Students Section: Review Article

Epigenetic Risk Factors in Diabetes and The 'Life Course' Model

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Abstract

Lifestyle related diseases like diabetes have shown an immense increase in prevalence in India during recent times. On the other hand it has been plagued by malnutrition since ages. Researchers all over the world are exploring the cause for this geographical coexistence of under and over nutrition. Numerous studies have shown a higher prevalence of cardiovascular diseases in individuals who had lower birth weight or height, but who had 'normal' weight as adults. A number of hypotheses have been put forward to explain the above phenomenon, all emphasizing the changes in fetal metabolism in order to attain normal development of brain despite intrauterine environmental limitations. The propensity to central obesity in Indians has been shown to be programmed in-utero. The life course model proposes that a combination of antenatal, epigenetic as well as post-natal influences are responsible for the recent epidemic of diabetes in the Indian population. Therefore, avoiding maternal malnutrition and decreasing the prevalence of low birth weight could be possible additions to the conventional method of lifestyle intervention in the prevention of diabetes.

Key Words: Low birth weight, intrauterine growth retardation, type 2 diabetes.

India is heading towards acquiring the title of the capital of diabetes and cardiovascular diseases in the very near future. At the same time a significant number of low birth weight babies are being born, maternal malnutrition and growth retardation in under-five children are rampant. The over-nutrition and under-nutrition epidemics have a mutual geographic existence and are both escalating at an overwhelming rate. Malnutrition has plagued the country for centuries. Indians have a similar genetic pool which has remained stable for a while and lifestyle related diseases have established genetic predispositions. Why is there a sudden surge in diabetes and related diseases in the twenty first century? Is there a remote possibility that the two epidemics of over and under-nutrition are actually related?

Low birth weight has been associated with an increased risk of type 2 diabetes in adulthood. Numerous studies have shown the interaction between small birth size and adult obesity in relation to insulin resistance syndrome, diabetes, hypertension, obesity and cardiovascular diseases. Cardiovascular mortality was even higher in those who were born small but became obese as children. The first landmark study in this field consisting of a cohort of 30,000 by Ravilli et al who showed that maternal malnutrition in the later half of pregnancy due to the great Dutch famine led to the offspring being obese at 19 years of age [1]. Subsequent studies of English men demonstrated a relationship between low birth weight and the later development of cardiovascular disease [1] and impaired glucose tolerance [2-5]. Other studies of populations in the United States [6-8] Sweden [9], France [10], Norway [11], and Finland [12], have demonstrated a significant correlation between low birth weight and the later development of adult diseases. These relationships remain consistent even after adjustments are made for lifestyle factors, dietary differences and socioeconomic divide.

Work from India shows similar results. In a study of people born in Mysore, the highest prevalence of coronary heart disease (CHD) at 45 years of age was found in individuals who had lower weight, height or head circumference at birth, but who had 'normal' weight as adults [13] In a follow up study in Pune, Yagnik CS et al found that at 4 years of age insulin and IGF-1 concentrations were inversely related to the birth weight. At 8 years, insulin resistance and other cardiovascular risk factors including blood

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lipids, blood pressure and central adiposity were higher in those children who had the lowest birth weights but had grown the biggest [14].

The ‘thrifty genotype’ hypothesis was put forward to explain the increasing prevalence of diabetes and insulin resistance in a population which was known to have suffered from a food famine for years. It proposes that these bodies were programmed into storing all fat for phases of deficiency. But over the centuries the food deficit disappeared, eating habits changed and physical activity drastically declined. The change was faster than the slowly evolving genetic change to suit the new condition and so the “obesity-dysglycemia-dyslipidemia” epidemic started off. The thrifty genotype has an obvious evolutionary advantage as such; a hypothesis implies that poor fetal environment causes adaptive responses to maximize the chance of proper development of important organs (such as the developing brain and liver) at the expense of others, resulting in a metabolism designed to enhance survival under the food shortage situations [15]. It is when the genotypic expression remains the same but the environment changes to that having no food deficiency that the problem arises.

An even more interesting model, ‘the thrifty phenotype’ has been proposed by Hales and Barker [16] to explain the relation between fetal growth restriction and subsequent diabetes mellitus. It says that poor nutrition in early life leads to permanent changes in the glucose – insulin pathways. These changes are reflected in the fetal programming and are irreversible. These changes include reduced capacity for insulin secretion and insulin resistance which, combined with effects of obesity, ageing and physical inactivity, are the most important factors in determining type 2 diabetes [17]. Early-life metabolic adaptations promote survival, with the developing organism responding to cues of environmental quality by selecting an appropriate trajectory of growth. The thrifty phenotype refers to the capacity of all offspring to respond to environmental information during early ontogenetic development and is a consequence of three different processes: niche construction, maternal effects, and developmental plasticity. All these three processes have one common aim- which is selectively promoting the brain growth in the fetus at the expense of other organ systems and account for the differential growth rates of different body systems. It is proposed that the process of niche construction is moving at a more rapid pace than the physiological combination of developmental plasticity and parental effects and it may be the factor responsible for the accelerated rates of metabolic syndrome in the 20th century [18].

