Hb A_{1c} in relation to intrauterine growth among male adolescents in southern Brazil

A Nazmi[1], SR Huttly[2], CG Victora[1], RC Lima[1], PR Post[3], JWL Elizalde[4] and BMC Gerson[4]

[1]*Post-Graduate Program in Epidemiology, Federal University of Pelotas, Pelotas, RS, Brazil;* [2]*Nutrition and Public Health Intervention Research Unit, London School of Hygiene and Tropical Medicine, London, UK;* [3]*Department of Microbiology and Parasitology, Federal University of Pelotas, Pelotas, RS, Brazil and* [4]*Brazilian Army, Tuiuti Regiment- 8th Motorised Infantry Brigade, Pelotas, RS, Brazil*

The fetal origins hypothesis states that nutritional deprivation *in utero* affects fetal development and contributes to the incidence of diseases associated with the metabolic syndrome in later life. This study investigated whether haemoglobin (Hb) A_{1c}, an indicator of blood glucose, varied among healthy male adolescents according to their fetal growth rate, in a middle-income setting. Participants were men aged 18 years, belonging to the 1982 Pelotas birth cohort. Complete data, including gestational age and Hb A_{1c} at age 18 years, were available for 197 individuals. There was an inverse association between mean Hb A_{1c} and birthweight for the gestational age, but not birthweight alone. The association remained significant after adjustment for family income and mother's education, as well as for body mass index at 18 years (P for trend = 0.01 and 0.03, respectively).

Keywords: fetal development; birthweight; glycosylated hemoglobin A; cohort study; fetal growth retardation; small for gestational age

Background

In the early 1990s, Barker and co-workers proposed the hypothesis that undernutrition *in utero* and during infancy permanently affects the body's physiology and metabolism, thus leading to disease states in later life (Barker *et al*., 1993; Barker, 1994). They suggested that disease states associated with the metabolic syndrome originate during these developmentally sensitive periods (Barker, 2003). Hales and co-workers suggested that undernutrition during critical periods, leading to impaired development of β-cell function and muscle response to insulin, is the root cause of impaired glucose tolerance and diabetes – the 'thrifty phenotype hypothesis' (Hales *et al*., 1991; Barker, 1994). Many longitudinal studies have since provided supporting evidence for these hypotheses among diverse populations, mostly in high-income countries using data from historical cohorts (Hales *et al*., 1991; Leon *et al*., 1998; Bavdekar *et al*., 1999; Eriksson *et al*., 2001; Yajnik, 2001; Barker *et al*., 2002). This study, drawing on longitudinal birth cohort data, assessed levels of haemoglobin (Hb) A_{1c} in adolescence in relation to fetal growth rate in an urban Brazilian population. Hb A_{1c} is a convenient method for indicating blood glucose concentration over the preceding months and is more practical to administer than the standard alternatives as it does not require the subject to be in a fasted state.

Study population

The city of Pelotas is located in the extreme south of Brazil. At the time of the study, the infant mortality rate was 38 per thousand and 9.9% of infants were born with low birthweight (LBW, <2500 g).

The 1982 Pelotas (Brazil) birth cohort study recruited all births in the city that year in the three maternity hospitals (6011 births, 99.2% of births) (Barros *et al*., 1990, 2001; Victora *et al*., 2003). In 2000, all cohort male subjects were legally required to enlist themselves in the Brazilian army. Of the 3037 original cohort male subjects, 2890 were presumed to be alive and 2047 were identified when enlisting and their birth records were traced. Attempts to locate the remainder resulted in 2250 boys (79%) being located, interviewed and measured.

All boys born with LBW were selected to participate in a lung function test for another study (Lima *et al*., 2005). For each of these 118 LBW boys, two subjects born with appropriate BW ($\geqslant$2500 g) were randomly selected. This sub-sample ($n=354$) forms the basis for the analyses presented here. BW for gestational age (BW/GA) was analysed in quartiles in order to avoid the problems associated with using a single cutoff.

Methods

As an indicator of fetal growth rate, BW/GA *z*-scores were computed based on Williams' growth curves (Horta *et al*., 2003). GA was estimated (in 1982) from the mothers' recall of the date of their last menstrual period and could not be determined for 24% of the samples (Barros and Victora, 1999).

Glycosylated Hb (GHb) is used clinically as a marker of blood glucose concentration over the preceding 30–90 days. Hb A_{1c}, representing a fraction of GHb, is the most prevalent glycated Hb species and is widely used to assess blood glucose concentration.

Testing was performed by trained army biochemists. The Abbott IMx Ion Capture Assay (Abbott Park, IL, USA) was used for the measurement of per cent glycated Hb in whole blood. The results (in %Hb A_{1c} of total Hb) are indicative of the time-averaged blood glucose concentration over the past 1–3 months.

