Fetal origins of diabetes in developing countries

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There is a rapidly rising epidemic of Type 2 diabetes throughout the world. It is particularly severe in developing countries. In 1995, 62% of people with diabetes in the world lived in developing countries. By 2025 this is predicted to rise to more than 75%. In India there are an estimated 25 million people with diabetes, and this will rise to more than 60 million by 2025. One in five people with diabetes in the world will then be Indian. A parallel rise in ischaemic heart disease (IHD) is also projected. Other developing countries will be similarly affected.

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Susceptibility to diabetes: genes, nutrition and growth

Traditionally, susceptibility to Type 2 diabetes is ascribed to 'thrifty genes'. Neel proposed that these genes helped the human race to survive in the distant past when food supply was intermittent and scarce. When food was available, these genes promoted body fat deposition (energy stores), which helped survival during lean seasons. In recent times, the argument goes, with food supply plentiful and regular, this process has led to obesity and diabetes. Although this is an attractive idea, no specific genes have been consistently associated with Type 2 diabetes.

The genetic view has recently been challenged by the 'thrifty phenotype' ('fetal origins') hypothesis. Hales and Barker found an inverse relationship between birth weight and diabetes in many Western populations. They interpreted these findings to suggest that the susceptibility to diabetes originates during one's life in the mother's womb. A number of environmental factors can influence a baby's growth and development. They suggested that poor nutrition in the womb causes changes in the metabolic and hormonal pathways and structure of the baby's developing systems ('programming'). Such a baby is, as it were, equipped to survive in famine conditions. If food supply improves or physical activity is poor, this leads to obesity and diabetes. Animal models of maternal food restriction promote insulin resistance as well as beta-cell (producers of insulin in the pancreas) dysfunction in the offspring, thus supporting this idea.

The two ideas may not be mutually exclusive. A third suggestion by Hattersley and Tooke ('fetal insulin hypothesis') suggests that birth size may be determined by genes which also cause diabetes. However, it is known that the interaction between a baby's genes and a mother's metabolism during pregnancy affects the baby's size and future risk of diabetes.

Developing countries – a more complicated situation

Indian people, especially women, have faced undernutrition for many generations. The reasons for this are many and include food shortages and social and political systems which discriminated against women. Indian babies are amongst the smallest in the world – almost one third of them are born with low birth weight (below 2500 g). This should in theory increase susceptibility to diabetes.

However, while Indian babies have been small for many generations, the epidemic of diabetes is only a recent one. Therefore, factors in later life must be equally if not more important. Also, babies in cities are heavier than babies in rural areas, but the risks of the urban babies developing Type 2 diabetes and IHD are five times higher. This implies that matters may be more complicated than the explanations discussed above suggest. Indeed, 'overnutrition' of the baby in the womb (like in a diabetic pregnancy) may also increase the risk of Type 2 diabetes in later life.

> The picture is more complicated than a simple relationship between small size at birth and later diabetes.

India . . .

There are two reported studies in India which have related size at birth to future risk of Type 2 diabetes. In Mysore, a study looked at middle-aged men and women in whom birth measurements were available. Lower birth weight did not increase the risk of diabetes but babies who were short and 'fat' (higher body mass index, BMI) at birth were at increased risk. Such babies were born to mothers who were heavier and had larger pelvic sizes, suggesting that they were relatively better nourished or had genes for larger size.

Another study, in Pune, investigated glucose and insulin metabolism in young children. It was found that at both 4 and 8 years, insulin resistance was strongly related to body size. When the effect of current body size was statistically adjusted for, lower birth weight was predictive of insulin resistance and other cardiovascular risk factors. The lightest babies who grew to be the heaviest or tallest were the most insulin resistant and had the highest levels of other cardiovascular risk factors including blood pressure and lipids (fats). It is important to remember that these children are still 'small' in comparison to international standards.

. . . China and the Americas

The situation in China is different. Small babies born to small mothers have an increased risk of diabetes. Whereas in Guatemala, low birth weight was not predictive of a later risk of diabetes. Thus, the picture is more complicated than a simple relationship between small size at birth and later diabetes. Indeed, the relationship appears to be U-shaped, as demonstrated in the Pima Indians in Arizona, US. Impaired glucose metabolism in the mother is thought to be responsible for the relationship with high birth weight. This may be happening in urban India.

> Indian babies are fat even though they are thin.

