RESEARCH PAPER

Markers of Fetal Onset Adult Diseases: A Comparison among Low Birthweight and Normal Birthweight Adolescents

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Objective: To observe and compare the markers of fetal onset adult diseases among low birthweight (<2500 grams, LBW) and normal birthweight (≥2500 grams, NBW) babies at 16 years of age.

Methods: Comparative cross sectional analysis of two groups of cohorts followed-up at 1 year and 16 years of age at Child Development Centre (CDC), Medical College, Thiruvananthapuram. 189 LBW babies formed the study group and 213 NBW babies formed the comparison group. At 16 years, the parameters used for assessment of both the groups were, body mass index (BMI) and the markers of fetal onset adult diseases – fasting blood glucose level, fasting plasma insulin level, total cholesterol, low density lipoprotein, high density lipoprotein and triglycerides.

Results: High triglyceride values and overweight/obesity were significantly more in LBW adolescents when compared to NBW adolescents. This has policy implications in planning adolescent nutrition and care programs in India.

Keywords: *Birthweight, India, Markers, Overweight/obesity, Triglycerides.*

The period of intrauterine growth and development is the most vulnerable period in the human life cycle and aberrations in this period can result in later sinister effects. Nutritional deprivation of the fetus during critical periods of development forces the baby to resort to adaptive survival strategies leading to increased susceptibility to two important adult diseases-coronary heart disease and type 2 diabetes. The Barker hypothesis, otherwise known as the "fetal origins hypothesis", states that cardiovascular disease and type 2 diabetes originate through the adaptations that the fetus makes when it is undernourished(1). In relation to insulin action and diabetes, Hales and Barker have described this phenomenon as the "thrifty phenotype"(2-6). The basic premise of the thrifty gene hypothesis is that certain populations may have genes that determine increased fat storage, which in times of famine represent a survival advantage, but in a modern environment of plenty, result in obesity and type 2 diabetes(7,8). Thus, as a group, people who are small at birth or during infancy remain biologically different throughout their lives and are more likely to develop type 2 diabetes and have different patterns of blood lipids(9-11). A correlation of hyperlipidemia with early CAD in young individuals has been well established(12).

Substantial variation in the prevalence of diabetes in different regions of India is well documented with very high prevalence reported in Trivandrum(13,14). Our department has a cohort of low birthweight (<2500grams, LBW) and normal birthweight (≥2500 grams, NBW) babies, now at 16 years of age, whose accurate record of anthropometric measurements at birth and one year are available. Hence, this study was done with the specific objective of observing and comparing the markers of fetal onset adult diseases among low birthweight and normal birthweight adolescents at 16 years of age.

METHODS

The study design was a comparative cross sectional analysis of two cohorts, followed up at 1 year and 16 years of age at Child Development Centre, Medical College, Thiruvananthapuram. The anthropometric measurements-weight, height and head circumference of the babies had been recorded at birth and at 1 year of age by a single observer. At 16 years, the parameters used for assessment of both the groups were, body mass index (BMI) and the following markers of fetal onset adult diseases; fasting blood glucose level, fasting plasma insulin level, total cholesterol, Low density lipoprotein (LDL), High density lipoprotein (HDL) and triglycerides.

The study group consisted of 189 LBW adolescents and the comparison group, 213 NBW adolescents. Sample size adequacy was arrived at on the basis of assumptions on the expected difference in different variables and the largest was taken. For an expected difference in fasting blood glucose of 3.5 mg/dL between the two birthweight groups, assuming a standard deviation of 10 mg/dL for a power of 90 % with alpha error of 0.05, the required sample size in the two groups was 175 and allowing for additional 25 % for loss to follow up gave 220 in each group.

With the approval of CDC human ethical committee and after obtaining informed written consent from parents of study subjects, a performa was used to update the baseline information for each adolescent. Height and weight were recorded by a single observer, as per standard procedure. Body mass index (BMI) was calculated as weight (kg) per height squared (m^2).