The 'fetal origins' hypothesis, as a modification of the ‘thrifty phenotype’ one, suggests that these adjustments are 'imprinted', affecting the response of the system in future life ('programming'). Insulin resistance seems to be one such survival mechanism in response to fetal malnutrition [16]. Enthusiastic workers have proposed that ‘thrifty phenotypes’ may actually be a direct consequence of the older ‘thrifty genotype’ model [19].

Multiple animal models of intrauterine growth restriction demonstrate impaired ß-cell function and development. Decreased ß-cell proliferation leads to a progressive decline in ß-cell mass leading to progressive decline in insulin secretion, finally burnout and diabetes in its florid form. Work carried out on a rat model suggests that uteroplacental insufficiency disrupts the function of the electron transport chain in the fetal ß-cell and leads to a debilitating cascade of events: increased production of reactive oxygen species, which in turn damage mitochondrial DNA and causes further production of reactive oxygen species. The net result is progressive loss of ß-cell function and eventual development of type 2 diabetes in the adult [20]. Oxidative stress and insulin resistance have been associated with small for gestational age as well as macrosomic babies, increased oxidative stress and insulin resistance is already present in pre-pubertal normal weight children who were born with a low birth weight and obesity only adds on to this existing situation [21]. Neonates with intrauterine growth restriction were found to have significantly higher oxidative stress, lipid peroxidation and underdeveloped antioxidant mechanisms when measured in the cord blood [22]. Supplementation with L-arginine during pregnancy managed to bring down this total oxidative stress [23].

The ‘thin and fat’ Indian prototype adult has a higher risk for diabetes. For a given body mass index (BMI), Indians have a higher percentage of body fat and more visceral fat than members of other populations. A very interesting observation is that

this thin-fat phenotype is not unique to adults in South East Asia but is present even at birth. Indian babies were small in all respects but there was a scheme in their smallness. Birth weight, head circumference and height were smaller to a similar extent, whereas soft tissues were differentially affected. Protein rich soft tissues (skeletal muscle and abdominal viscera) were the most affected, while subcutaneous fat was the most preserved body component [17]. Hence, the propensity of the Indians for central obesity is programmed in utero!

Environmental and postnatal influences also deserve their due share of merit and attention. If only the fetal disease origins were to be believed there would be huge discrepancies. Even though rural Indians have more low birth weight babies the incidence of diabetes is rising about 5 times faster in urban India as compared to the villages.

In a critical appraisal of the fetal origin hypothesis in the developing country scenario, Yagnik CS proposes the life-course model of evolution of insulin resistance and type 2 diabetes, incorporating fetal, postnatal and adult components. The life course model seems to be the most relevant by far, with the rationale being that people in the Indian subcontinent have faced undernutrition for many generations, and Indian babies are amongst the smallest in the world. However, the diabetes epidemic is of recent origin, and diabetes is more common among urban than rural Indians despite the higher birth weight of urban babies. Thus it is not just fetal programming or thrifty genes at play but a combination of antenatal, epigenetic as well as post natal influences [24].

We can safely conclude by saying that though low birth weight and intrauterine growth restriction are important risk factors, they are not the only mechanisms at play. We already know that the key to prevention of lifestyle related diseases is living and eating healthy, regularly exercising and staying active. What we can add to our preventive strategies is avoiding maternal malnutrition, decreasing the prevalence of low birth weight babies and regularly following up babies with low birth weight, especially those showing adequate catch-up growth.

Key Points

- Diabetes mellitus and other lifestyle related diseases like metabolic syndrome are assuming pandemic proportions worldwide. The twenty first century is witnessing a sharp escalation in the prevalence of these diseases, particularly in developing countries.
- Low birth weight and intrauterine growth retardation are less known risk factors which have been consistently associated with higher risk of diabetes in later life.
- Various models have been proposed to explain the link between diabetes and low birth weight.
- The 'thrifty genotype model' suggests that fetal metabolism is programmed to enhance survival during famines and phases of food scarcity, which were very common in the past. The food deficit has been overcome now but our genetic constitution remains the same, leading to accelerated rates of diabetes.
- The 'thrifty phenotype' states that poor nutrition in early life leads to changes in the glucose – insulin pathways finally culminating in irreversible alterations in the pancreatic ß cells.
- The mechanisms for these models propose the role of epigenetics – in-utero fetal programming in response to the stress and oxidative damage.
- A comprehensive theory – the 'life course' model is an attempt to explain all old and new risk factors and proposes that antenatal, postnatal and environmental factors act together, from conception through adulthood, and cumulatively predict the risk of developing diabetes.

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