Body composition at birth

In a prospective study in six villages near Pune, India, we made detailed measurements of mothers' size and nutrition, and different aspects of their babies' size at birth. We compared these results with those of white Europid babies born in Britain. Indian mothers were much smaller compared to white Europid mothers (42 kg, 1.52 m vs 63 kg, 1.63 m, respectively) and Indian babies were on average 800 g lighter and 'thinner' (lower BMI). Despite this, Indian babies had very similar measurements of skinfold thickness (subcutaneous fat). The thinness of the Indian babies was predominantly due to small visceral size and small muscle mass.

This was a rather unexpected finding, and suggested that Indian babies are fat even though they are thin. It was supported by the detection of higher leptin (from the Greek leptos, meaning thin – a protein hormone with important effects in regulating body weight and metabolism) and insulin levels in the umbilical cord blood of Indian babies compared to those in the British babies.

Studies in adult Indians have reported similar findings in the past. It appears that higher percent body fat in Indians, despite apparent thinness, is responsible for their insulin resistance and increased risk of diabetes. This body composition >>

may be determined partly by genetic factors, about which we know little. It may also be affected by the mother's body composition and her diet during pregnancy. In the Pune study, the baby's size was not related to their mother's intake of calories and proteins, but to higher intake of green leafy vegetables, fruits and milk which are high in micronutrient content. Circulating concentrations of glucose (even in the normal range) and triglycerides also predicted larger size of the baby. Finally, the father's size predicted the baby's size, independent of maternal size.

Childhood growth

The relationship between larger size in childhood and insulin resistance may be linked to accelerated growth. In the Indian study, as well as in a study in South Africa, the speed of growth was a stronger predictor of insulin resistance than the size of the child at the time of testing. This was confirmed in Finland, where birth measurements and serial childhood measurements were available in a large number of people. People who developed diabetes were born smaller, remained small in infancy, but had grown rapidly during childhood. Such people started putting on weight at an earlier age in childhood ('adiposity rebound'). This was most noticeable in those who were born small to larger mothers. A rapid 'catch-up' growth during childhood is associated with insulin resistance and obesity and increases chances of diabetes.

> Preventative measures are likely to succeed at different stages in life.

The life-course model

It appears that the factors which affect a person's growth, development, size, and body composition are important determinants of insulin resistance and risk of diabetes. It is also apparent that although the process starts very early, it continues throughout life. Genetic as well as environmental, intra-uterine, and extra-uterine factors seem to contribute. Preventative measures are likely to succeed at different stages in life. There are 'critical windows' of time, including the intra-uterine period, when different organs and systems develop. More research is necessary to define these periods and to study what determines health and disease susceptibility.

The intrauterine period may be particularly important for the development of adiposity and future risk of insulin resistance and diabetes. We do not know how this is influenced by genetic or maternal factors. Rapid childhood growth is associated with worsening obesity. Fat storing cells (adipocytes) secrete substances which affect insulin sensitivity and other cardiovascular risk factors. In Pune, India levels of circulating fat cell products were higher in urban residents compared to those resident in the villages. These elevated levels may be linked to the increased risk of Type 2 diabetes and IHD in cities.

Summary

In summary, aberrations of intra-uterine as well as post-natal growth increase the risk of diabetes. Increasing adiposity is an important component of these aberrations. Nutritional and metabolic factors in mothers and the baby's genes are also involved. Diabetes prevention will have to start in early life (*in utero*) and continue in later years.

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Further reading

1. Barker DJP. Mothers, babies and health in later life. 1998 Churchill Livingstone, Edinburgh.

2. Yajnik CS. The insulin resistance epidemic in India: fetal origins, later lifestyle, or both? Nutrition Reviews 2001; 59: 1-9.

3. Yajnik CS. The lifecycle effects of nutrition and body size on adult adiposity, diabetes and cardiovascular disease. Obesity Reviews 2002; 3: 217-224.

4. Yajnik CS, Lubree HG, Rege SS, Naik SS, Deshpande JA, Deshpande SS, Joglekar CV, Yudkin JS. Adiposity and hyperinsulinemia in Indians are present at birth. Journal of Clinical Endocrinology & Metabolism 2002; 87: 5575-5580.

5. Yajnik CS, Fall CHD, Coyaji KJ, Hirve SS, Rao S, Barker DJP, Joglekar C, Kellingray S. Neonatal Anthropometry: The Thin-Fat Indian Baby, The Pune Maternal Nutrition Study. International Journal of Obesity 2003; 27: 173-180.