For the purpose of drawing blood for fasting blood glucose estimation, fasting blood insulin level and lipid profile, the subjects were requested to report in a fasting state to the Advanced Clinical Research Laboratory under quality control of Christian Medical College, Vellore, which in turn is under constant quality control of WHO. After the collection of blood, refreshments were provided to the adolescents. In addition, scholastic counseling was provided to all by a clinical psychologist. Cholesterol estimations were done by the Cholesterol oxidase peroxidase enzymatic method. Triglyceride levels were estimated by the Glycerol 3 phosphate oxidase peroxidase enzymatic method. HDL levels were estimated by the Cholesterol ester hydrolase oxidase peroxidase enzymatic method. LDL levels were calculated by the laboratory once total cholesterol, HDL and Triglyceride estimates were available. The homeostasis model assessment for insulin resistance (HOMA-IR) index was calculated as fasting insulin concentration (μU/mL) X fasting glucose concentration (mmol/L)/22.5, assuming that normal young subjects have an insulin resistance of 1.

Student's *t* test was used to compare the means, Fishers exact test to compare the percentages between the two groups and multiple logistic regression analysis for multivariate analysis. Two tailed *P* value ≤0.05 was considered for statistical significance.

RESULTS

The outcome measurements at 16 years of age were available for a total of 402 adolescents, 189 in the LBW (male 92, female 97) and 213 in the NBW group (male 122, female 91). The mean weight of the LBW group at one year (7.77 Kg, SD 1.047) was significantly less (*P*=0.000) than the mean weight of the normal birth weight group at one year (8.4 Kg, SD 1.01).

***Table* I** shows the comparison of mean values of different parameters at 16 years between LBW and NBW groups. No significant differences were noted in the parameters of fasting plasma glucose, fasting plasma insulin and homeostasis model assessment for insulin resistance (HOMA-IR) values among the low birthweight and normal birthweight group. Also no significant difference was noted in the total cholesterol, LDL and HDL values among the LBW and NBW groups. ***Table* II** compares the percentage of adolescents in both groups with abnormal values for the markers of fetal onset adult diseases. Seven (3.7%) LBW adolescents had high levels of triglycerides (>150 mg/dL) whereas only one (0.5%) normal birthweight adolescent had a high triglyceride level and this difference was observed to be statistically significant (*P=0.03*).

TABLE I COMPARISON OF MEAN VALUES AT 16 YEARS IN LOW BIRTHWEIGHT AND NORMAL BIRTHWEIGHT GROUPS

Parameters	Males		Females		Total		*P* value
	LBW Mean (SD)	NBW Mean (SD)	LBW Mean (SD)	NBW Mean (SD)	LBW Mean (SD)	NBW Mean (SD)	
Fasting glucose levels	83.62 (7.85)	85.85 (08.98)	83.97 (8.71)	84.64 (8.55)	83.80 (8.28)	85.34 (8.80)	0.074
Fasting insulin levels	7.38 (6.47)	6.75 (5.11)	7.83 (3.21)	8.02 (3.31)	7.61 (5.07)	7.29 (4.47)	0.508
HOMA-IR	1.54 (1.44)	1.44 (1.21)	1.61 (0.67)	1.68 (0.80)	1.57 (1.11)	1.55 (1.06)	0.803
Total cholesterol	145.85 (31.98)	150.40 (31.55)	165.22 (32.25)	172.09 (35.72)	155.79 (33.47)	159.65 (35.01)	0.263
Low density lipoprotein (LDL)	85.24 (28.70)	91.34 (30.90)	106.81 (31.39)	113.21 (33.35)	96.32 (31.91)	100.67 (33.68)	0.188
High density lipoprotein (HDL)	43.68 (4.55)	44.33 (4.08)	43.81 (4.06)	44.42 (6.41)	43.75 (4.29)	44.37 (5.19)	0.197
Triglycerides	84.62 (46.49)	74.71 (24.16)	70.51 (25.35)	72.44 (23.12)	77.37 (37.74)	73.74 (23.69)	0.246
Body mass index	18.29 (3.41)	18.25 (2.96)	18.96 (2.95)	19.89 (2.76)	18.63 (3.19)	18.96 (2.98)	0.293

LBW: *Low birthweight group; NBW*: Normal birthweight group; *HOMA-IR:Homeostasis Model Assessment for Insulin Resistance*

***Table* III** gives the results of multiple logistic regression analysis, showing the odds ratios relating birthweight to markers of fetal onset adult diseases after adjusting for sex, gestational age and weight at one year. High triglyceride levels were seen more in LBW adolescents when compared to the NBW group (Odds ratio, 95% CI 0.004-0.503, *P*=0.01). Also overweight/obesity was significantly more in LBW adolescents at 16 years when compared to NBW adolescents (Odds ratio, 95% CI 0.146-0.869, *P*=0.02).

