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Associations of birthweight with glucose and insulin metabolism in 4 year old Indian children

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High prevalence of type 2 diabetes and associated cardiovascular disease in India is a matter of concern. This high prevalence is seen in both, the native residents of India and also in those who have migrated to the more affluent countries. It is generally believed that natural selection has allowed a 'thrifty genotype' to concentrate in the underpriviledged population which helps survival in the famine conditions by promoting anabolism. When food is available in plenty this genotype becomes detrimental, leading to obesity and diabetes. This hypothesis envisages a process of natural selection over millions of year with little possibility of changing in the near future. Though the argument is attractive, no genetic markers have yet been found. Thrifty genotype remains a working hypothesis.

A paradoxical finding in cardiovascular epidemiology in the U.K. was the high mortality from coronary heart disease in the underpriviledged classes of the industrial areas. The traditional lifestyle risk factors (smoking, obesity, lack of exercise etc) explained only a part of the geographical differences in cardiovascular mortality. A number of original observations at the Environmental Epidemiology Unit of the Medical Research Council, Southampton, U.K. have helped us understand this paradox. It was observed that the rate of cardiovascular mortality in adult life correlated strongly with the differences in neonatal and infant mortality in these areas many years ago. These areas were characterised by poor maternal nutrition and high prevalence of low birthweight.

This original finding was followed by a series of studies of cardiovascular risk factors in the adult population in whom birthweight and other parameters of early life growth were available. In short, low birthweight was shown to be associated with increased prevalence in adult life of diabetes and impaired glucose tolerance, insulin resistance, dyslipidemias, central obesity, hypertension, elevated serum fibrinogen concentration and increased cardiovascular mortality. It is suggested that poor intrauterine growth leads to a 'thrifty phenotype' characterised by low birthweight and thinness at birth, predisposing these individuals to develop different cardiovascular risk factors due to the 'programming' of different metabolic pathways and organ systems in-utero. It is not difficult to envisage why this could be so, if we remember that the major share of cellular divisions and organ development in our life is over before we are born. Nutritional or other insults in the intra-uterine life are likely to have far reaching effects. Such individuals when exposed to 'plentiful' situations in later life express various biochemical risk factors. We do not know yet which metabolic pathways are crucial in the programming sequence but glucose-insulin metabolism seems a prime candidate. Endocrine pancreas develops and secretes insulin in the intra-uterine life, ensuring that growth rate is commensurate with the nutrient supply. Abnormalities in this pathway could affect not only glucose metabolism but also lipid metabolism and development of vascular system, thus leading to widespread manifestations in different systems in later life.

We have been involved in the study of the so called 'malnutrition related diabetes (MRDM)' for the last few years. We have objected to the present day definition of MRDM based entirely on the presence of malnutrition at the time of diagnosis of diabetes. We have also commented on the lack of prospective data of the nutritional status of the so called MRDM patients. Prof. Barker's hypothesis offers a unique opportunity to test the interaction of early life nutrition with later development of diabetes and related

disorders in Indian population which has a high prevalence of low birthweight, type 2 diabetes and coronary artery disease. I present a preliminary analysis of our results in 4 year old Indian children in a prospective study of diabetes and cardiovascular risk factors in collaboration with Prof. Barker and his colleagues at the Environmental Epidemiology Unit of the Medical Research Council and the Department of Human Nutrition in Southampton, U.K.

Subjects and methods

A total of 404 singleton babies, born in our hospital during October 1987 to April 1989, weighing over 2000gm and admitted to the routine post natal wards were selected from 1998 live births recorded in the labour ward register for that period, using random number tables.

Of these 404 children, 84 were no longer living at the given addresses. Of the remaining 320, the parents of 201 (63%) agreed for their child to take part in our study. Children were admitted to hospital the evening before the test, and fasted overnight. In the morning an indwelling venous cannula (22G) was inserted in a forearm vein and fasting blood taken for measurement of plasma glucose and insulin. The child was then given a drink containing 1.75gm of anhydrous glucose per kilogram body weight in 150 ml of water. Further blood samples were taken at 30 and 120 minutes after the glucose load, for measurement of plasma glucose and insulin concentration.

The child's weight, height, triceps and subscapular skinfold thickness, waist to hip circumference ratio and head circumference were measured. The child's socio-economic (SE) status was assessed by a social worker using the Kuppuswamy score, range from 1 down to 5, the least advantaged category.

Plasma glucose was measured using glucose oxidase method. Plasma insulin concentrations were measured in Cambridge, U.K. by Prof Hales, using a two-site immunometric assay.

Variable showing skewed distribution were 'normalised' for the analysis using appropriate transformations (logarithms etc.). Adjustments of plasma glucose and insulin concentrations for current parameters: weight, age and sex, were made using multiple linear regression. Analysis of the relation between glucose, insulin and birthweight was by tabulation of means and trend tests from one-way analysis of variance.

Results

The children's ages ranged from 3.7 to 4.4 year (median 4.0 yr). Table 1 shows mean birthweight of these children and anthropometry at the age of 4 years. Mean birthweight, 4 year weight and height were low by Western standards, but consistent with population studies in India. Girls had smaller head circumferences and greater subscapular and triceps skinfold thickness than boys, but their waist hip ratios were similar.