Linear regression was used to compare means between the subgroups of BW/GA and BW in four groups (<2500, 2500–2999, 3000–3499 and 3500+ g). Analyses were adjusted for maternal education and family income groups from 1982 and body mass index (BMI) from 2000. Intercooled Stata 8.2 was used for statistical analyses.

Results

Blood samples were collected from 262 subjects (74% of those eligible) and GA data were available for 197 subjects. Table 1 shows the characteristics at birth and in adolescence according to the quartile of BW/GA age *z*-score. Family income, mother's education, adolescent weight and height were strongly and positively associated with BW/GA *z*-score.

Mean %Hb A_{1c} for the entire sample was 5.22 (95% confidence interval 5.15; 5.30). Table 2 shows the linear regression coefficients for the association between %Hb A_{1c} in 2000 and quartiles of BW/GA *z*-score in crude and adjusted analyses. In each model, there was a significant inverse association between Hb A_{1c} levels in adolescence and fetal growth rate. Adjusting for mother's education, family income, and/or BMI in 2000 affected the regression

Table 1 Mean (s.d.) of characteristics measured in 1982 and 2000 according to BW/GA quartiles

	BW/GA z-score quartile (range)				
	1 (−4.12, −1.38)	*2 (−1.34, −0.60)*	*3 (−0.56, 0.25)*	*4 (0.25, 2.12)*	P[a]
N	50	49	49	49	—
1982					
BW/GA *z*-score	−2.18 (0.74)	−0.93 (0.22)	−0.13 (0.25)	0.83 (0.48)	—
Birthweight (g)	2298 (348)	2755 (440)	3367 (251)	3754 (466)	<0.0001
Gestational age (weeks)	38.5 (1.9)	38.0 (2.5)	39.3 (1.5)	39.1 (2.2)	0.03
Family income, in minimum wage	2.0 (1.1)	2.5 (1.1)	2.3 (1.0)	2.7 (1.0)	0.004
Mother's education (years)	5.8 (3.9)	6.9 (4.6)	6.8 (4.4)	8.5 (4.9)	0.005
2000					
Weight (kg)	62.7 (7.4)	66.6 (13.1)	63.5 (10.1)	70.7 (10.7)	0.003
Height (cm)	170.7 (6.6)	171.9 (7.0)	172.1 (6.6)	176.3 (5.9)	0.0001
BMI	21.5 (2.3)	22.4 (3.4)	21.4 (3.1)	22.7 (3.0)	0.14

[a]Crude *P*-values derived by linear regression.
Abbreviations: BMI, body mass index; BW/GA, birthweight for the gestational age; s.d., standard deviation.

Table 2 Linear regression coefficients for the association between %Hb A_{1c} in 2000 and quartiles of BW/GA ($n=197$)

Regression model	*Regression coefficient*	*95% CI*	P-*value*
Crude	−0.09	−0.16; −0.02	0.01
Adjusted for mother's education and family income in 1982	−0.08	−0.15; −0.01	0.03
Adjusted for BMI in 2000	−0.09	−0.15; −0.02	0.01
Adjusted for mother's education and family income in 1982 and BMI in 2000	−0.08	−0.15; −0.07	0.03

Abbreviations: BMI, body mass index; BW/GA, birthweight for gestational age; CI, confidence interval; Hb, haemoglobin.

Table 3 Linear regression coefficients for the association between %Hb A_{1c} in 2000 and birthweight in four groups ($n = 197$)

Regression model	*Regression coefficient*	*95% CI*	P-*value*
Crude	−0.05	−0.10; 0.01	0.10
Adjusted for mother's education and family income in 1982	−0.04	−0.10; 0.01	0.30
Adjusted for BMI in 2000	−0.05	−0.10; 0.01	0.10
Adjusted for mother's education and family income in 1982 and BMI in 2000	−0.04	−0.10; 0.01	0.41

Abbreviations: BMI, body mass index; CI, confidence interval; Hb, haemoglobin.

coefficient only slightly. Conversely, none of the models using BW as the exposure variable showed an association with Hb A_{1c} (Table 3).

Discussion

This study showed that in this urban Brazilian population, BW/GA – an indicator of intrauterine growth restriction – was inversely associated with mean Hb A_{1c} in adolescence. This finding remained significant after adjustment for key confounding variables, and is consistent with the fetal origins hypothesis. These findings suggest that the fetal environment of those born with low BW/GA may have affected the development of metabolic regulatory systems. Hb A_{1c} levels were within the normal range, suggesting that even at clinically insignificant levels, baseline blood glucose levels vary inversely with fetal growth rate and may confer greater risk of future metabolic disorders to those with higher levels. Studies in young Indians have shown similar associations between elevated blood glucose levels and early growth factors (Yajnik *et al*., 1995; Bavdekar *et al*., 1999).

