0.80)	.690
Female (%)	53.8%	52.0%	.862
Low birth weight (%)	46.2%	29.3%	.089
Gestational age (weeks)*	36.61 (3.07)	37.38 (2.92)	.252
Waist circumference (cm)	75.15 (12.63)	74.20 (13.39)	.736
BMI (kg/m^2)	23.25 (6.03)	21.93 (5.46)	.264
Fasting glucose (mg/dl)	79.88 (10.83)	79.81 (7.91)	.968
Fasting insulin (μU/ml)	13.48 (6.31)	12.96 (6.28)	.697
Ln[Homa]	0.878 (0.51)	0.822 (0.51)	.608
Physical activity (met-hrs)	14.82 (9.93)	13.34 (12.11)	.556
Income (<US$2500)	23.1%	12.0%	.129

* *N*=23 for those with FamHx(+) and *N*=121 for those with FamHx(−).

average of approximately 3500 live births per year over the 3-year period of interest for this study. Although estimates of the prevalence of LBW during this period are difficult to obtain since consistent tabulation was not standard procedure, Pan American Health Organization (PAHO) 1996 estimates of LBW were 10%.[11] Both the mothers and their adolescent child signed consent forms approved by the biomedical institutional review boards of the University of the West Indies and the University of Pittsburgh. Adolescents who were not of African descent, pregnant at the time of recruitment, or unable to give informed consent were excluded from participation during screening interview.

DEMOGRAPHIC/ SOCIOECONOMIC VARIABLES

Demographic data, including household income, and information about family history of diabetes were collected from the sample of mothers by questionnaire. An adolescent participant was considered positive for a family history of diabetes (FamHx) if either his/her mother or the father had diabetes. Physical activity level was determined with the Modifiable Activity Questionnaire[12] which measures the metabolic cost in hours of time engaged in leisure time physical activity each week over the past year.

CLINICAL MEASURES

Weight at birth in grams (g) and gestational age in weeks was confirmed by review of medical records. Low birth weight (LBW) was classified as weight at birth below 2.5 kg, as is consistent with the International Classification of Diseases, 9th Revision. Gestational age was not routinely recorded in the medical records of each woman during the pregnancy during the targeted birth years. As a result only a subset of the total study population has reported values for gestational age. Current weight of each adolescent participant was measured twice using a balance beam scale. Waist circumference (WC), an estimate of abdominal fat, was measured twice at the level of the umbilicus to the nearest centimeter (cm) using a standard tape measure. Height was measured to the nearest cm using a wall-mounted stadiometer. Body mass index (BMI), an estimate of overall obesity, was calculated by using a ratio of weight in kilograms to height in meters (kg/m^2).

Fasting blood glucose and insulin were measured from blood samples drawn from each adolescent participant after an overnight fast of 10–12 hours. Serum glucose (mg/dL) was quantitatively determined by a colometric enzymic determination read at 340/380 nm with a procedure similar to that described by Bondar and Mead (1974). Insulin (μU/mL) was measured using a radioactive immunoassay procedure developed by Linco Research, Inc. Cross reactivity with proinsulin was under 2%. Insulin resistance was calculated using the homeostasis model assessment (HOMA) (insulin resistance=fasting insulin [μU/mL] × fasting glucose [mmol/L]/22.5).[13] The HOMA technique is highly correlated with the standard clamp technique for measuring insulin resistance[14,15] and is a useful tool for assessing insulin resistance in epidemiologic field studies where use of invasive clamp techniques is not practical.

STATISTICAL ANALYSES

The differences between variable means were assessed by using the *t* test. The chi-square was used to compare the frequency of categorical variables. Since the distribution of HOMA scores are skewed, the log-transformed (Ln[HOMA]) values were used in analyses. The nonparametric Mann-Whitney U test of two independent samples was used for mean analyses of subgroups. Spearman correlation analyses were used to determine if gestational

Table 2. Mean values of metabolic and anthropometric variables by family history of diabetes (FamHx) in low birth weight adolescents

	Girls (*N*=29)			Boys (*N*=27)		
	FamHx (+) (*n*=7)	FamHx (−) (*n*=22)	*P* Value*	FamHx (+) (*n*=5)	FamHx (−) (*n*=22)	*P* Value*
Fasting insulin (μU/ml)	16.20 (3.60)	12.72 (5.42)	.074	10.12 (5.35)	11.11 (5.50)	.827
Fasting glucose (mg/dl)	87.57 (7.25)	78.27 (5.47)	.005	75.80 (14.70)	81.73 (7.96)	.399
Ln[HOMA]	1.22 (.298)	0.811 (0.452)	.032	0.535 (0.603)	0.603 (0.269)	.417
Waist (cm)	77.71 (16.46)	69.70 (9.88)	.202	70.90 (9.12)	69.31 (5.60)	.827
Weight (lbs)	143.71 (54.33)	120.56 (29.07)	.429	124.00 (26.49)	125.68 (23.28)	.876
BMI (kg/m²)	25.89 (9.38)	20.93 (4.54)	.333	20.78 (3.14)	19.61 (2.46)	.417

* Mann-Whitney U test.

age and current age was significantly associated with Ln[HOMA]. Partial correlation analysis was used to determine if these relationships were independent of birth weight.