DISCUSSION

In view of the serious public health consequences predicted for countries like India, with high low birthweight rates and rapid socioeconomic transition from lack of food to plenty, the fetal

TABLE II COMPARISON OF ADOLESCENTS WITH ABNORMAL VALUES AT 16 YEARS IN THE TWO GROUPS

Parameters	*LBW	*NBW	*P* value
Fasting glucose (>90 mg/dL)	21.5	23.7	0.63
Fasting insulin (>24mU/mL)	1.1	0.9	1.00
HOMA-IR (≥3)	9.0	16.0	0.30
Total cholesterol (≥200mg/dL)	9.1	14.7	0.09
LDL (≥130mg/dL)	15.0	19.4	0.29
HDL (<45mg/dL)	59.9	58.8	0.84
Triglycerides ≥150mg/dL	3.7	0.5	0.03
Body Mass Index (>22)	14.9	13.8	0.77

*LBW: Low birthweight group, NBW: Normal birthweight group.HOMA–IR:Homeostasis model assessment for insulin resistance, LDL:Low density lipoprotens , HDL:High density lipoproteins, * values in percentage of total*

TABLE III ADJUSTED ODDS RATIO RELATING BIRTHWEIGHT TO MARKERS OF FETAL ONSET ADULT DISEASES: RESULTS OF MULTIPLE LOGISTIC REGRESSION ANALYSIS

Parameters	*P* value	Odds Ratio	95% CI
High fasting plasma glucose (>90 mg/dL)	0.840	1.08	0.50, 2.35
High fasting plasma insulin (>24mU/mL)	0.979	0.95	0.02, 54.4
HOMA-IR (≥3)	0.054	7.66	0.96, 60.92
High total cholesterol (≥200mg/dL)	0.117	2.49	0.80, 7.76
High LDL (≥130mg/dL)	0.197	1.81	0.73, 4.48
Low HDL (<45mg/dL)	0.159	1.61	0.83, 3.11
High triglyceride (≥150mg/dL)	0.011	0.05	0.00, 0.50
Body Mass Index (>22 overweight and obese)	0.023	0.36	0.15, 0.87

All models adjusted for sex, gestational age and bodyweight at one year

WHAT THIS STUDY ADDS?

- Low birthweight is a risk factor for overweight/obesity and high triglyceride levels at 16 years of age.

origin of adult diseases theory has to be tested in different parts of India with geographic and ethnic variations. The availability of a cohort of low birthweight and normal birthweight babies with reliable anthropometric measurements at birth and one year was taken advantage of in this study. In Kerala some marriages occur among girls at around the school leaving age of 16 years (thus they are not available for follow up) and hence it was thought appropriate to measure the parameters at 16 years of age itself.

The number of low birthweight adolescents in the study is near equal to the number of normal birthweight adolescents and also the number of males in the study group is near equal to the number of females making them a comparable group. The Pune children's study observed that lower birthweight children had higher plasma insulin and glucose concentrations after an oral glucose load (15,16). In this study, no significant differences were noted in the parameters of fasting plasma glucose and fasting plasma insulin values among the low birthweight and normal birthweight group.

A notable feature in this study was that high levels of triglycerides (>150 mg/dL) were found in significantly higher proportion of LBW adolescents when compared to the normal birthweight adolescents (P=0.029). High triglyceride levels have been implicated as one of the components of metabolic syndrome by the National Cholesterol Education Panel-III (NCEP ATP-III) along with upper body obesity(17). A 2003 review of studies on the relationship between birthweight and blood lipid concentrations in later life, has reported studies with regard to triglycerides with unadjusted analysis showing a similar negative association in adolescents(18).

The observation that overweight/obesity and high triglycerides are significantly more in LBW adolescents at 16 years has policy implications for planning adolescent nutrition programs in India.

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