In comparison with the extensive literature on older adults, few studies have explored the fetal origins hypothesis in young people, especially in the context of the thrifty phenotype hypothesis (Hales *et al*., 1991). Furthermore, most studies investigating early origins rely on BW alone as an indicator of fetal growth. In this study, associations were only significant when BW was analysed in relation to GA, indicating that BW alone may not discriminate the effects of a short gestation from those of nutritional exposures (Adair and Prentice, 2004; Kuzawa, 2004). However, BW/GA also has its limitations, if a single cutoff point is used, for example, the 10th percentile. Some infants born small for GA may represent the lower end of the normal fetal growth distribution, whereas others experiencing intrauterine growth restriction may be born with appropriate weight for GA (WHO, 1995; Horta, 2001). By using quartiles of BW/GA and looking for an association across its whole spectrum, we were able to avoid these pitfalls.

This study adds to the literature by confirming a developmental origins effect in a relatively deprived population among adolescents within a birth cohort. Furthermore, it has underscored the importance of using BW/GA, as opposed to BW alone, as a proxy for fetal growth. A potential limitation of this study was the missing GA data. Subjects without GA data had lower BW and their mothers were less educated; however, they showed no difference in HbA_{1c} levels as compared to those with complete information.

In summary, this study contributes evidence in support of the developmental origins of adult disease hypothesis among a healthy adolescent population in a developing country setting. Further research should aim to determine how best to analyse the relevant exposure and outcome variables throughout the life course. Of fundamental importance will be in the context of the mechanisms that drive the chronic disease processes related to the early experiences. Understanding the aetiology of these mechanisms could prove fundamental in addressing public health concerns related to chronic disease epidemiology.

References

Adair LS, Prentice AM (2004). A critical evaluation of the fetal origins hypothesis and its implications for developing countries. *J Nutr* **134**, 191–193.

Barker D (2003). The developmental origins of adult disease. *Eur J Epidemiol* **18**, 733–736.

Barker D, Eriksson J, Forsen T, Osmond C (2002). Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemio* **31**, 1235–1239.

Barker D, Gluckman P, Godfrey K, Harding J, Owens J, Robinson J (1993). Fetal nutrition and cardiovascular disease in adult life. *Lancet* **341**, 938–941.

Barker DJP (1994). *Mothers, Babies, and Disease in Later Life*. BMJ Publishing Group: London.

Barros FC, Victora CG (1999). Increased blood pressure in adolescents who were small for gestational age at birth: a cohort study in Brazil. *Int J Epidemiol* **28**, 676–681.

Barros FC, Victora CG, Horta BL (2001). Ethnicity and infant health in southern Brazil: a birth cohort study. *Int J Epidemiol* **30**, 1001–1008.

Barros FC, Victora CG, Vaughan JP (1990). The Pelotas (Brazil) birth cohort study 1982–1987: strategies for following up 6000 children in a developing country. *Paediatr Perinat Epidemiol* **4**, 205–220.

Bavdekar A, Yajnik CS, Fall CH, Bapat S, Pandit AN, Deshpande V *et al*. (1999). Insulin resistance syndrome in 8-year-old Indian children. *Diabetes* **48**, 2422–2429.

Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJP (2001). Early growth and coronary heart disease in later life: longitudinal study. *BMJ* **322**, 949–953.

Hales C, Barker D, Clark P, Cox L, Fall C, Osmond C *et al*. (1991). Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* **303**, 1019–1022.

Horta BL (2001). Determinants of catch-up growth in small-for-gestational age infants. Doctoral dissertation, McGill University.

Horta BL, Barros FC, Victora CG, Cole TJ (2003). Early and late growth and blood pressure in adolescence. *J Epidemiol Commun Health* **57**, 226–230.

Kuzawa CW (2004). Modeling fetal adaptation to nutrient restriction: testing the fetal origins hypothesis with a supply–demand model. *J Nutr* **134**, 194–200.

Leon DA, Lithell HO, Vagero D, Koupilova I, Mohsen R, Berglund L *et al*. (1998). Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–29. *BMJ* **317**, 241–245.

Lima R, Victora CG, Menezes AMB, Barros FC (2005). Respiratory function in adolescence in relation to low birth weight, preterm delivery, and intrauterine growth restriction. *Chest* **128**, 2400–2407.

Victora CG, Barros FC, Lima RC, Behague DP, Goncalves H, Horta BL *et al*. (2003). The Pelotas birth cohort study, Rio Grande do Sul, Brazil, 1982–2001. *Cad Saúde Pública* **19**, 1241–1256.

WHO Expert Committee on Physical Status (1995): the Use and Interpretation of Anthropometry. Report of a WHO expert committee. WHO technical report series: Geneva, 854.

Yajnik C (2001). The insulin resistance epidemic in India: fetal origins, later lifestyle, or both? *Nutr Rev* **59**, 1–9.

Yajnik CS, Fall C, Vaidya U, Pandit A, Bavdekar A, Bhat D *et al*. (1995). Fetal growth and glucose and insulin metabolism in four year old Indian children. *Diabetic Med* **12**, 330–336.