Of the 184 singleton adolescents recruited for the study, eight were removed because of incomplete blood analyses or abnormally high fasting insulin results. These individuals were not different with respect to age, sex, household income, and reported family history of diabetes than those remaining in the cohort. All analyses were performed by using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA).

RESULTS

The characteristics of the study sample are presented by family history of diabetes in Table 1. No difference was seen with respect to age, sex, physical activity, and metabolic or anthropometric variables between those with and without a family history of diabetes. However, a preponderance of LBW individuals was found among those with a positive family history of diabetes, although this finding was not statistically significant (P=.089). In Spearman correlation analysis among those with a positive FamHx, gestational age and current age were not significantly correlated with Ln[HOMA] (r=0.222, P=.308 and r=−0.078, P=.704; respectively). Among those with a negative FamHx, gestational age was significantly associated with Ln[HOMA] (r=0.261, P=.004), however, once adjusted for birth weight (BW) the correlation was no longer significant (r=0.131, P=.153). Current age was only marginally correlated with Ln[HOMA] in this group (FamHx(−): r=−0.145, P=.076).

In Tables 2 and 3, t tests were used to compare mean values of anthropometric (BMI and waist circumference) and metabolic variables (fasting glucose, insulin, and Ln[HOMA]) between those with and without a family history of diabetes among the BW groups. These data show that a positive FamHx was associated with higher fasting glucose, insulin, insulin resistance, and BMI only among girls who were born with LBW. No difference was seen with respect to the study variables by FamHx in boys or among those in the NBW group in either sex.

In Tables 4 and 5, the mean values of body size were compared between LBW and NBW groups stratified by family history of diabetes, to examine whether FamHx influences current body size. These data show that compared to their NBW counterparts, LBW adolescents without FamHx, had lower BMI and waist circumference values. In contrast, LBW adolescents with a positive

Table 3. Mean values of metabolic and anthropometric variables by family history of diabetes (FamHx) in normal birth weight adolescents

	Girls (*N*=63)			Boys (*N*=57)		
	FamHx (+) (*n*=7)	FamHx (−) (*n*=56)	*P* Value*	FamHx (+) (*n*=7)	FamHx (−) (*n*=50)	*P* Value*
Fasting insulin (μU/ml)	12.83 (5.49)	14.37 (6.95)	.654	13.81 (9.21)	12.30 (6.00)	.894
Fasting glucose (mg/dl)	77.14 (13.31)	78.52 (9.09)	.895	77.86 (4.33)	81.10 (7.15)	.128
Ln[HOMA]	0.798 (0.542)	0.890 (0.708)	.555	.855 (.460)	.803 (.434)	.836
Waist (cm)	17.50 (10.38)	76.70 (15.64)	.375	79.28 (13.13)	75.52 (13.68)	.268
Weight (lbs)	130.21 (31.54)	138.48 (41.04)	.607	159.78 (57.24)	141.74 (40.33)	.181
BMI (kg/m²)	22.18 (4.17)	23.29 (6.54)	.827	23.45 (5.01)	21.86 (5.13)	.253

* Mann-Whitney U test.

Table 4. Mean values for anthropometric variables by family history of diabetes in girls

	FamHx (+) (*N*=14)			FamHx (−) (*N*=78)		
	LBW (*n*=7) Mean (SD)	NBW (*n*=7) Mean (SD)	*P* Value*	LBW (*n*=22) Mean (SD)	NBW (*n*=56) Mean (SD)	*P* Value*
BMI (kg/m²)	25.89 (9.38)	22.12 (4.17)	.482	20.93 (4.54)	23.29 (6.54)	.125
Waist (cm)	77.71 (16.46)	71.50 (10.38)	.405	69.70 (9.88)	76.70 (15.64)	.055
Weight (lbs)	143.71 (54.33)	130.21 (31.54)	.949	120.56 (29.07)	138.48 (41.04)	.066
Insulin (μU/ml)	16.20 (3.60)	12.83 (5.49)	.180	12.72 (5.42)	14.37 (6.95)	.322
Glucose (mg/dl)	87.57 (7.25)	77.14 (13.31)	.109	78.27 (5.47)	78.52 (9.09)	.906
Ln[HOMA]	1.22 (0.298)	0.798 (0.542)	.085	0.811 (0.452)	0.890 (0.608)	.582

* Mann-Whitney U test.

FamHx had no difference in current weight so that their current mean BMI and waist circumference values were not different from those of NBW adolescents with a positive FamHx.