Table 1

Mean Birthweight and Current Anthropometry of Four Year Old Children

	Boys (n=105)	Girls (n=96)
At birth (kg)	2.789 (0.39)	2.744 (0.33)
At 4 years		
Weight (kg)	13.2 (1.6)	12.9(1.9)
Height (cm)	97.8 (4.4)	97.6 (4.5)
Head circumference (cm)	48.4(1.4)	47.6(1.2)
Subscapular skinfold (mm)	5.7 (1.6)	6.4 (1.8)
Triceps skinfold (mm)	8.3 (2.0)	9.1 (1.9)
Waist/hip ratio(cm)	0.95 (0.11)	0.95 (0.06)

Numbers in parenthesis = standard deviations

Table 2 shows mean plasma glucose and insulin concentrations at 0, 30 and 120 minutes. There were no differences between boys and girls in plasma glucose concentration but girls had higher plasma insulin concentration at all points. Plasma glucose and insulin concentrations were positively related to current weight, subscapular and triceps skinfold thickness. Higher plasma insulin concentration in girls were partly accounted for by their smaller head circumference and greater subcutaneous fat.

Table 2
Mean Plasma Glucose and Insulin Concentrations In Four Year Old Children

Time	0	30	120
Plasma Glucose (mmol/L)			
Boys (n = 105)	4.4	7.9	5.4
Girls (n = 96)	4.4	7.8	5.4
Plasma insulin (pmol/L)			
Boys (n = 105)	25	283	110
Girls (n = 96)	30*	340*	135*

*P<0.05 compared to boys

Table 3 shows mean plasma glucose and insulin concentration according to birthweight. Thirty minute plasma glucose concentration fell with increasing birthweight (p=0.04), this trend was stronger after allowing for present weight (p=0.01). The highest 30 minute plasma glucose concentration were in children who were light at birth and heavy at four years. The relationship of glucose and birthweight was not altered by allowing for socio-economic status. Fasting and 120 minute plasma glucose concentrations showed no relationship to birthweight. Similarly, 30 minute plasma insulin concentrations fell with increasing birthweight (p=0.04), allowing for four year weight, age and sex and SE status. Plasma insulin concentrations at 0 and 120 minutes were not related to birthweight.

Table 3
Mean Body Weight and Plasma Glucose and Insulin Concentrations According to Birthweight

Birthweight (kg)	Weight at four years	Glucose (mmol/L) 0 mins	30 mins	120 mins	Insulin (pmol/L) 0 mins	30 mins	120 mins
≤ 2.4 (36)	12.4	4.5	8.1	5.1	27	321	94
-2.6(36)	13.0	4.5	8.3	5.6	29	337	127
-2.8(44)	13.0	4.4	7.8	5.7	28	309	143
>3.0(42)	13.1	4.3	7.9	5.2	24	298	120
8.0 (43)	13.9	4.4	7.5	5.4	31	289	123
p value for trend	0.0008	0.1[a]	0.01[a]	0.7[a]	0.5[a]	0.04[a]	1.0[a]

Numbers in parenthesis = Number of children
a Allowing for Childrens' current weight, age and sex.

Discussion

We have studied plasma glucose and insulin concentrations after an oral glucose load in 4 year old children in India. Children who had lower birthweight had higher 30 minute plasma glucose and insulin

concentration, independently of their current body size and SE status. Thus, our results suggests that Indian children with reduced intra-uterine growth show impairment of glucose homeostasis after a glucose challenge. This might be interpreted to suggest that glucose and insulin metabolism is to an extent programmed in-utero in Indian children.

A link between low birthweight and raised concentrations of glucose after an oral load has been shown in studies of adults in Britain, and confirmed in two studies in the USA. The associations are independent of the social class and adult body mass index. In adult studies in Britain, birthweight is linked to both 30 and 120 minute plasma glucose and to 120 but not 30 minute plasma insulin. In our 4year children we found no relationship between birthweight and 120 minute glucose or insulin concentrations. Thus at such young age the reduced glucose homeostasis associated with low birthweight is evident only at 30 minutes after an oral glucose challenge, the most 'stressed' point of the test in our study. It would appear that as the age advances the disturbance in glucose homeostasis persists for a longer time i.e. 120 mins after glucose load.

Impaired fetal growth could be linked to reduced glucose tolerance through either insulin deficiency or resistance. Fasting insulin concentrations, often used as a proxy for insulin resistance in adults, were not raised in children of lower birthweight. Both glucose and insulin concentrations were higher at 30 minutes, suggesting insulin resistance rather than deficiency. A link between insulin resistance and impaired fetal growth is also suggested by the association between lower head circumference and raised fasting plasma insulin concentrations. Head circumference at four years is largely determined by growth in-utero and during the first 6 post natal months.

As in many other studies, we found that girls had higher fasting insulin concentrations than boys, this could reflect greater insulin resistance in girls than boys. This was partly explained by their fatness (greater skinfold thicknesses) and partly by their smaller intra-uterine growth (smaller head circumference). These observations could have important implications in the aetiology of insulin resistance commonly seen in clinical practice in young women.

In the Western countries plasma insulin concentrations are related to current weight across its whole range in both children and adults. We found that this continuous relationship was present even in relatively underweight children in India, similar to our observation in non-obese adults in India.

Low birthweight and thinness at birth are common in India. We suggest that the high prevalence of NIDDM and IGT in Indian people could be partly linked to foetal undernutrition. If true, improvement in maternal nutrition might be one of the many ways of reducing the incidence of NIDDM in our population.

Further Reading

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