DISCUSSION

The results from the current study show that a positive family history of diabetes is related to increasing fasting glucose, insulin, and insulin resistance score. This finding is consistent with the findings of a study by Danadian et al in African-American youth which reported that family history of diabetes was associated with decreased insulin sensitivity in childhood.[4] An important observation in the current study was that a significant relationship between positive family history of diabetes and greater insulin resistance was seen only in LBW girls. The specific reasons for this finding are unclear. However, the apparent sex differential in this effect may reflect a greater influence of protective lifestyle behaviors such as physical activity among adolescent LBW boys. Although the data are not shown in this report, boys were observed to have significantly higher leisure time physical activity levels than girls irrespective of birth weight. Another possibility is that a positive FamHx might indicate familial risk factors that operate independent of genetic predisposition to differentially influence weight gain and metabolic risk in girls compared to boys with LBW.

In the current study the univariate assessment of gestational age was not significantly correlated to insulin resistance among those with a positive FamHx. These results suggest that gestational age is not a confounder of the association of LBW to insulin resistance among those with a positive FamHx. A preponderance of data suggest that birth size is an important indicator of disease development in later life.[5] Many studies have shown LBW to be related to insulin resistance independent of gestational age.[5,16] It may be that BW is a crude measure of intrauterine development, apparent even among full-term infants. When combined with a high-risk post-natal growth trajectory LBW increases the risk for insulin resistance and diabetes.

The risk of developing metabolic abnormalities in LBW youth is apparent among those that catch-up in weight from infancy to childhood.[6,7,17] Crowther et al[6] showed that 7-year-old Black South Africans with LBW and a high weight at 7 years old had higher levels of insulin and insulin resistance than those with LBW and low weight at 7 years old. They concluded that rapid weight gain (catch-up) in LBW children may increase the risk for diabetes.[6] In the current study, LBW girls with a family history of diabetes have a similar body size compared to those with a NBW, suggesting they may have experienced catch-up weight gain. This finding is consistent with higher insulin and glucose levels observed in this subset of girls. While no

Table 5. Mean values for anthropometric variables by family history of diabetes in boys

	FamHx (+) (*N*=12)			FamHx (−) (*N*=72)		
	LBW (*n*=5) Mean (SD)	NBW (*n*=7) Mean (SD)	*P* Value*	LBW (*n*=22) Mean (SD)	NBW (*n*=50) Mean (SD)	*P* Value*
BMI (kg/m²)	20.78 (3.14)	23.45 (5.01)	.570	20.12 (3.81)	21.86 (5.13)	.055
Waist (cm)	70.90 (9.12)	79.28 (13.13)	.222	0.54 (8.89)	75.52 (13.68)	.045
Weight (lbs)	124.00 (26.49)	159.78 (37.24)	.104	128.59 (29.70)	141.74 (40.33)	.086
Insulin (μU/ml)	10.12 (5.35)	13.81 (9.21)	.088	12.09 (9.35)	12.30 (6.00)	.433
Glucose (mg/dl)	75.81 (14.70)	77.86 (4.33)	.569	81.68 (7.94)	81.10 (7.15)	.742
Ln[HOMA]	0.535 (0.603)	0.855 (0.460)	.123	0.700 (0.505)	0.803 (0.434)	.381

* Mann-Whitney U test.

The results from the current study show that a positive family history of diabetes is related to increasing fasting glucose, insulin, and insulin resistance score.

statistically significant difference in current body weight was seen between LBW and NBW boys with a positive FamHx, the trend in boys appears to favor lower levels of fasting insulin and glucose and smaller body size in the LBW groups. Additional study is needed to elucidate the reasons for the observed differential relationships by sex.

The limitations of this study include the inability to distinguish between the types of maternal or paternal diabetes and the small size of the study cohort. In the current study no distinction was made between a family history of type 1 or type 2 diabetes. Previous studies have shown that the heritability of type 1 and type 2 diabetes may differ and can be reflected in the phenotype of the offspring.[18] Although adolescents identifying themselves as diabetic were excluded from this study, a more severe phenotype consistent with the heritability of type 1 and/or type 2 diabetes cannot be ruled out in this cohort.

Since the current findings were not based on evaluation of an a priori hypothesis but are a part of a study designed to look more broadly at the relationship of birth weight and insulin resistance, the small sample size of some subgroups is a study limitation. However, given the consistency of the findings with other studies and the use of nonparametric techniques in analyses, the findings are not likely to be merely chance occurrences, and stronger associations may be more apparent with larger sample sizes.

Despite these limitations, the data do suggest that LBW African-Caribbean adolescent girls with a family history of diabetes are at greater risk for adverse metabolic consequences compared to other adolescent girls on Barbados. The catch-up weight phenomenon may play a role in the observed increased insulin resistance in this group of girls. These findings indicate that studies are needed to identify the factors, be they behavioral, environmental, or genetic, that predispose to weight gain and metabolic health risk in this subset of adolescent girls.

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